CHEM 232 - ORGANIC CHEMISTRY II



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CHEM 232 - Organic Chemistry II

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Licensing

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CHAPTER OVERVIEW

1: Conjugated Compounds and Ultraviolet Spectroscopy

Learning Objectives

After you have completed Chapter 1, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. use the reactions discussed, along with those from previous chapters, when designing multi-step syntheses.
3. use the reactions and concepts discussed to solve road-map problems.
4. use ultraviolet-spectral data, in conjunction with other spectral data, to elucidate the structure of an unknown compound.
5. define, and use in context, the key terms introduced.

You have already studied the chemistry of compounds that contain one carbon-carbon double bond. In this chapter, you will focus your attention on compounds that contain two or more such bonds. In particular you will study the properties of those compounds that contain two carbon-carbon double bonds which are separated by one carbon-carbon single bond. These compounds are called “conjugated dienes.”

To understand the properties exhibited by conjugated dienes, you must first examine their bonding in terms of the molecular orbital theory introduced in Section 1.11. Then, you must learn how the products of a reaction are dependent on both thermodynamic and kinetic considerations. Which of these two factors is the most important can sometimes determine which of two possible products will predominate when a reaction is carried out under specific conditions. Although we shall not make extensive use of ultraviolet spectroscopy, this technique can often provide important information when conjugated compounds are being investigated. In general, ultraviolet spectroscopy is less useful than the other spectroscopic techniques introduced earlier.

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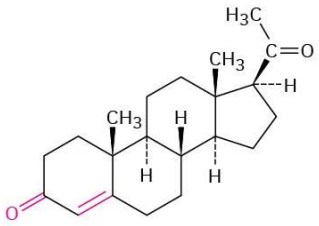
1.0: Introduction

Objective

After completing this section, you should be able to determine whether or not a molecule contains a conjugated system, given its Kekulé, condensed, or shorthand formula.



β-Carotene
(orange pigment and vitamin A precursor)



Progesterone, a conjugated enone



Benzene,
a cyclic conjugated molecule

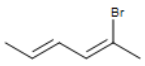
Dienes

A diene is a hydrocarbon chain that has two double bonds that may or may not be adjacent to each other. This section focuses on the delocalization of π systems by comparing two neighboring double bonds. The arrangements of these double bonds have varying effects on the compound's reactivity and stability.

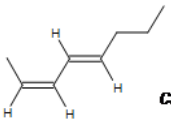
Naming Dienes

First identify the longest chain containing both carbons with double bonds in the compound. Then, give the lowest possible number for the location of the carbons with double bonds and any other functional groups present (remember when naming alkenes that some groups take priority, such as alcohols). Do not forget stereochemistry or any other orientation of the double bond such as (E/Z,cis or trans).

Examples:



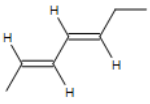
2-Bromo-2,4-hexadiene



***cis*-2-*trans*-4-octadiene**



1,3-cyclopentadiene

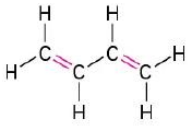


***trans*-2,4-heptadiene**

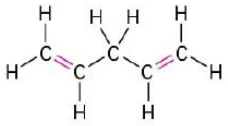
Classification of Dienes

Most of the unsaturated compounds we looked at in the previous chapters on alkenes had only one double bond, but many compounds have numerous sites of unsaturation. If the different unsaturations are well separated in a molecule, they react independently, but if they're close together, they may interact. In particular, compounds that have alternating single and double

bonds—so-called conjugated compounds—have some distinctive characteristics. The conjugated diene 1,3-butadiene, for instance, has some properties quite different from those of the nonconjugated 1,4-pentadiene.



1,3-Butadiene
(conjugated; alternating double and single bonds)



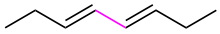
1,4-Pentadiene
(nonconjugated; nonalternating double and single bonds)

Conjugated vs. Isolated Dienes

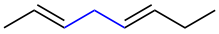
Dienes are compounds that contain two double bonds. These dienes can be conjugated, non-conjugated (isolated), or cumulated dienes. Conjugated dienes have properties and reactivity distinctly different from non-conjugated or cumulated dienes. Determining if double bonds are conjugated represents a critical skill in organic chemistry.

Conjugated dienes have the two double bonds separated by a single bond.

Nonconjugated (Isolated) dienes are two double bonds separated by more than one single bond. The two double bonds are separated by at least one sp^3 hybridized atom, and can not resonate.



3,5-Octadiene
(Conjugated)



2,5-Octadiene
(Non-Conjugated)



1,3-Cyclohexadiene
(Conjugated)



1,4-Cyclohexadiene
(Non-Conjugated)

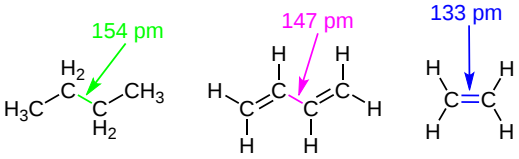


1,3-Butadiene
(Conjugated)

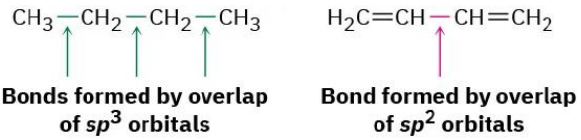


1,4-Pentadiene
(Non-Conjugated)

Evidence of conjugation in 1,3 dienes is seen in the single bond being stronger and shorter (147 pm) than an ordinary alkane C-C bond (154 pm). The resonance hybrid of a 1,3-butadiene shows this bond to contain a significant double bond character, with its bond length being roughly the average of a single and double bond.



Typical C–C single bonds, like those in alkanes, result from σ overlap of sp^3 orbitals on both carbons, but in a conjugated diene, the central C–C single bond results from σ overlap of sp^2 orbitals on both carbons. Because sp^2 orbitals have more *s* character (33% *s*) than sp^3 orbitals (25% *s*), the electrons in sp^2 orbitals are closer to the nucleus and the bonds they form are somewhat shorter and stronger. Thus, the “extra” stability of a conjugated diene results in part from the greater amount of *s* character in the orbitals forming the C–C single bond.



Cumulated Dienes

Another Classification for dienes is **Cumulated dienes** (allenes). In these, two double bonds are connected to the same atom, a sp hybridized atom.

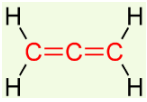


Figure 1.0.1: 1,2-Propadiene. (credit: Jü, Wikimedia Commons, CC BY 1.0)

Conjugated Dienes in Nature

Conjugated compounds of many different sorts are common in nature. Many of the pigments responsible for the brilliant colors of fruits, flowers, and even animals have numerous alternating single and double bonds. *β*-Carotene, for instance, the orange pigment responsible for the color of carrots and an important source of vitamin A, is a conjugated *polyene* with 11 double bonds. Conjugated *enones* (alk*ene* + ket*one*) are common structural features of many biologically important molecules, such as progesterone, the hormone that prepares the uterus for the implantation of a fertilized ovum. Cyclic conjugated molecules such as benzene are a major field of study in themselves. In this chapter, we'll look at some of the distinctive properties of conjugated molecules and at the reasons for those properties.

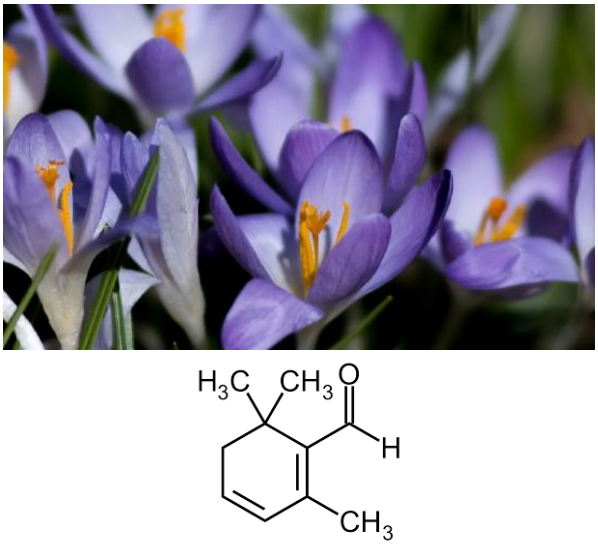


Figure 1.0.2: Saffron, derived from stigmas of the saffron crocus, is the world's most expensive spice. Its color is caused by the presence of alternating single and double bonds. (credit: "Welcome to My World! ~ Huron River Watershed" by j van cise photos/Flickr, CC BY 2.0)

Key Terms

Make certain that you can define, and use in context, the key terms below.

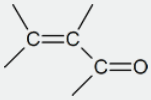
- Conjugated dienes / double bonds
- Nonconjugated (Isolated) dienes
- Cumulated dienes
- enone
- polyene

Study Notes

Conjugated double bonds are double bonds separated by one carbon-carbon single bond. Thus, the double bonds in butadiene, CH_2=CH-CH=CH_2, are conjugated, and this compound is an example of a *conjugated diene*.

Just as the term *diene* indicates the presence of two carbon-carbon double bonds in a compound, the term *polyene* is used to describe compounds containing many carbon-carbon double bonds.

An *enone* is a compound containing a carbon-carbon double bond (ene) and a carbonyl group (one). A conjugated enone contains the structural unit:



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1.1: Stability of Conjugated Dienes- Molecular Orbital Theory

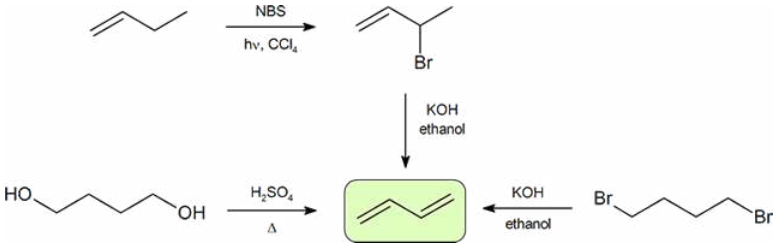
Objectives

After completing this section, you should be able to

1. Write a reaction sequence to show a convenient method for preparing a given conjugated diene from an alkene, allyl halide, alkyl dihalide or alcohol (diol).
2. Identify the reagents needed to prepare a given diene from one of the starting materials listed in Objective 1, above.
3. Compare the stabilities of conjugated and non-conjugated dienes, using evidence obtained from hydrogenation experiments.
4. Discuss the bonding in a conjugated diene, such as 1,3-butadiene, in terms of the hybridization of the carbon atoms involved.
5. Discuss the bonding in 1,3-butadiene in terms of the molecular orbital theory, and draw a molecular orbital for this and similar compounds.

Synthesis of Dienes

Conjugated dienes can be prepared using many of the methods used for the preparation of alkenes previously discussed (Organic Chemistry I Section 8.3). A convenient method starts with the free radical halogenation of the allylic carbon of an alkene using NBS. The resulting halide can then be reacted with a strong base to result in E2 elimination and create a diene product. The compound, 1,3-butadiene, is the simplest conjugated diene and has an important use in the synthesis of polymers which will be discussed in **Section 1.7**. Many simple dienes, such as 1,3-butadiene and isoprene, can be prepared industrially by the double dehydration of alcohols and the double dehydrohalogenation of organohalides.



Stability of Conjugated Dienes

Conjugated dienes are known to be more stable than non-conjugated dienes, as shown by their experimentally determined heats of hydrogenation. In Organic Chemistry I **Section 7-6**, it was shown that as alkenes become more stable, they contain less energy, and therefore release less heat during hydrogenation.

Table 1.1.1: Heats of Hydrogenation for Some Alkenes and Dienes

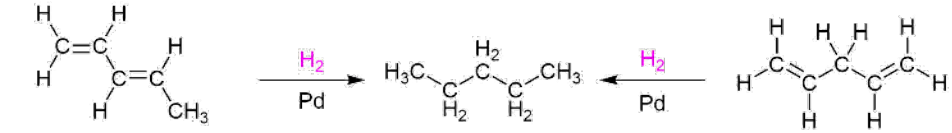
Alkene or diene	Product	ΔH°_{hydrog}		Classification
		(kJ/mol)	(kcal/mol)	
$CH_3CH_2CH{=}CH_2$	$CH_3CH_2CH_2CH_3$	–126	–30.1	Terminal Alkene
$CH_3C(CH_3){=}CH_2$	$CH_3CH(CH_3)CH_3$	–119	–28.4	More substituted Terminal Alkene
$H_2C{=}CHCH_2CH{=}CH_2$	$CH_3CH_2CH_2CH_2CH_3$	–253	–60.5	Isolated diene
$H_2C{=}CH{-}CH{=}CH_2$	$CH_3CH_2CH_2CH_3$	–236	–56.4	Conjugated diene
$H_2C{=}CH{-}C(CH_3){=}CH_2$	$CH_3CH_2CH(CH_3)CH_3$	–229	–54.7	More substituted Conjugated diene

Because a monosubstituted alkene has a ΔH°_{hydrog} of approximately –126 kJ/mol, (Table 1.1.1), we might expect that a compound with two monosubstituted double bonds would have a ΔH°_{hydrog} approximately twice that value, or –252 kJ/mol. Non-conjugated dienes, such as 1,4-pentadiene (ΔH°_{hydrog} =−253 kJ/mol), meet this expectation, but the conjugated diene 1,3-butadiene (ΔH°_{hydrog} =−236 kJ/mol) does not. 1,3-Butadiene is approximately 16 kJ/mol (3.8 kcal/mol), more stable than expected.

	ΔH°_{hydrog} (kJ/mol)	
$H_2C{=}CHCH_2CH{=}CH_2$	−126 + (−126) = −252	Expected
1,4-Pentadiene	−253	Observed
	1	Difference
$H_2C{=}CHCH{=}CH_2$	−126 + (−126) = −252	Expected
1,3-Butadiene	−236	Observed
	−16	Difference

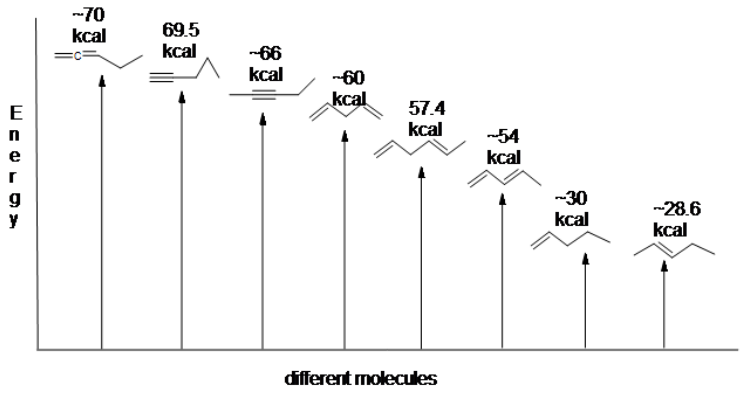
Combination of Stabilization Factors

Experiments have shown that conjugated dienes have a lower heat of hydrogenation (-226 kJ/mol) than non-conjugated dienes (-253 kJ/mol). Using the differences in heat of hydrogenation, the stabilization energy for 1,3-pentadiene is approximately 27 kJ/mol, which accounts not only for the conjugation of the diene, but the additional substituent of the second double bond.



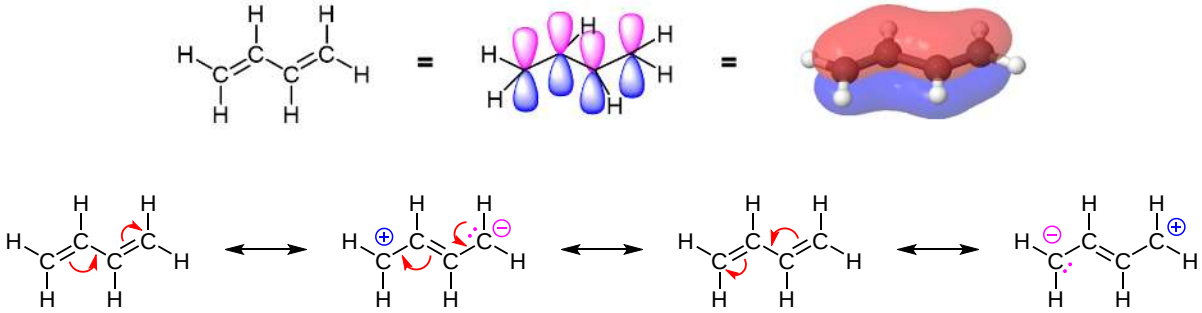
1,3-Pentadiene (ΔH_{hydrog} = -226 kJ/mol) — **Pentane** — **1,4-Pentadiene** (ΔH_{hydrog} = -252 kJ/mol)

Here is an energy diagram comparing different types of bonds with their heats of hydrogenation to show the relative stability of each molecule:

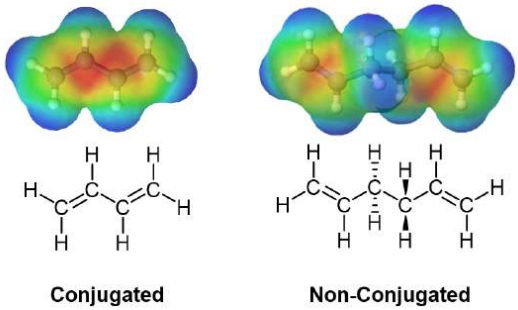


Resonance forms of Conjugated Dienes

What accounts for the stability of conjugated dienes? According to valence bond theory (Organic Chemistry I, Section 1.5 and Section 1.8), their stability is due to orbital hybridization. Each alkene carbon are sp^2 hybridized and therefore have one unhybridized *p* orbital. In 1,3 dienes, like 1,3-butadiene, the four *p* orbitals overlap to form a conjugated system which can be represented by the resonance forms shown below. This delocalization of charges stabilizes conjugated diene, making them more stable than non-conjugated dienes.



The delocalized electron density of a 1,3 diene can be seen in the electrostatic potential maps. In conjugated dienes, it is observed that the pi electron density overlap (shown in red) is closer together and delocalized in conjugated dienes, while in non-conjugated dienes the pi electron density is located completely on the double bonds.



Molecular Orbitals of 1,3 Dienes

According to MO theory, when a double bond is non-conjugated, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy π bonding orbital and one a high-energy **π-star (π*) anti-bonding molecular orbital**. These are sometimes denoted, in MO diagrams like the one below, with the Greek letter psi (Ψ) instead of π. In the bonding Ψ_1 orbital, the two (+) lobes of the $2p_z$ orbitals interact constructively with each other, as do the two (-) lobes. Therefore, there is increased

electron density between the nuclei in the molecular orbital – this is why it is a bonding orbital. In the higher-energy anti-bonding Ψ_2* orbital, the (+) lobes of one $2p_z$ orbital interacts destructively with the (-) lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy $\Psi_1$orbital when the molecule is in the ground state.

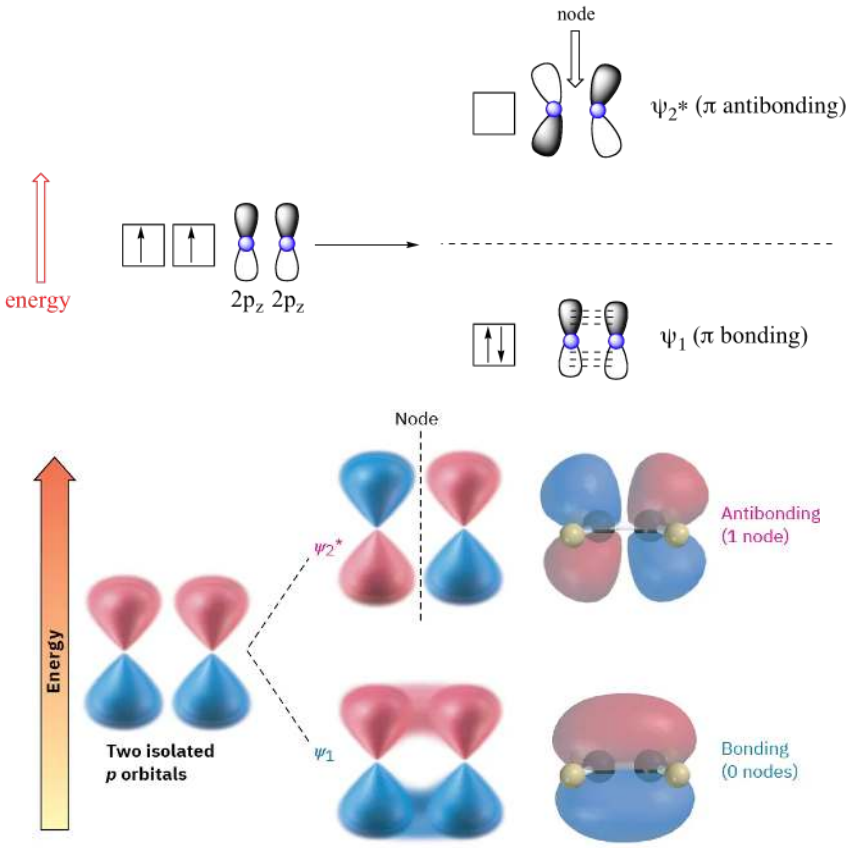


Figure 1.1.1: Two *p* orbitals combine to form two π molecular orbitals. Both electrons occupy the low-energy, bonding orbital, leading to a net lowering of energy and formation of a stable bond. The asterisk on ψ_2^* indicates an antibonding orbital.

Now let's combine four adjacent *p* atomic orbitals, as occurs in a conjugated diene. With a conjugated diene, such as 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two anti-bonding pi* orbitals. The combination of four pi molecular orbitals allow for the formation of a bonding molecular orbital that is lower in energy than those created by an unconjugated alkene. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.

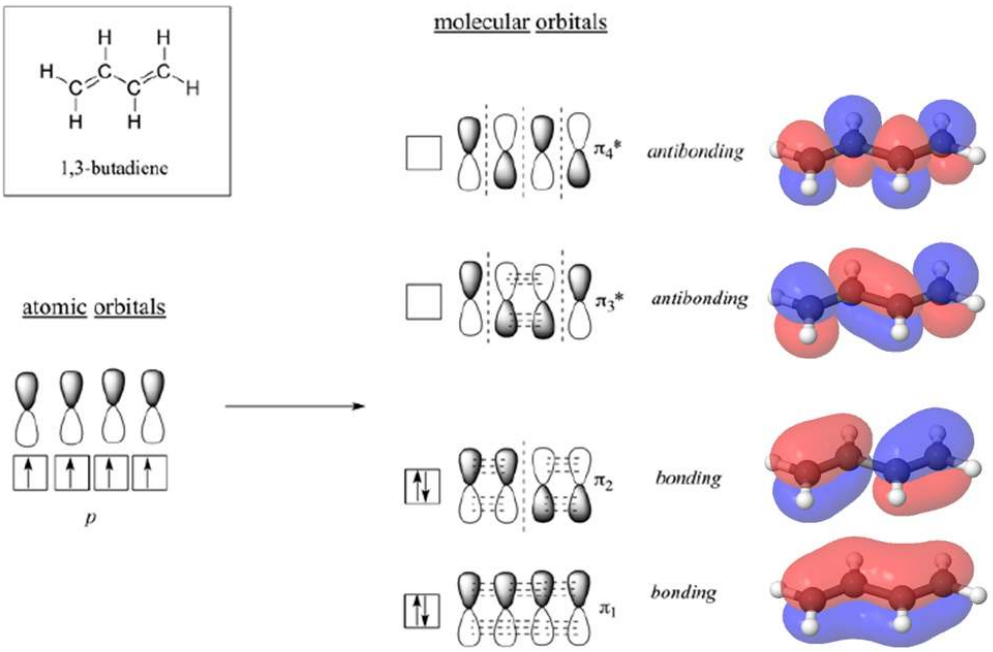


Figure 1.1.2: Four π molecular orbitals in 1,3-butadiene. Note that the number of nodes between nuclei increases as the energy level of the orbital increases (from 0 to 3 nodes).

The lowest-energy π molecular orbital (denoted ψ_1, Greek psi) has no nodes between the nuclei and is therefore bonding. The π MO of next-lowest energy, ψ2, has one node between nuclei and is also bonding. Above ψ_1 and ψ_2 in energy are the two antibonding π MOs, ψ_3^* and ψ_4^*. (The asterisks indicate antibonding orbitals.) Note that the number of nodes between nuclei increases as the energy level of the orbital increases. The ψ_3^* orbital has two nodes between nuclei, and ψ_4^*, the highest-energy MO, has three nodes between nuclei.

In describing 1,3-butadiene, we say that the π electrons are spread out, or *delocalized*, over the entire π framework, rather than localized between two specific nuclei. Delocalization allows the bonding electrons to be closer to more nuclei, thus leading to lower energy and greater stability.

? Exercise 1.1.1

Allene, $H_2C{=}C{=}CH_2$, has a heat of hydrogenation of –298 kJ/mol (–71.3 kcal/mol). Rank a conjugated diene, a nonconjugated diene, and an allene in order of stability.

Answer

Expected $\Delta H^\circ_{\text{hydrog}}$ for allene is −252 kJ/mol. Allene is less stable than a nonconjugated diene, which is less stable than a conjugated diene.

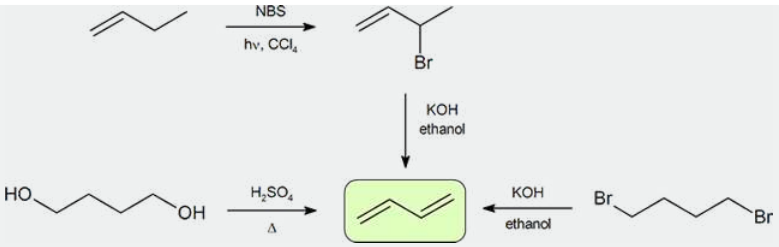
Key Terms

Make certain that you can define, and use in context, the key terms below.

- delocalized electrons
- node

Study Notes

The two most frequent ways to synthesize conjugated dienes are dehydration of alcohols and dehydrohalogenation of organohalides, which were introduced in the preparation of alkenes (Organic Chemistry I Section 8.3). The following scheme illustrates some of the routes to preparing a conjugated diene.



The formation of synthetic polymers from dienes such as 1,3-butadiene and isoprene is discussed in Section 14.6. Synthetic polymers are large molecules made up of smaller repeating units. You are probably somewhat familiar with a number of these polymers; for example, polyethylene, polypropylene, polystyrene and poly(vinyl chloride).

As the hydrogenation of 1,3-butadiene releases less than the predicted amount of energy, the energy content of 1,3-butadiene must be lower than we might have expected. In other words, 1,3-butadiene is more stable than its formula suggests.

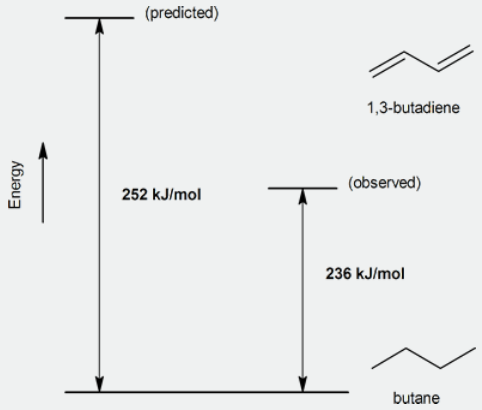


Figure 1.1.3:Energy diagram for the hydrogenation of 1,3-butadiene (not to scale).

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1.2: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations

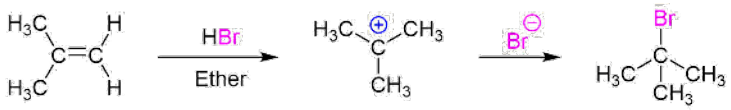
Objectives

After completing this section, you should be able to

1. write an equation for the addition of one or two-mole equivalents of a halogen or a hydrogen halide to a non-conjugated diene.
2. Write an equation for the addition of one or two-mole equivalents of a halogen or a hydrogen halide to a conjugated diene.
3. Write the mechanism for the addition of one mole equivalent of hydrogen halide to a conjugated diene, and hence account for the formation of 1,2- and 1,4-addition products.
4. Explain the stability of allylic carbocations in terms of resonance.
5. Draw the resonance contributors for a given allylic carbocation.
6. Predict the products formed from the reaction of a given conjugated diene with one-mole equivalent of halogen or hydrogen halide.
7. Predict which of the possible 1,2- and 1,4-addition products is likely to predominate when one-mole equivalent of a hydrogen halide is reacted with a given conjugated diene.
8. Use the concept of carbocation stability to explain the ratio of the products obtained when a given conjugated diene is reacted with one mole equivalent of hydrogen halide.

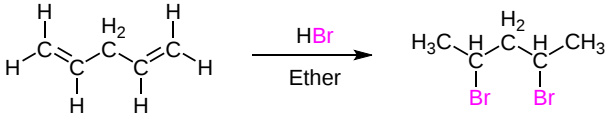
In Organic Chemistry I Section 7.7, we saw that electrophilic addition to a simple alkene would follow Markovnikov's rule. Markovnikov's rule states that for the electrophilic addition of HX, the carbocation intermediate forms on the double bond carbon with the greatest number of alkyl substitutents. Because the stability of carbocation intermediates depends on hyperconjugation, the stability increases as it number of alky groups increases (primary < secondary < tertiary), this regioselectivity is provided by preferably forming a more stable carbocation intermediate during the reaction.

During the electrophilic addition of HBr to 2-methylpropene, the more stable tertiary carbocation intermediate is preferably formed which yields the Markovnikov addition product 2-bromo-2-methylpropane. Formation of 1-bromo-2-methylpropane does not occur because it would require the formation of a less stable primary carbocation intermediate.



2-Methylpropene | **Tertiary Carbocation** | **2-Bromo-2-Methylpropane (Markovnikov addition product)**

When an electrophilic addition is performed on a non-conjugated diene, the double bonds react in much the same manner as individual alkenes. During the addition of two equivalents of HBr to 1,4-pentadiene, a non-conjugated diene, Markovnikov's rule is still followed producing 2,4-dibromopentane as the product.

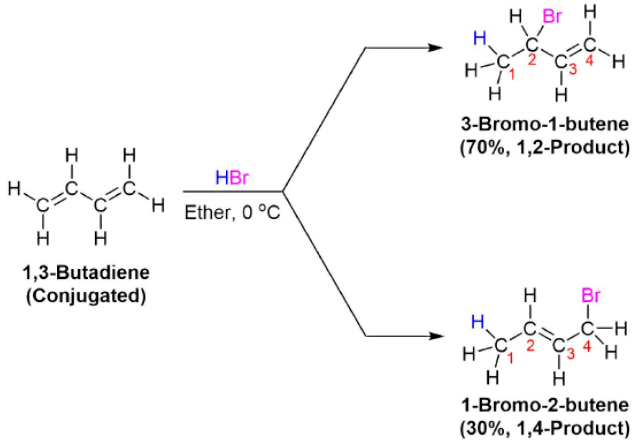


1,4-Pentadiene (Non-conjugated) | **2,4-Dibromopentane (Markovnikov addition product)**

Conjugated dienes also undergo electrophilic addition reactions readily, but mixtures of products are invariably obtained. The addition of HBr to 1,3-butadiene, for instance, yields a mixture of two products, constitutional isomers (not counting cis-trans isomers). 3-Bromo-1-butene is the typical Markovnikov product of 1,2-addition to a double bond, but 1-bromo-2-butene seems unusual. The double bond in this product has moved to a position between carbons 2 and 3, and HBr has added to carbons 1 and 4, a result described as 1,4-addition.

Note

The numbers (1, 2, and 4) refer to which of the four carbons making up the conjugated diene the H and Br are bonded to in the products and are not related nor used for the compound's IUPAC nomenclature.

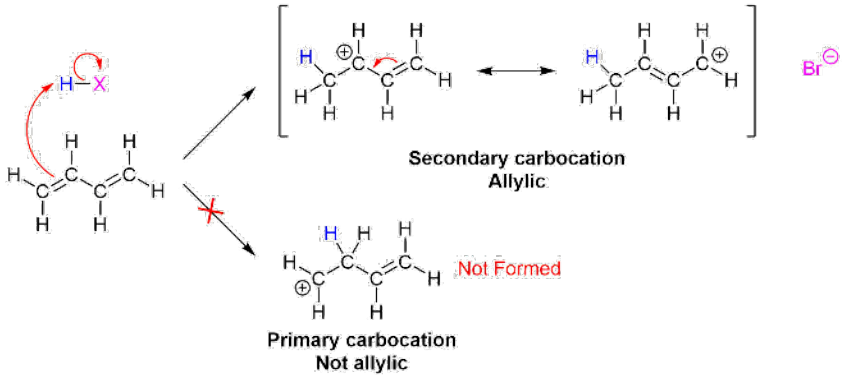


Although there are various methods for effecting the relative ratio of 1,2 and 1,4 addition products during the electrophilic addition to a conjugated diene, a mixture of these products is almost always produced. When one equivalent HBr undergoes electrophilic addition to 1,3-butadiene, 1,2 addition provides the expected Markovnikov product 3-bromo-1-butene in a 70% yield. This process is called a 1,2 addition because the hydrogen from HBr (labeled blue) bonds to the first carbon of the diene and the bromine from HBr bonds to the second carbon of the diene. The compound 1-bromo-2-butene is also produced in a 30% yield during the reaction as product of 1,4 addition. Here the hydrogen of HBr bonds to the first carbon of the diene and the Br bonds to the fourth carbon of the diene.

The Mechanism for Electrophilic Addition of HBr to a Conjugated Diene

Regardless if the 1,2 or 1,4 addition product is formed, the first step of the mechanism is the protonation of one of the double bonds. In the same manner as the electrophilic addition of HX to an alkene, the protonation occurs regioselectively to give the more stable carbocation. In the case of a conjugated diene, the more stable cation is not only secondary, but also *allylic*, and therefore enjoys the stabilization created from the positive charge being distributed over two carbons by resonance. The resonance hybrid of the allylic carbocation intermediate can be depicted by two resonance forms (shown below), both of which have a full positive charge.

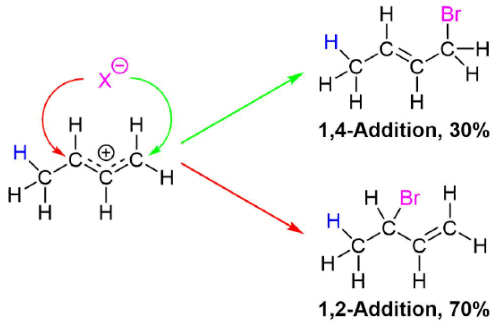
Step 1



Step 2

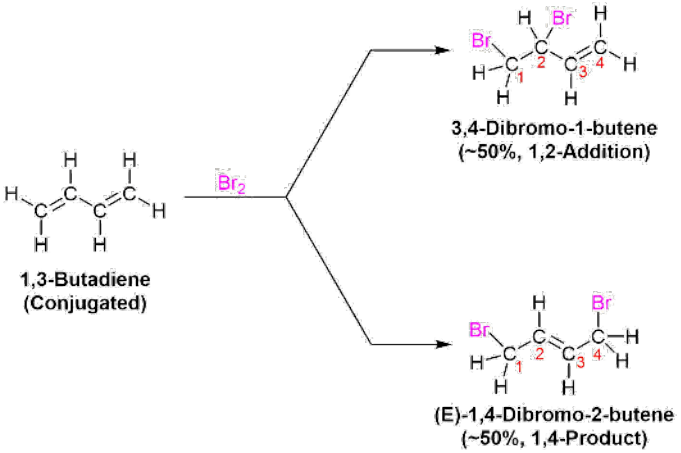
This allylic carbocation, more properly denoted as the resonance hybrid shown below, has two carbons (C-2 and C-4 , considering C-1 the one that H was added) which have a significant positive charge. The halide ion can attack either carbon. Attacking the

central carbon, adjacent to the site of protonation, leads to the the 1,2-addition product. Attacking the terminal carbon, distant from the site of protonation, leads to the 1,4 addition product.



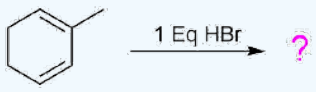
Other Electrophilic Additions

Formation of both 1,2- and 1,4-addition products occurs not only with hydrogen halides, but also with other electrophiles such as the halogens (X_2). The electrophilic addition of bromine to 1,3-butadiene is an example. As shown below, a roughly 50:50 mixture of 3,4-dibromo-1-butene (the expected 1,2 addition product) and 1,4-dibromo-2-butene (the 1,4 addition product) is obtained. The double bond of the 1,4 addition product is primarily formed as the (E) isomer.



Worked Example 1.2.1

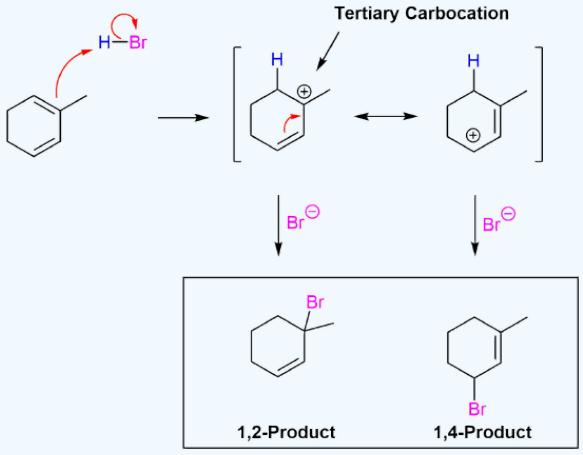
Give the expected products from the following reaction. Show both 1,2 and 1,4 addition products.



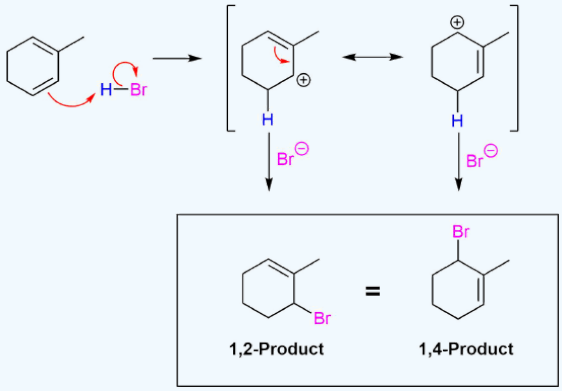
Solution

For this example the two double bonds in the diene are not equivalent and must be considered separately. Each double bond of the reactant has the possibility of forming a 1,2 and a 1,4 addition product so the reaction has the possibility of forming four product. Protonate each double bond separately and draw out the resonance forms of the allylic carbocation intermediate created. Then react each resonance form with Br- to create the two possible products. Repeat this process with the second double bond to create the four possible product. Lastly, look for symmetry in the products to see if any are same molecule. Also, consider the stability of each carbocation created during this process. The most stable carbocation will generally product the favored product of the reaction.

Addition to the first double bond creates a resonance form with a tertiary carbocation intermediate. Due to the stability of the tertiary carbocation this product will most likely go one to be the preferred product of this reaction.



The Addition to the second double bond gives a symmetrical carbocation, whose two resonance forms are equivalent. Thus, the 1,2 adduct and the 1,4 adduct have the same structure: 6-Bromo-1-methylcyclohexene.



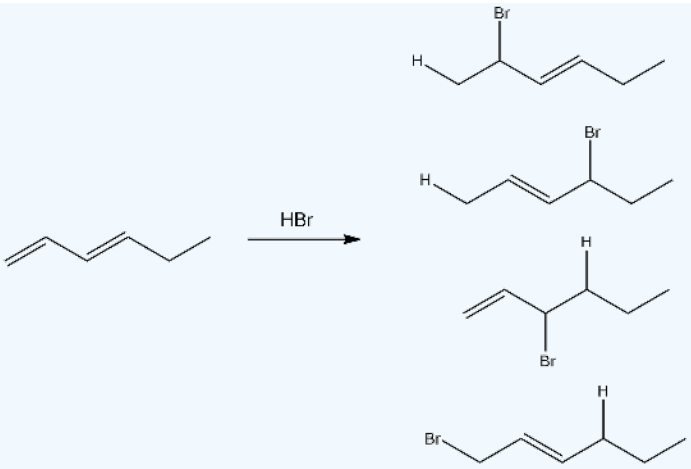
The reaction would be expected to form three products. Of the two possible modes of protonation, the first yields a more stable tertiary allylic cation rather than a less stable secondary allylic cation, given the major product under kinetic conditions.

Exercise 1.2.1

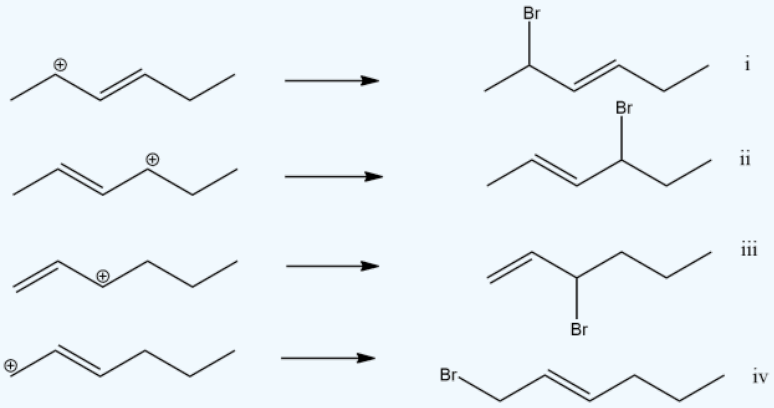
1. Give the structure of 1,2 and the 1,4 products of the addition of one equivalent of HBr to 1,3-hexa-diene.
2. Look at the possible carbocation intermediates produced during addition of HBr to 1,3-hexa-diene, and predict which 1,2 adduct predominates. Which 1,4 adduct predominates?

Answer

1)



2) Products i and iii are 1,2 adducts; both show a secondary cation intermediate. Both are likely to form as they have the same energy. Products ii and iv are 1,4 adducts; Product ii shows a secondary cation intermediate, which is more stable than primary.



Therefore, Products i, ii, and iii would be major products, and the iv product would be the minor product.

Exercise 1.2.2

1. Give the structures of both 1,2 and 1,4 adducts resulting from reaction of 1 equivalent of HCl with 1,3-pentadiene.
2. Look at the possible carbocation intermediates produced during the addition of HCl to 1,3-pentadiene (the problem above) and predict which 1,2 adduct predominates. Which 1,4 adduct predominates?

Answer

1- It's your time to draw the structures. 1-Chloro-2-pentene, 3-chloro-1-pentene, 4-chloro-2-pentene

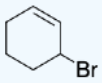
2- 4-Chloro-2-pentene predominates in both.

Exercise 1.2.3

1. Write out the products of 1,2 addition and 1,4- addition of HBr to 1,3-cyclohexadiene.
2. What is unusual about the products of 1,2- and 1,4- addition of HX to an unsubstituted cyclic 1,3-diene?

Answer

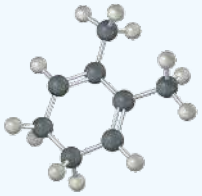
1-The same product will result from 1,2 and 1,4 addition.



2- The addition of the HX to unsubstituted cycloalkyl-1,3-dienes in either 1,2- or 1,4- manner gives the same product because of symmetry.

Exercise 1.2.4

Give the structures of both 1,2 and 1,4 adducts resulting from the reaction of 1 equivalent of HBr with the following compound:



Answer

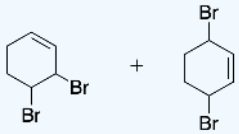
1,2 Addition: 6-bromo-1,6-dimethylcyclohexene. 1,4 Addition: 3-bromo-1,2-dimethylcyclohexene.

Exercise 1.2.5

Write out the products of 1,2 addition and 1,4- addition of Br_2 to 1,3-cyclohexadiene.

Answer

Both 1,2 and 1,4 products will form.



Key Terms

Make certain that you can define, and use in context, the key terms below.

- 1,2-addition
- 1,4-addition

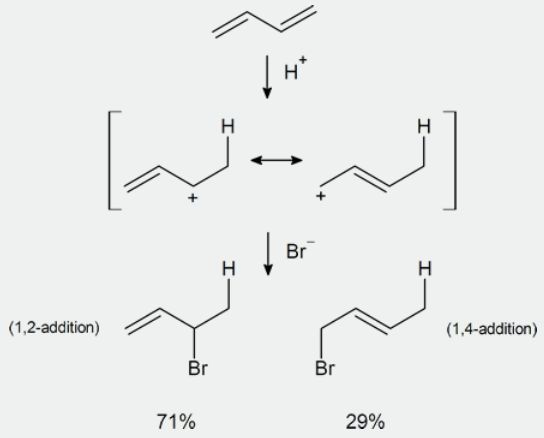
Study Notes

Notice that the numbers used in the expressions 1,2-addition and 1,4-addition do *not* refer to the positions of the carbon atoms in the diene molecule. Here, 1,2 indicates two neighbouring carbon atoms, while 1,4 indicates two carbon atoms which are separated in the carbon chain by two additional carbon atoms. Thus in 1,2- and 1,4-additions to 2,4-hexadiene, the additions actually occur at carbons 2 and 3, and 2 and 5, respectively.

The term “monoadduct” should be interpreted as meaning the product or products formed when one mole of reagent adds to one mole of substrate. In the objectives above, this process is referred to as the addition of one mole equivalent (or one mol equiv).

In Section 7.9 we saw that electrophilic addition to a simple alkene would follow Markovnikov’s rule, where the stability of the carbocation intermediate would increase: primary < secondary < tertiary. With conjugated dienes the allylic carbocation

intermediately generated has different resonance forms. The following scheme represents the mechanism for the addition of HBr to 1,3-butadiene (at 0°C). Note the resonance contributors for the allylic carbocation intermediate and that the product resulting from the secondary cation is generated in higher yield than from the primary cation as you might expect from our discussions until now. However, in the next section you will see that the resulting product ratio can be drastically affected by a number of reaction conditions, including temperature.



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1.3: Kinetic vs. Thermodynamic Control of Reactions

Objectives

After completing this section, you should be able to

1. Explain the difference between thermodynamic and kinetic control of a chemical reaction, for example, the reaction of a conjugated diene with one equivalent of hydrogen halide.
2. Draw a reaction energy diagram for a reaction that can result in both a thermodynamically controlled product and a kinetically controlled product.
3. Explain how reaction conditions can determine the product ratio in a reaction in which there is competition between thermodynamic and kinetic control.

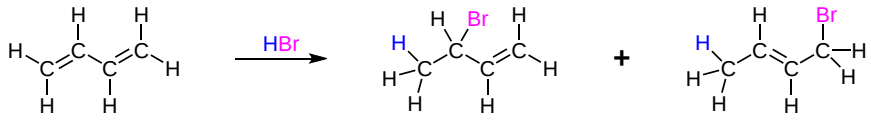
Key Terms

Make certain that you can define, and use in context, the key terms below.

- kinetic control
- thermodynamic control

Like non-conjugated dienes, conjugated dienes are subject to attack by electrophiles. In fact, conjugated dienes experience relatively greater kinetic reactivity when reacted with electrophiles than non-conjugated dienes do. The reaction mechanism is similar to other electrophilic addition reactions to alkenes (Section 7.9). During the electrophilic addition of HBr to a 1,3-butadiene, However, there are two possible outcomes once the carbocation intermediate is formed. The allyl carbocation is stabilized by resonance structures that vary in the position of the carbocation. This allows the bromide ion to add to either of these carbons resulting in the formation 1,2 and 1,4 addition products. When this reaction is run at a temperature of 0 ^{o}C or lower, the 1,2 addition product dominates. However, if the same reaction is run at 40 ^{o}C the 1,4 addition product dominates.

The reaction of one equivalent of hydrogen bromide with 1,3-butadiene yields different product ratios under different reaction conditions and is a classic example of the concept of **thermodynamic** versus **kinetic** control of a reaction.



1,3-Butadiene | **1,2-Addition Product** | **1,4-Addition Product**

At -80 ^{o}C:	80%	20%	**Kinetic Control**
At 0 ^{o}C:	70%	30%	**Kinetic Control**
At 40 ^{o}C:	15%	85%	**Thermodynamic Control**
At 60 ^{o}C:	10%	90%	**Thermodynamic Control**

At lower temperatures the formation of the 1,2 and 1,4 addition products are irreversible and thus do not reach equilibrium. When a reaction is irreversible the major product is determined by the relative reaction rates and not by thermodynamic stability. Of the two products, the formation of the 1,2 addition product has a higher rate of reaction and forms faster making it the major product. The reaction product which forms with a higher rate of reaction is called the **Kinetic Product** and when the kinetic product dominates, the reaction is said to be under **Kinetic Control**.

At higher temperatures the reaction to form both products becomes reversible and a reaction equilibrium is reached. When a reaction is reversible the major product is determined by thermodynamic stability. The 1,4 addition product is more stable and becomes the major product under these reaction conditions. The more stable product is called the **Thermodynamic Product** and when the thermodynamic product dominates, the reaction is said to be under **Thermodynamic Control**.

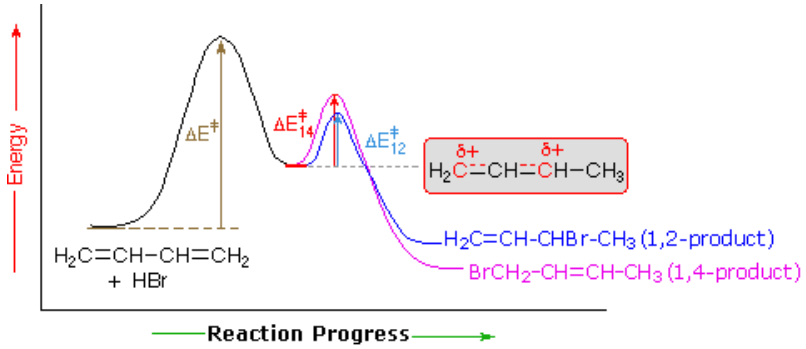
The 1,4 addition product is more stable because it has an internal, disubstituted double bond, and we know that as a general rule that the thermodynamic stability of an alkene increases with increasing substitution. So, when compared to the terminal,

monosubstituted alkene of the 1,2 addition product, the 1,4 addition product is expected to be more stable.

> *A simple definition is that the kinetic product is the product that is formed faster, and the thermodynamic product is the product that is more stable. This is precisely what is happening here. The kinetic product is 3-bromobut-1-ene, and the thermodynamic product is 1-bromobut-2-ene (specifically, the trans isomer).*

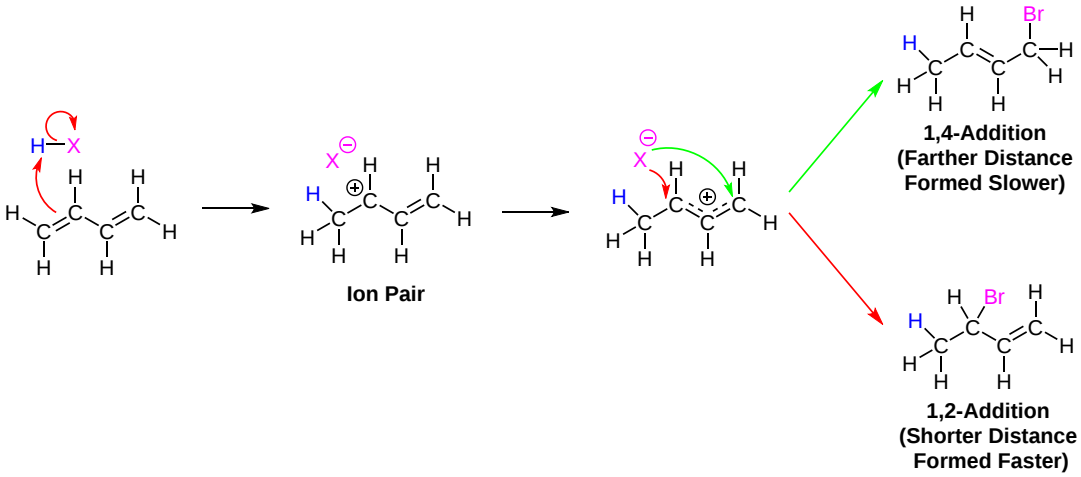
An explanation for the temperature influence is shown in the following energy diagram for the addition of HBr to 1,3-butadiene. The initial step in which a proton bonds to carbon #1 is the **rate determining step**, as indicated by the large activation energy (light gray arrow). The second faster step is the **product determining step**, and there are two reaction paths (colored blue for 1,2-addition and magenta for 1,4-addition).

At elevated temperatures, the products are more likely to have enough energy to overcome the reverse activation barrier for the second step allowing regeneration of the carbocation intermediate. Under these conditions, this step of the mechanism will be reversible and an equilibrium will be established. Since the system is no longer limited by temperature, the system will minimize its Gibbs free energy, which is the thermodynamic criterion for chemical equilibrium. This places the reaction under *thermodynamic control* and the most thermodynamically stable molecule, the 1,4 addition product, will be predominantly formed.



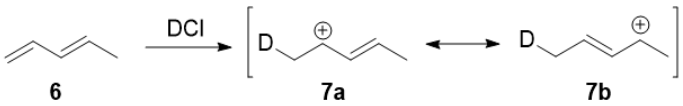
If the reaction temperature is kept sufficiently *low*, the products will not have enough energy to overcome the reverse activation barrier to regenerate the carbocation intermediate, making this step of the mechanism effectively irreversible. This reaction is under kinetic control meaning the product which forms faster, the kinetic product, will predominate.

Of the two reaction pathways, the 1,2-addition has a smaller activation energy and would be expected to have a higher reaction rate than the 1,4-addition. The high reaction rate for 1,2-addition can be attributed to the formation of an ion pair during the reaction mechanism. This means that, after a double bond is protonated, the halide counterion remains in close proximity to the carbocation generated. Immediately following the dissociation of HX, the chloride ion is going to be much closer to C−2 than it is to C−4, and therefore attack at C−2 is much faster. This ion pair mechanism is a pre-exponential constant effects that is attributed to the proximity and frequency of collision rather than a activation barrier effect.

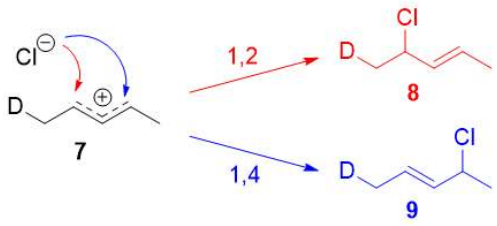


Experimental Evidence for the Ion-Pair Mechanism

In 1979, Nordlander *et al.* carried out a similar investigation on the addition of DCl (deuterated hydrochloric acid) to a different substrate, 1,3-pentadiene. This experiment was ingenious, because it was designed to proceed via an almost symmetrical intermediate:



Resonance forms **7a** and **7b** are both allylic and secondary. There is a very minor difference in their stabilities arising from the different hyperconjugative ability of C-D *vs* C-H bonds, but in any case, it is not very large. Therefore, if we adopt the explanation in the previous section, one would expect there not to be any major *kinetic* pathway, and both 1,2- and 1,4-addition products (**8** and **9**) would theoretically be formed roughly equally.



Instead, it was found that the 1,2-addition product was favored over the 1,4-addition product. For example, at -78°C in the absence of solvent, there was a roughly (75:25) ratio of 1,2- to 1,4-addition products. Clearly, there is a factor that favors 1,2-addition that does not depend on the electrophilicity of the carbon being attacked! The authors attributed this effect to an *ion pair* mechanism. This means that, after the double bond is protonated (deuterated in this case), the chloride counterion remains in close proximity to the carbocation generated. Immediately following dissociation of DCl, the chloride ion is going to be much closer to *C-2* than it is to *C-4*, and therefore attack at *C-2* is much faster. In fact, normal electrophilic addition of HX to conjugated alkenes in polar solvents can also proceed via similar ion pair mechanisms. This is reflected by the greater proportion of *syn* addition products to such substrates.

? Exercise 1.3.1

The reaction of one equivalent of hydrogen bromide with 1,3-butadiene yields different products. Why is the 1,4-addition product the thermodynamically more stable product?

Answer

The 1,4- product is more thermodynamically stable because there are two alkyl groups on each side of the double bond, and more substituted alkenes are more stable.

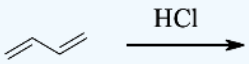
? Exercise 1.3.2

The Addition of 1 equivalent of bromine to 2,4-hexadiene at 0 degrees C gives 4,5-dibromo-2-hexene plus an isomer. What is the structure of that isomer?

Answer

Your time to draw the structure of 2,5-Dibromo-3-hexene

Exercise 1.3.3

For the following reaction: 

- a- Identify the kinetically controlled product.
- b- which product is the result of 1,4-addition?

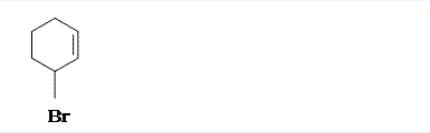
Answer

a- 3-Chloro-1-butene b- 1-Chloro-2-butene

Exercise 1.3.4

What would be the major product of the addition of HBr to 2,3-dimethyl-1,3-cyclohexadiene under thermodynamic conditions?

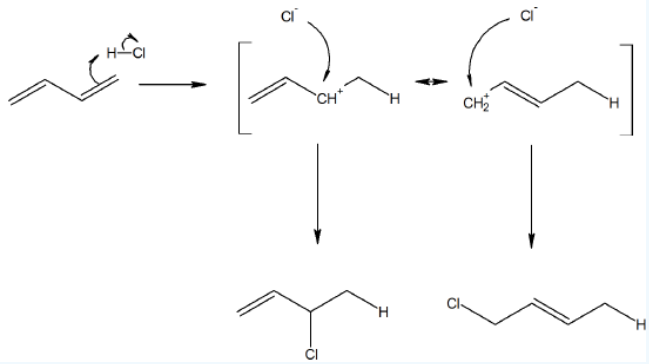
Answer



Exercise 1.3.5

Consider the reaction with 1,3-buta-diene reacting with HCl. Propose a mechanism for the reaction. Also, Predict why the 1,4 adduct is the major product in this reaction compared to the 1,2.

Answer



Even though the cation would prefer to be in a secondary position in the transition state, the final product is less stable with a terminal alkene. Therefore the major product will be the 1,4 adduct.

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1.4: The Diels-Alder Cycloaddition Reaction

Objectives

After completing this section, you should be able to

1. write an equation to represent a typical Diels-Alder reaction.
2. draw the structure of the product formed when a given conjugated diene reacts with a given dienophile in a Diels-Alder reaction.
3. identify the diene and dienophile that must be used to prepare a given compound by a Diels-Alder reaction.
4. explain the general mechanism of the Diels-Alder reaction, without necessarily being able to describe it in detail.

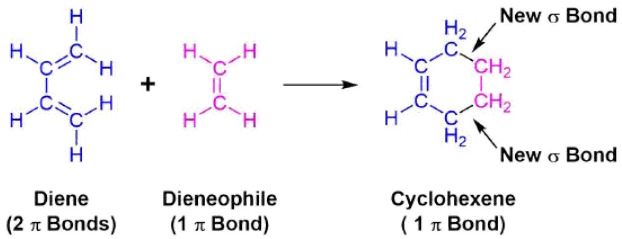
Key Terms

Make certain that you can define, and use in context, the key terms below.

- Diels-Alder cycloaddition
- pericyclic reaction
- Diene
- Dienophile

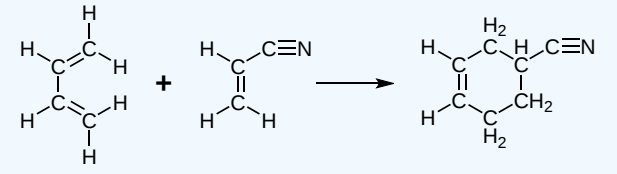
The unique character of conjugated dienes manifests itself dramatically in the **Diels-Alder Cycloaddition Reaction**. The Diels-Alder reaction is an important and widely used synthetic method for making six-membered rings. In the Diels-Alder reaction, a conjugated diene, simply referred to as the **diene**, reacts with a double or triple bond co-reactant called the **dienophile**, because it combines with (has an affinity for) the diene. During the reaction, two pi-bonds are converted to two sigma-bonds. The Diels-Alder cycloaddition is classified as a pericyclic process. Pericyclic reactions involve the redistribution of bonding electrons in a single step mechanism and will be discussed in greater detail in **Chapter 15**. In particular, the Diels-alder reaction is called a [4+2] process because the diene has four pi-electrons that shift position in the reaction and the dienophile has two.

General Reaction



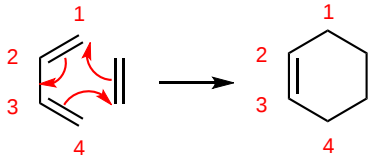
An example of the Diels-Alder reaction is the cycloaddition of 1,3-butadiene to cyanoethene (acrylonitrile) to form 4-cyanocyclohexene.

Example 1.4.1

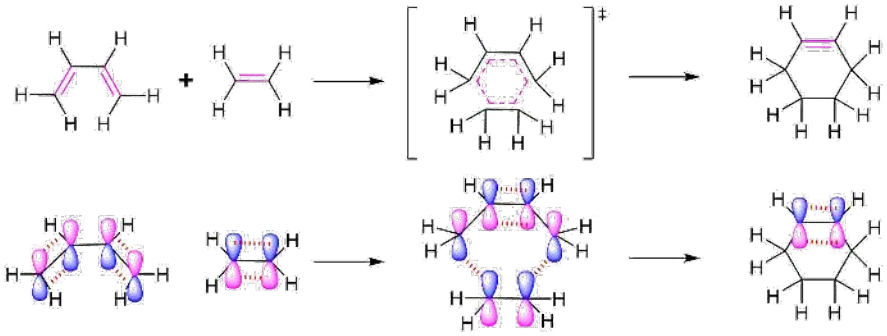


Mechanism

All of the electron rearrangements of the Diels-Alder reaction take place once in a single mechanistic step. During this step carbons 1 and 4 of the diene and both alkene carbons of the dienophile, rehybridize from sp^2 to sp^3 and electrons rearrange to create two new sigma bonds in the cyclic product. Carbons 2 and 3 of the diene remain sp^2 hybridized and form a new pi bond in the product.

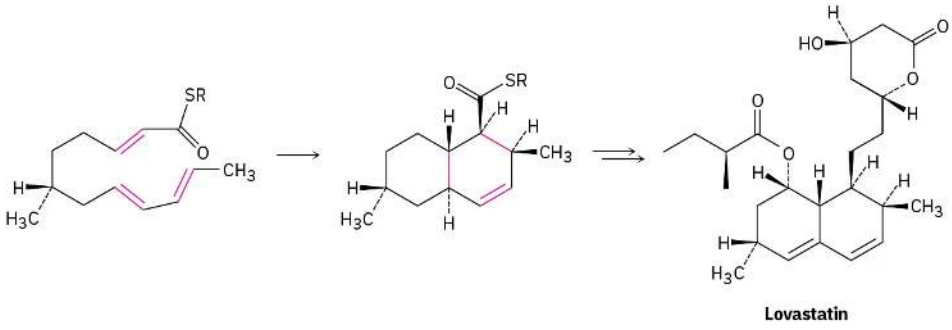


The mechanism occurs through a cyclic transition state in which there is head-on overlap of two p orbitals on carbons 1 and 4 of the diene with the two p orbitals from the alkene of the dienophile to form two new sigma bonds in the cyclohexene product. The remaining two p orbitals from the diene overlap to form the new pi bond.



Biological Diels–Alder reactions

Biological Diels–Alder reactions are also known but are uncommon. One example occurs in the biosynthesis of the cholesterol-lowering drug lovastatin (trade name Mevacor) isolated from the bacterium *Aspergillus terreus*. The key step is the *intramolecular* Diels–Alder reaction of a triene, in which the diene and dienophile components are within the same molecule.



Lovastatin

Lovastatin is in a class of medications called **HMG CoA reductase inhibitors (statins)**. It works by slowing the production of cholesterol in the body to decrease the amount of cholesterol that may build up on the walls of the arteries and block blood flow to the heart, brain, and other parts of the body.

Study Notes

The Diels-Alder reaction is an example of an organic chemical reaction that does not proceed by a polar or a free radical pathway but rather a pericyclic reaction.

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1.5: Characteristics of the Diels-Alder Reaction

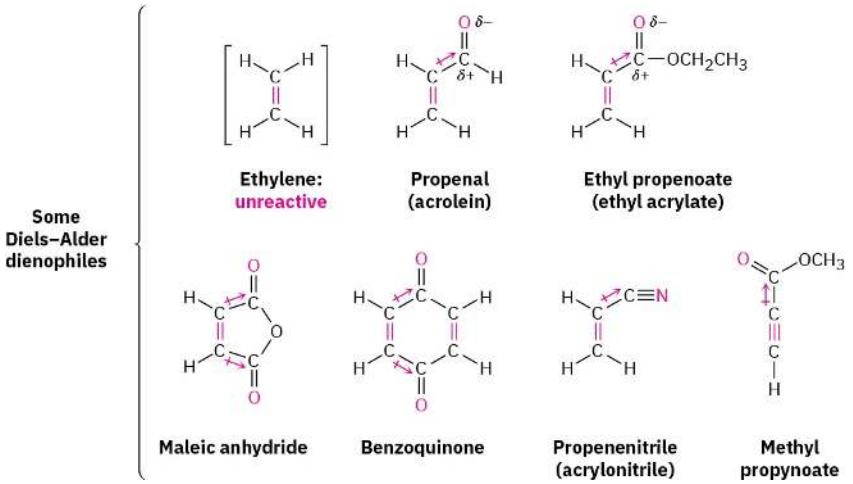
Objectives

After completing this section, you should be able to

1. determine whether or not a given compound would behave as a reactive dienophile in a Diels-Alder reaction.
2. predict the stereochemistry of the product obtained from the reaction of a given diene with a given dienophile.
3. recognize that in order to undergo a Diels-Alder reaction, a diene must be able to assume ans-cis geometry, and determine whether or not a given diene can assume this geometry.

The Dienophile

In general, Diels-Alder reactions proceed fastest with electron-withdrawing groups on the dienophile (diene lover). Ethylene reacts slowly while **propenal, ethyl propenoate, and other molecules shown below** are highly reactive in a Diels-Alder reaction.



In much the same manner as electron-withdrawing substituents on a benzene ring, these are typically a double or triple bond in conjugation with the double bond in the dienophile. A resonance form can be drawn which places a positive charge in the dienophile double bond. This results in the double bond being less electron rich (greater electron density shown in Red/Orange) than ethylene. Electrostatic potential maps in Figure 1.5.1 show that the electron-withdrawing groups pull electron density away from the double bond.

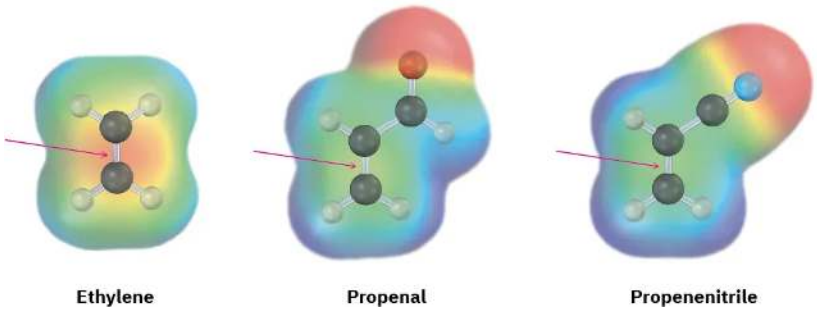
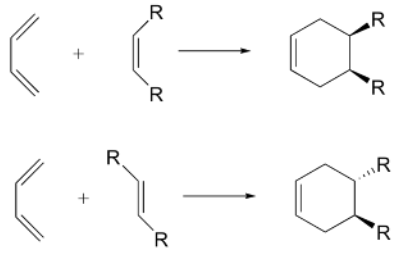


Figure 1.5.1: Electrostatic potential maps of ethylene, propenal, and propenenitrile show that electron-withdrawing groups make the double-bond carbons less electron-rich.

Stereochemistry of Diels-Alder (dienophile)

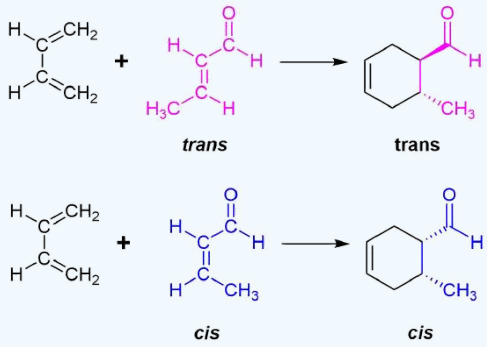
The Diels-Alder reaction is enormously useful for synthetic organic chemists, not only because ring-forming reactions are useful in general but also because in many cases multiple new stereocenters are formed, and the reaction is inherently stereospecific. During a Diels-Alder reaction the stereochemistry of the dienophile is retained in the product. A *cis* dienophile will generate a cyclohexene

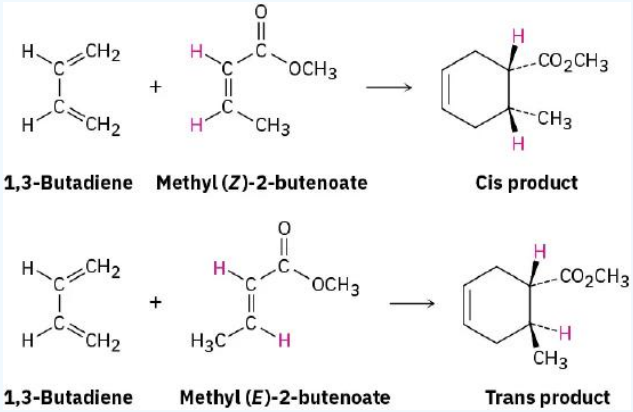
ring with *cis (syn)* substitution on the two carbons from the dienophile. Likewise a *trans* dienophile will generate a cyclohexene ring with *trans (anti)* substitution on these two carbon.



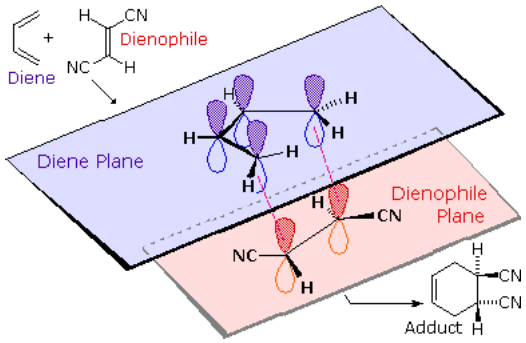
Example 1.5.1

During a Diels-Alder reaction the stereochemistry of the dienophile is retained in the product. A *cis* dienophile will generate a cyclohexene ring with *cis (syn)* substitution on the two carbons from the dienophile. Likewise a *trans* dienophile will generate a cyclohexene ring with *trans (anti)* substitution on these two carbon.



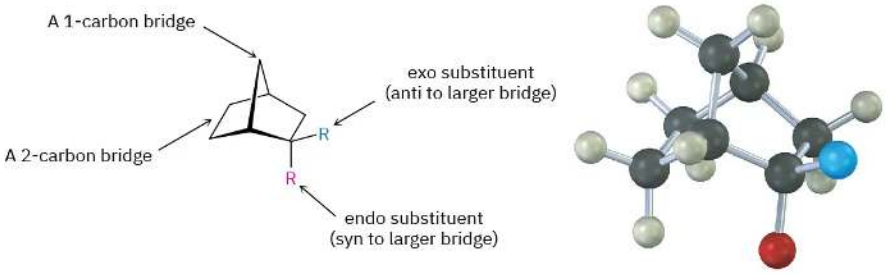


The retention of stereochemistry is due to the planar nature of both reactants and that the forming process is **suprafacial** (i.e. to or from the same face of each plane). This stereospecificity also confirms the concerted nature of the Diels-Alder mechanism. The drawing below illustrates this fact for the reaction of 1,3-butadiene with (E)-dicyanoethene. The trans relationship of the cyano groups in the dienophile is preserved in the six-membered ring of the adduct.

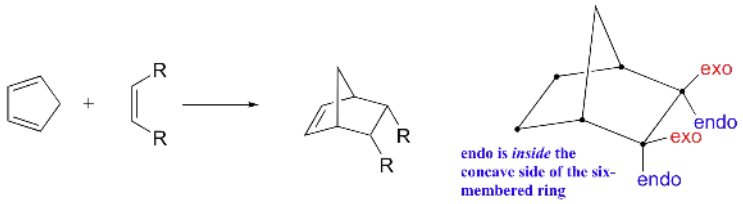


Formation of Bicyclic Structures

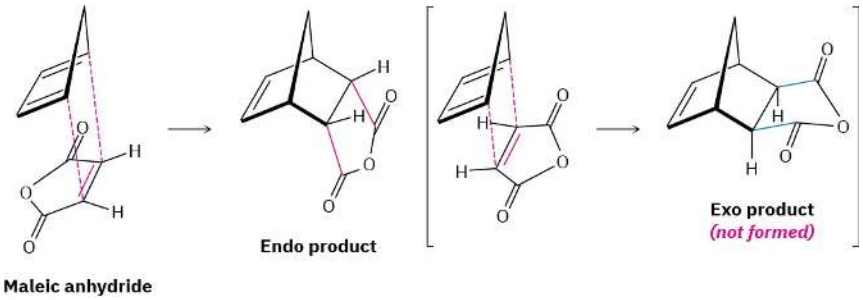
Another facet of the stereochemical retention of the dienophile is that only the endo product, rather than the alternative exo product, is formed. The words *endo* and *exo* are used to indicate relative stereochemistry when referring to bicyclic structures like substituted norbornanes. The endo position on a bicyclic structure refers to the position that is *inside* the concave shape of the larger (six-membered) ring. As you might predict, the **exo position** refers to the *outside* position.



Diels-Alder reactions with cyclic dienes favor the formation of bicyclic structures in which substituents are in the **endo position**. Preference of the endo position is also a facet of the suprafacial nature of the Diels-Alder reaction. The orbital overlap required for the reaction is greater when the dienophile lies directly underneath the diene.

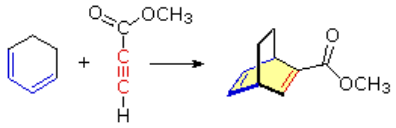


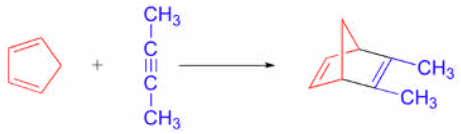
In the reaction of 1,3-cyclopentadiene with maleic anhydride, for instance, the following result is obtained:



Other Dienophiles

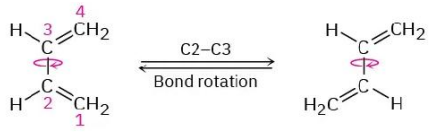
Alkynes can also serve as dienophiles in Diels-Alder reactions:





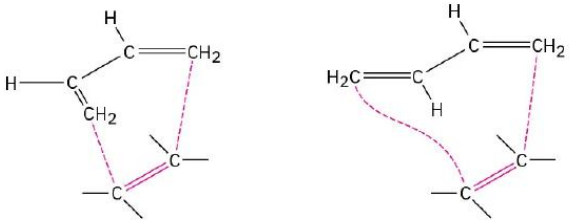
The Diene

In general, Diels-Alder reactions proceed fastest with electron-donating groups on the diene (eg. alkyl groups). The Diels-Alder reaction is a single step process, so the diene component must adopt an s-cis conformation in order for the end carbon atoms (#1 & #4) to bond simultaneously to the dienophile. For many acyclic dienes the s-trans conformer is more stable than the s-cis conformer (due to steric crowding of the end groups), but the two are generally in rapid equilibrium, permitting the use of all but the most hindered dienes as reactants in Diels-Alder reactions.



s-Cis conformation **s-Trans conformation**

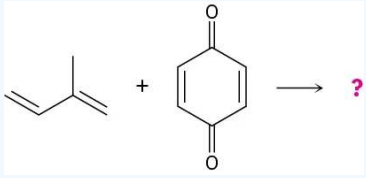
In the alternative *s*-trans conformation, the ends of the diene partner are too far apart to overlap with the dienophile *p* orbitals.



Successful reaction **No reaction (ends too far apart)**

Worked Example 1.5.1: Predicting the Product of a Diels–Alder Reaction

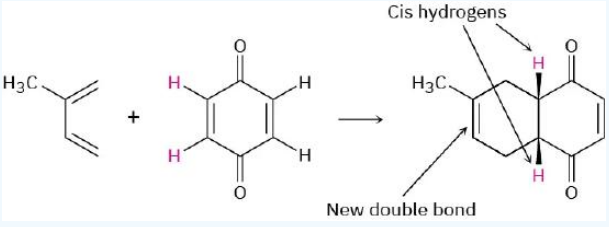
Predict the product of the following Diels–Alder reaction:



Strategy

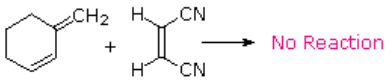
Draw the diene so that the ends of its two double bonds are near the dienophile double bond. Then form two single bonds between the partners, convert the three double bonds into single bonds, and convert the former single bond of the diene into a double bond. Because the dienophile double bond is cis to begin with, the two attached hydrogens must remain cis in the product.

Solution



Unreactive Dienes

The dienes that can't adopt an *s*-cis conformation, don't undergo Diels–Alder reactions. Examples of fixed dienes in an *s*-trans arrangement and larger the substituents, more stable the s-trans geometry are shown in Figure 1.5.4. Those dienes can't achieve an *s*-cis conformation and thus can't undergo Diels–Alder reactions.



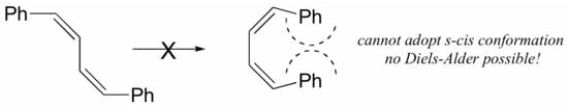


Figure 1.5.2: Examples of unreactive dienes: (a) Diene in an *s*-trans arrangement by a ring and (b) with large substituents

Examples are shown in Figure 1.5.3. In the bicyclic diene, the double bonds are rigidly fixed in an *s*-trans arrangement by geometric constraints of the rings. In (2*Z*,4*Z*)-2,4-hexadiene, steric strain between the two methyl groups prevents the molecule from adopting *s*-cis geometry.

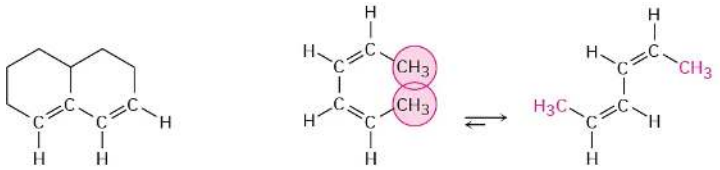
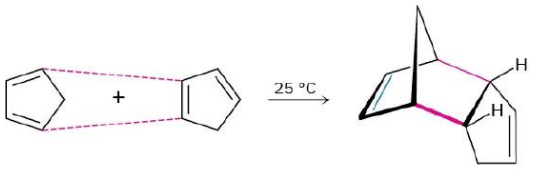


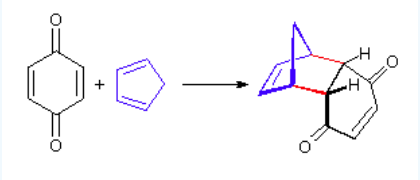
Figure 1.5.3: Fixed dienes in an *s*-trans arrangement and Larger the substituents, more stable the s-trans geometry. The dienes that can't achieve an *s*-cis conformation and thus can't undergo Diels–Alder reactions.

Highly reactive dienes

In contrast to these unreactive dienes that can't achieve an *s*-cis conformation, other dienes are fixed only in the correct *s*-cis geometry and are therefore highly reactive in Diels–Alder cycloaddition. 1,3-Cyclopentadiene, for example, is so reactive that it reacts with itself. At room temperature, 1,3-cyclopentadiene *dimerizes*. One molecule acts as diene and a second molecule acts as dienophile in a self-Diels–Alder reaction.

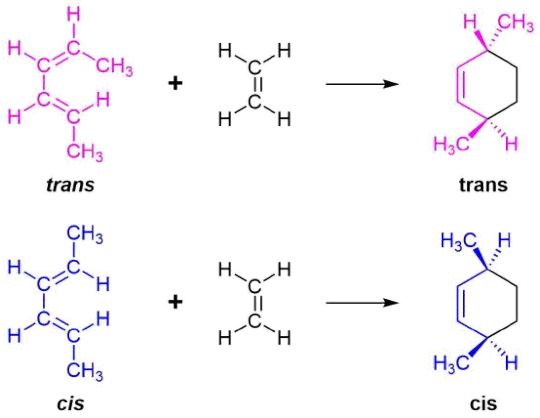


Examples 1.5.5

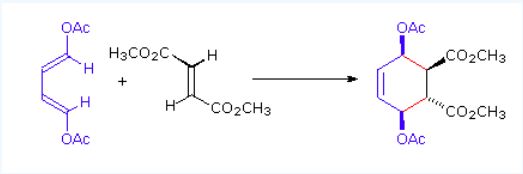


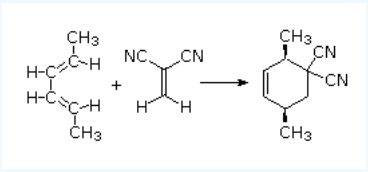
Stereochemistry of Diels-Alder (diene)

The 1 and 4 Carbons in the diene have the possibility of forming two new stereocenters in the cyclohexene product. Similarly to the effects of dienophile stereochemistry, the positioning of substituents on the 1 and 4 carbons in the diene determine the stereochemistry in the product. The diene substituents can be thought of as being either cis (both facing in or both facing out) or trans and the stereochemistry is retained to form a cis or trans cyclohexene product.



Examples 1.5.6

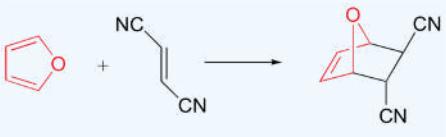




The Essential Characteristics of the Diels-Alder Cycloaddition Reaction:

i. The reaction always creates a new six-membered ring.
ii. The diene component must be able to assume an s-cis conformation.
iii. Electron withdrawing groups on the dienophile facilitate reaction.
iv. Electron donating groups on the diene facilitate reaction.
v. Steric hindrance at the bonding sites may inhibit or prevent reaction.
vi. The reaction is stereospecific with respect to substituent configuration in both the dienophile and the diene.

Published Examples 1.5.7

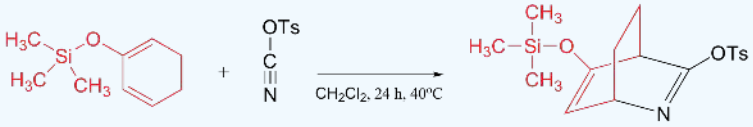


J. Med. Chem. **2008,** *51*, 424

https://chem.libretexts.org/@go/page/500351



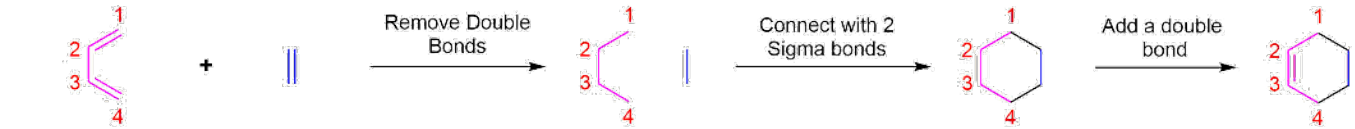
Org. Lett. **2001,** *3*, 1559



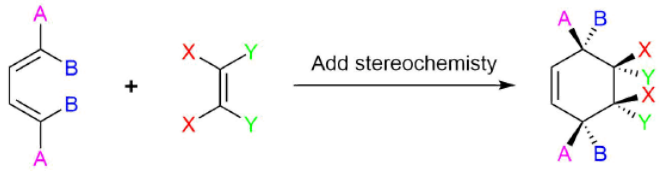
J. Org. Chem. **2003,** *68*, 8256

Predicting the Product of a Diels-Alder Reaction

Start by rotating the diene until it is in the s-cis conformation then point it towards the double bond of the dienophile. Remove the double bonds present in the diene and dieneophile. Connect carbons 1 and 4 of the the diene to a carbon in the dienophile double bond using a sigma bond to create a six-membered ring. Create a double bond between carbons 2 and 3 of diene.

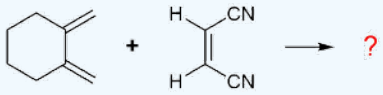


Determine if any substituents attached to either the double bond of the dieneophile or carbons 1 and 4 of the diene have a *cis*/*trans* conformation. If so, make sure the substituents have the same configuration as the cycloalkene product.



✔ Worked Example 1.5.2: Predicting the Product of a Diels–Alder Reaction

Predict the product of the following Diels–Alder reaction:

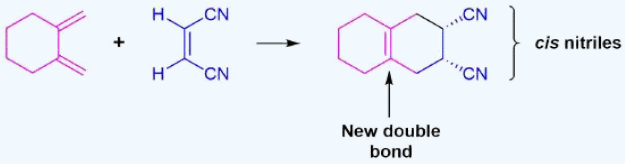


Strategy

The diene is locked into an s-cis configuration which will promote the reaction. The ring portion of the diene will act as electron donating groups which will also promote the reaction. Form two single bonds between the partners, convert the three double bonds into single bonds, and convert the former single bond of the diene into a double bond.

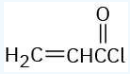
Because the diene already contained a ring the product will be bicyclic. The dienophile has two nitriles attached to it both of which are electron withdrawing. Since the two nitriles in the dieneophile are *cis* to each other the the two nitriles will be cis to each other in the product.

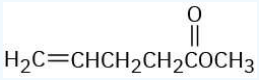
Solution

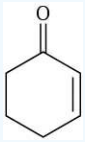


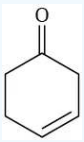
Exercise 1.5.2

Which of the following alkenes would you expect to be good Diels–Alder dienophiles?

(a) 

(b) 

(c) 
(d) 

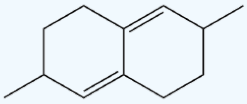
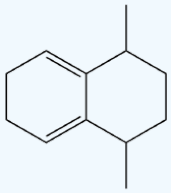
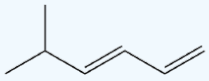
(e) 

Answer

Good dienophiles: (a), (d)

Exercise 1.5.3

Of the following dienes, which are S-trans and which are s-cis? Of those that are s-trans, are they able to rotate to become s-cis?

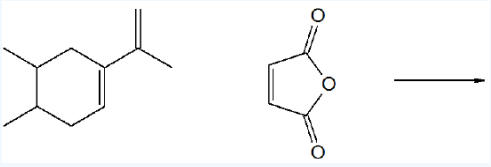
A) 
B) 
C) 

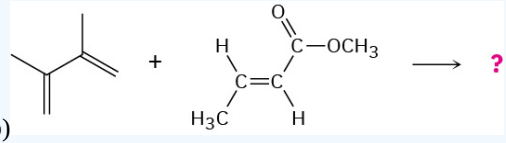
Answer

A) s-trans, unable to rotate to become s-cis. B) s-cis. C) s-trans, can rotate to become s-cis.

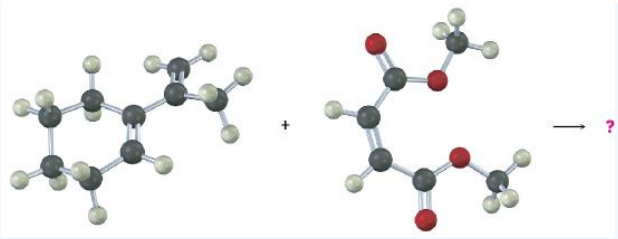
Exercise 1.5.4

Predict the product of the following reactions:

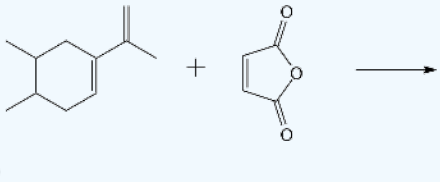
(a) 

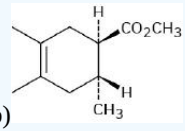
(b) 

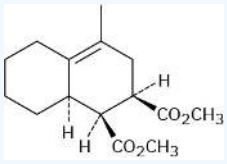
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(c) 

Answer

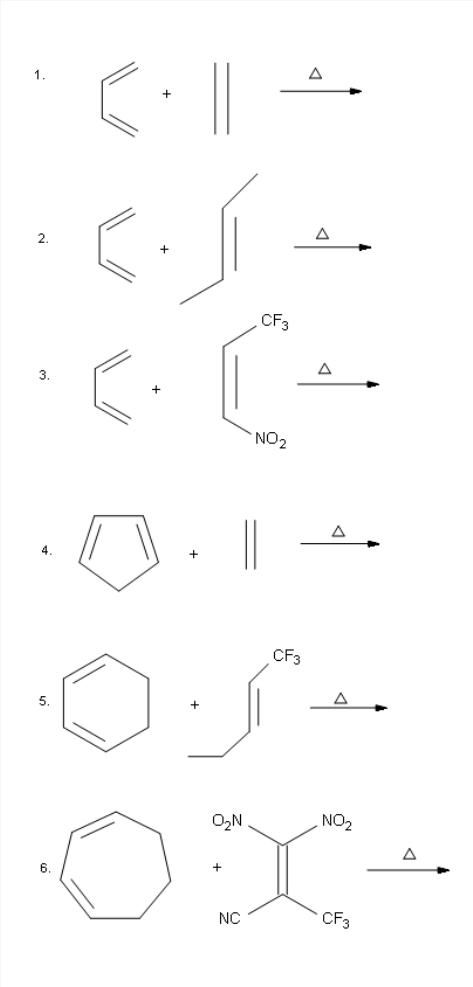
(a) 

(b) 

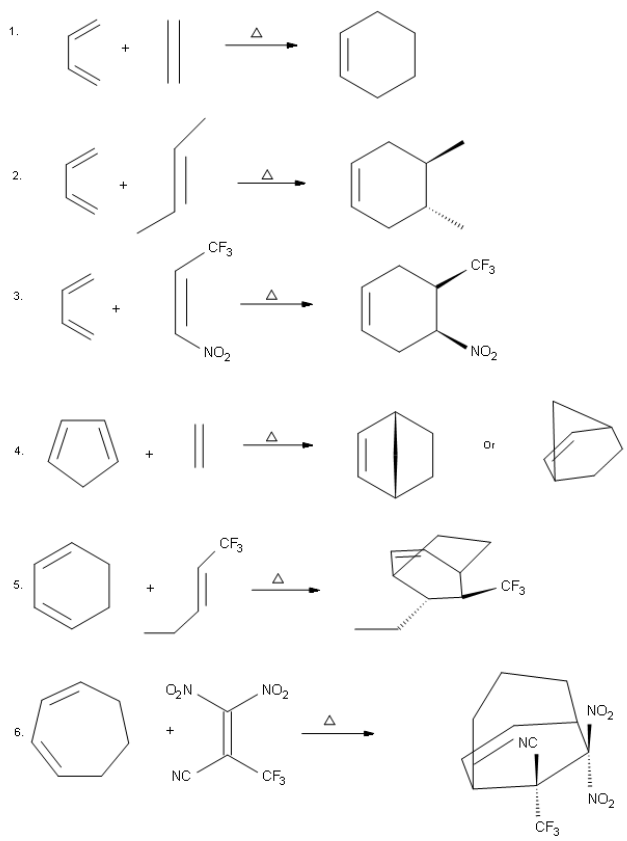
(c) 

Exercise 1.5.5

Draw the major product of each following Diels-Alder reaction:



Answer



Study Notes

Ensure to understand that the *s*-cis and *s*-trans forms of a diene such as 1,3-butadiene are conformers, not isomers. Note that some textbooks can confuse the issue further by referring to a compound such as (2Z, 4Z)-hexadiene as cis, cis-2,4-hexadiene, and saying that the most stable form of this compound is its *s*-trans conformer!

In fulfilling Objective 2, above, you must recognize that the Diels-Alder reaction is stereospecific.

Finally, note reaction **B** in the reading shows 1,3-cyclopentadiene reacting with another molecule of 1,3-cyclopentadiene. When the same compound acts as both diene and dienophile in a Diels-Alder reaction to couple it is a dimerization.

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1.6: Structure Determination in Conjugated Systems - Ultraviolet Spectroscopy

Objectives

After completing this section, you should be able to

1. identify the ultraviolet region of the electromagnetic spectrum which is of most use to organic chemists.
2. interpret the ultraviolet spectrum of 1,3-butadiene in terms of the molecular orbitals involved.
3. describe in general terms how the ultraviolet spectrum of a compound differs from its infrared and NMR spectra.

Key Terms

Make certain that you can define, and use in context, the key term below.

- ultraviolet (UV) spectroscopy
- Molar absorptivity

As we've seen, mass spectrometry, infrared spectroscopy, and nuclear magnetic resonance spectroscopy are techniques of structure determination applicable to all organic molecules. In addition to these three generally useful methods, there is a fourth—ultraviolet (UV) spectroscopy—that is applicable only to conjugated compounds. UV is less commonly used than the other three spectroscopic techniques because of the specialized information it gives, so we'll only discuss it briefly.

Mass spectrometry	Molecular size and formula
IR spectroscopy	Functional groups present
NMR spectroscopy	Carbon–hydrogen framework
UV spectroscopy	**Conjugated π electron systems**

UV-Visible Absorption Spectra

To understand why some compounds are colored and others are not, and to determine the relationship of conjugation to color, we must make accurate measurements of light absorption at different wavelengths in and near the visible part of the spectrum. Commercial optical spectrometers enable such experiments to be conducted with ease, and usually survey both the near ultraviolet and visible portions of the spectrum. Ultraviolet-visible absorption spectroscopy provides much less information about the structure of molecules than do the spectroscopic techniques studied earlier (infrared spectroscopy, mass spectroscopy, and NMR spectroscopy) and mainly provides information about conjugated pi systems. For an organic chemist, the most useful ultraviolet region of the electromagnetic spectrum involves radiation with a wavelength between 200 and 400 nm (Figure **1.6.1**). UV/Vis absorption spectra also involve radiation from the visible region of the electromagnetic spectrum with wavelengths between 400 and 800 nm.

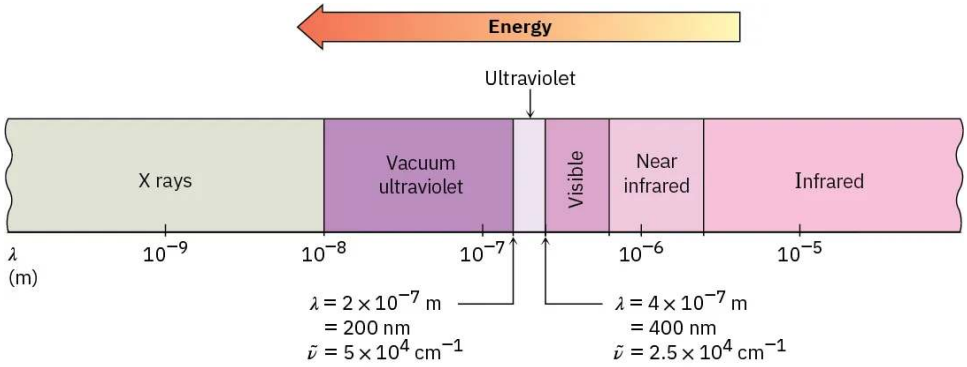
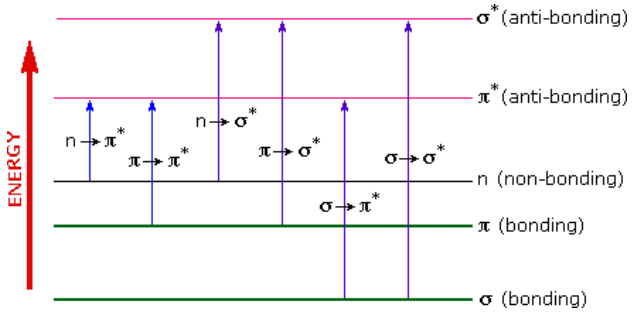


Figure **1.6.1**: The ultraviolet (UV) and neighboring regions of the electromagnetic spectrum.

A diagram highlighting the various kinds of electronic excitation that may occur in organic molecules is shown below. Of the six transitions outlined, only the two lowest energy ones, n to pi* and pi to pi* (colored blue) are achieved by the energies available in the 200 to 800 nm range of a UV/VIs spectrum. These energies are sufficient to promote or excite a molecular electron to a higher energy orbital in many conjugated compounds.



When sample molecules are exposed to light having an energy that matches a possible electronic transition within the molecule, some of the light energy will be absorbed as the electron is promoted to a higher energy orbital. With UV radiation, the energy absorbed corresponds to the amount needed to promote an electron from a lower-energy orbital to a higher-energy one in a conjugated molecule. The conjugated diene 1,3-butadiene, for instance, has four π molecular orbitals. The two lower-energy, bonding MOs are occupied in the ground state, and the two higher-energy, antibonding MOs are unoccupied.

On irradiation with ultraviolet light ($h\upsilon$), 1,3-butadiene absorbs energy and a π electron is promoted from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). Because the electron is promoted from a bonding π molecular orbital to an antibonding π* molecular orbital, we call this a $\pi \rightarrow \pi^*$ excitation (read as “pi to pi star”). The energy gap between the HOMO and the LUMO of 1,3-butadiene is such that UV light of 217 nm wavelength is required to effect the $\pi \rightarrow \pi^*$ electronic transition (Figure **1.6.2**).

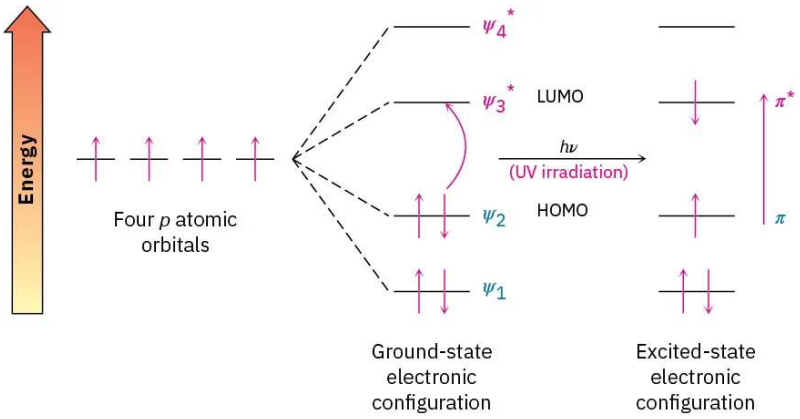


Figure **1.6.2**: Ultraviolet excitation of 1,3-butadiene results in the promotion of an electron from ψ_2, the highest occupied molecular orbital (HOMO), to ψ_3*, the lowest unoccupied molecular orbital (LUMO).

A UV/Vis spectrometer records the wavelengths at which absorption occurs, together with the degree of absorption at each wavelength. **Absorbance**, abbreviated 'A', is a unitless number which contains the same information as the 'percent transmittance' number used in IR spectroscopy. To calculate absorbance at a given wavelength, the computer in the spectrophotometer simply takes the intensity of light at that wavelength *before* it passes through the sample (I_0), divides this value by the intensity of the same wavelength *after* it passes through the sample (I), then takes the $\log_{10}$ of that number:

$$A = \log\left(\frac{I_0}{I}\right)$$

The resulting spectrum is presented as a graph of absorbance (A) versus wavelength, as in the isoprene spectrum shown below. Since 1,3-butadiene is colorless, it does not absorb in the visible part of the spectrum and this region is not displayed on the graph. Notice that the convention in UV-vis spectroscopy is to show the baseline at the bottom of the graph with the peaks pointing up.

Wavelength values on the x-axis are generally measured in nanometers (nm) rather than in cm^{-1} as is the convention in IR spectroscopy.

Typically, there are two things that are noted and recorded from a UV-Vis spectrum. The first is $\lambda_{max,}$ which is the wavelength at maximal light absorbance. As you can see, isoprene has $\lambda_{max,}$ = 217 nm. The second valuable piece of data is the absorbance at the λ_{max}. In the isoprene spectrum the absorbance at the value λ_{max} of 217 nm is about 0.88. (Figure **1.6.3**).

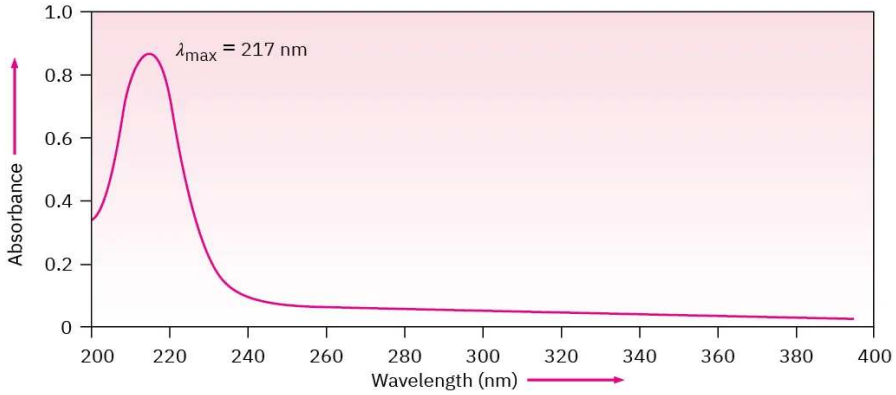


Figure **1.6.3**: The ultraviolet spectrum of 1,3-butadiene, λ_{max} = 217 nm.

Molar absorptivity

Molar absorptivity (***epsilon***) is a physical constant, characteristic of the particular substance being observed and thus characteristic of the particular electron system in the molecule. Molar absorptivities may be very large for strongly absorbing chromophores (>100,000) and very small if absorption is weak (10 to 100). The magnitude of ***epsilon*** reflects both the size of the chromophore and the probability that light of a given wavelength will be absorbed when it strikes the chromophore. Molar absorptivity (ϵ) is defined via Beer's law as:

$$\epsilon = \frac{A}{c\,l}$$

where

- A is the sample absorbance
- c is the sample concentration in moles/liter
- l is the length of light path through the sample in cm

If the isoprene spectrum show above was obtained from a dilute hexane solution (c = 4 * 10^{-5} moles per liter) in a 1 cm sample cuvette, a simple calculation using the above formula indicates a molar absorptivity of 20,000 at the maximum absorption wavelength, symbolized as λ_{max}.

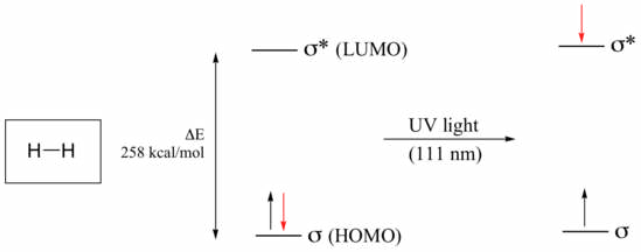
The only molecular moieties likely to absorb light in the 200 to 800 nm region are functional groups that contain pi-electrons and hetero atoms having non-bonding valence-shell electron pairs. Such light absorbing groups are referred to as **chromophores**. A list of some simple chromophores and their light absorption characteristics are provided below. The oxygen non-bonding electrons in alcohols and ethers do not give rise to absorption above 160 nm. Consequently, pure alcohol and ether solvents may be used for spectroscopic studies.

Electronic Transitions (cause of UV-Visible absorption)

As previously noted, electronic transitions in organic molecules lead to UV and visible absorption. As a rule, energetically favored electron promotion will be from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO), and the resulting species is called an **excited state.** The molecular orbital picture for the hydrogen molecule (H_2) consists of one bonding σ MO, and a higher energy antibonding σ* MO. When the molecule is in the ground state, both electrons are paired

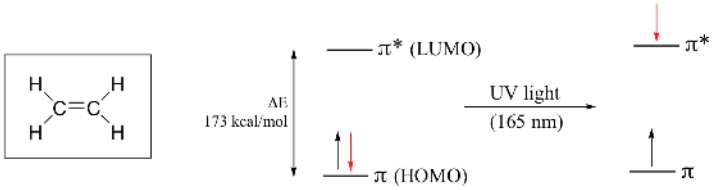
Chromophore	Example	Excitation	λmax, nm	ε @ λmax	Solvent
C=C	Ethene	π → π*	171	15,000	hexane
C≡C	1-Hexyne	π → π*	180	10,000	hexane
C=O	Ethanal	n → π* π → π*	290 180	15 10,000	hexane hexane
N=O	Nitromethane	n → π* π → π*	275 200	17 5,000	ethanol ethanol
C-X X=Br X=I	Methyl bromide Methyl Iodide	n → σ* n → σ*	205 255	200 360	hexane hexane

in the lower-energy bonding orbital – this is the Highest Occupied Molecular Orbital (HOMO). The antibonding σ* orbital, in turn, is the Lowest Unoccupied Molecular Orbital (LUMO).

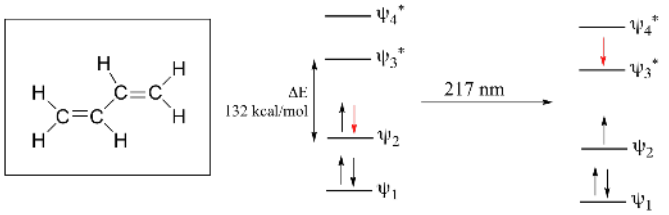


If the molecule is exposed to light of a wavelength with energy equal to ΔE, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. ΔE for this electronic transition is 258 kcal/mol, corresponding to light with a wavelength of 111 nm.

When a double-bonded molecule such as ethene (common name ethylene) absorbs light, it undergoes a **π - π* transition**. Because π- π* energy gaps are narrower than σ - σ* gaps, ethene absorbs light at 165 nm - a longer wavelength than molecular hydrogen.

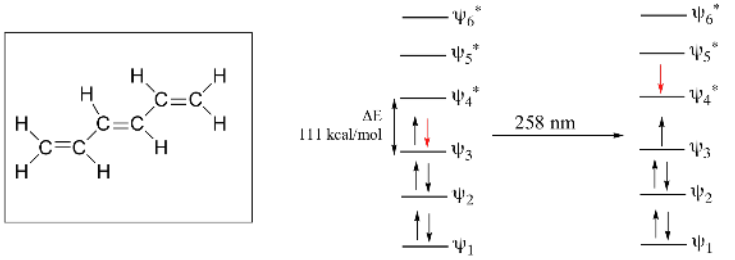


The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded. Where electronic transition becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. The MO diagram for 1,3-butadiene, the simplest conjugated system. Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are pi bonding, while the upper two are pi antibonding.

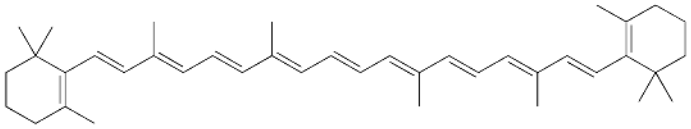


Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

As conjugated pi systems become larger, the energy gap for a π - π* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the π - π* transition in 1,3,5-hexatriene, for example, occurs at 258 nm, corresponding to a **Δ**E of 111 kcal/mol.

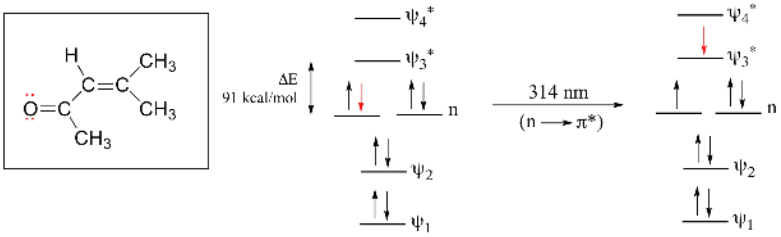


In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



β-carotene

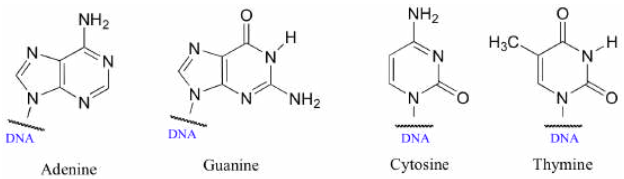
The conjugated pi system in 4-methyl-3-penten-2-one gives rise to a strong UV absorbance at 236 nm due to a π - π* transition. However, this molecule also absorbs at 314 nm. This second absorbance is due to the transition of a non-bonding (lone pair) electron on the oxygen up to a π* antibonding MO:



This is referred to as an $n - \pi^*$ transition. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an $n - \pi^*$ transition is smaller that that of a $\pi - \pi^*$ transition – and thus the $n - \pi^*$ peak is at a longer wavelength. In general, $n - \pi^*$ transitions are weaker (less light absorbed) than those due to $\pi - \pi^*$ transitions.

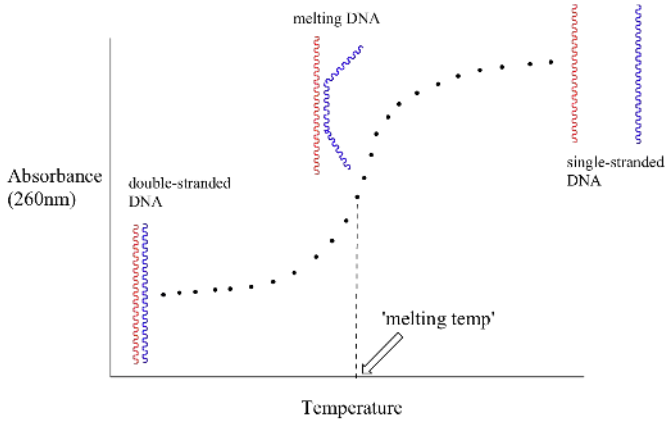
Use of UV/Vis Spectroscopy in Biological Systems

The bases of DNA and RNA are good chromophores:



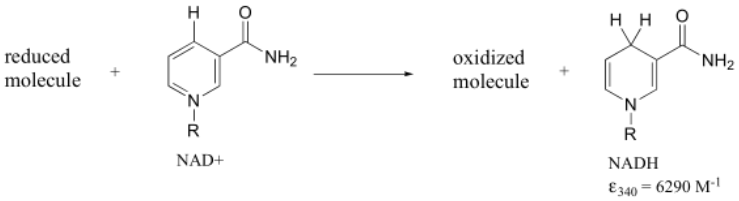
Biochemists and molecular biologists often determine the concentration of a DNA sample by assuming an average value of ε = 0.020 $ng^{-1} \times mL$ for double-stranded DNA at its λ_{max} of 260 nm (notice that concentration in this application is expressed in mass/volume rather than molarity: ng/mL is often a convenient unit for DNA concentration when doing molecular biology).

Because the extinction coefficient of double stranded DNA is slightly lower than that of single stranded DNA, we can use UV spectroscopy to monitor a process known as DNA melting. If a short stretch of double stranded DNA is gradually heated up, it will begin to 'melt', or break apart, as the temperature increases (recall that two strands of DNA are held together by a specific pattern of hydrogen bonds formed by 'base-pairing').

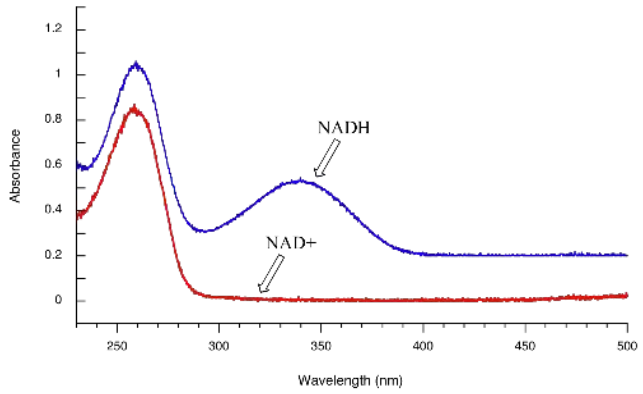


As melting proceeds, the absorbance value for the sample increases, eventually reaching a high plateau as all of the double-stranded DNA breaks apart, or 'melts'. The mid-point of this process, called the 'melting temperature', provides a good indication of how tightly the two strands of DNA are able to bind to each other.

Later we will see how the Beer - Lambert Law and UV spectroscopy provides us with a convenient way to follow the progress of many different enzymatic redox (oxidation-reduction) reactions. In biochemistry, oxidation of an organic molecule often occurs concurrently with reduction of nicotinamide adenine dinucleotide (NAD^+, the compound whose spectrum we saw earlier in this section) to NADH:

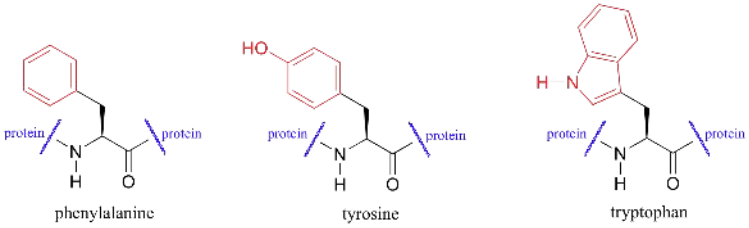


Both NAD^+ and NADH absorb at 260 nm. However NADH, unlike NAD^+, has a second absorbance band with λ_{max} = 340 nm and ε = 6290 $L_{*}mol^{-1}{}_{*}cm^{-1}$. The figure below shows the spectra of both compounds superimposed, with the NADH spectrum offset slightly on the y-axis:



By monitoring the absorbance of a reaction mixture at 340 nm, we can 'watch' NADH being formed as the reaction proceeds, and calculate the rate of the reaction.

UV spectroscopy is also very useful in the study of proteins. Proteins absorb light in the UV range due to the presence of the aromatic amino acids tryptophan, phenylalanine, and tyrosine, all of which are chromophores.



Biochemists frequently use UV spectroscopy to study conformational changes in proteins - how they change shape in response to different conditions. When a protein undergoes a conformational shift (partial unfolding, for example), the resulting change in the environment around an aromatic amino acid chromophore can cause its UV spectrum to be altered.

Exercise 1.6.1

What is the energy range for 300 nm to 500 nm in the ultraviolet spectrum? How does this compare to energy values from NMR and IR spectroscopy?

Answer

$E = hc/\lambda$ Example calculation for For $\lambda = 300$ nm

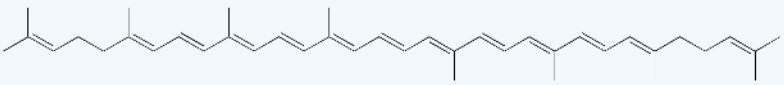
$E = (6.62 \times 10^{-34}\ \text{Js})(3.00 \times 10^{8}\ \text{m/s})/(3.00 \times 10^{-7}\ \text{m})$

$E = 6.62 \times 10^{-19}\ \text{J}$

The range of 3.972×10^{-19} to 6.62×10^{-19} joules. This energy range is greater than NMR and IR energy.

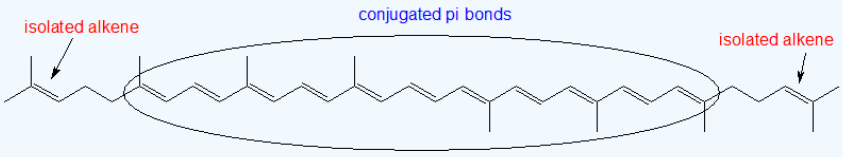
Exercise 1.6.2

Identify all isolated and conjugated pi bonds in lycopene, the red-colored compound in tomatoes. How many pi electrons are contained in the conjugated pi system?



lycopene

Answer



Exercise 1.6.3

If pure vitamin A has $\lambda_{max} = 325$ ($\varepsilon = 50{,}100$), what is the vitamin A concentration in a sample whose absorbance at 325 nm is $A = 0.735$ in a cell with a pathlength of 1.00 cm?

Answer

Using $\varepsilon = A/c$, we plug in our values for ε and A and find that $c = 1.46 \times 10^{-5}$ M.

Exercise 1.6.4

50 microliters of an aqueous sample of double stranded DNA is dissolved in 950 microliters of water. This diluted solution has a maximal absorbance of 0.326 at 260 nm. What is the concentration of the original (more concentrated) DNA sample, expressed in micrograms per microliter?

$\varepsilon = 0.020\ ng^{-1} \times mL$ for double-stranded DNA

Answer

Using $\varepsilon = A/c$, we plug in our values for ε and A and find that $c = 3.27 \times 10^{-5} M$, or 32.7 mM.

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1.7: Interpreting Ultraviolet Spectra- The Effect of Conjugation

Objective

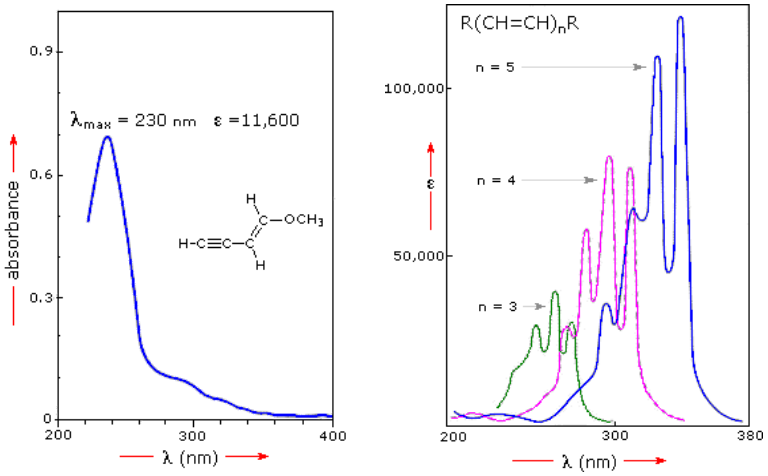
After completing this section, you should be able to use data from ultraviolet spectra to assist in the elucidation of unknown molecular structures.

Study Notes

It is important that you recognize that the ultraviolet absorption maximum of a conjugated molecule is dependent upon the extent of conjugation in the molecule.

The Importance of Conjugation

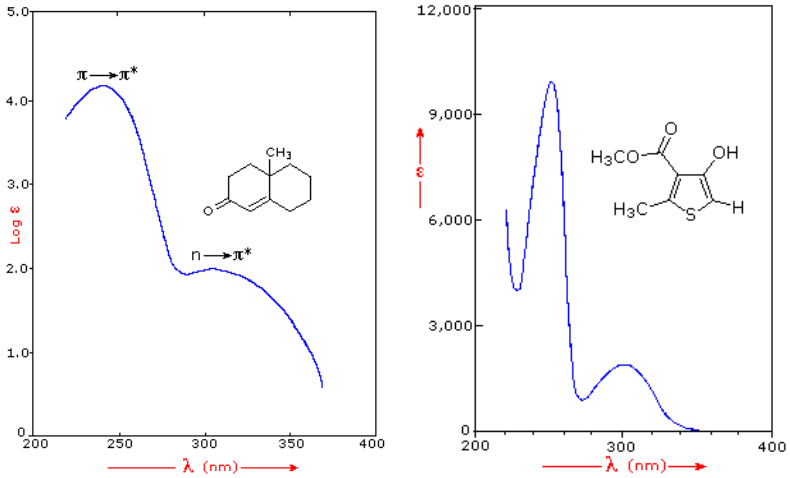
A comparison of the UV/Vis absorption spectrum of 1-butene, λ_{max} = 176 nm, with that of 1,3-butadiene, λ_{max} = 292 nm, clearly demonstrates that the effect of increasing conjugation is to shift toward longer wavelength (lower frequency, lower energy) absorptions. Further evidence of this effect is shown below. The spectrum on the left illustrates that conjugation of double and triple bonds also shifts the absorption maximum to longer wavelengths. From the polyene spectra displayed in the right it is clear that each additional double bond in the conjugated pi-electron system increases the absorption maximum about 30 nm. Also, the molar absorptivity (ε) roughly doubles with each new conjugated double bond. Spectroscopists use the terms defined in the table below when describing shifts in absorption. Thus, extending conjugation generally results in bathochromic and hyperchromic shifts in absorption.



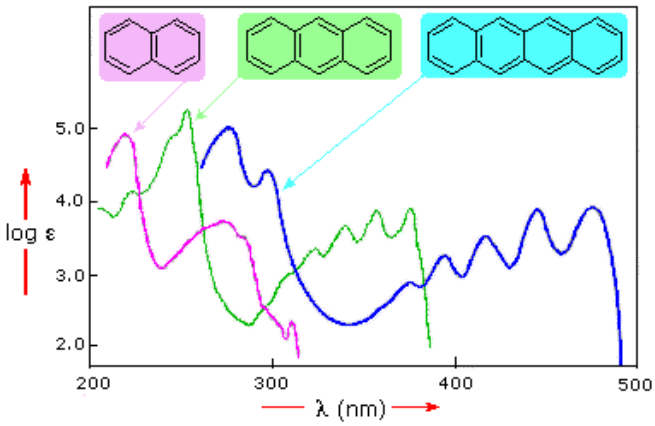
Terminology for Absorption Shifts

Nature of Shift	Descriptive Term
To Longer Wavelength	Bathochromic
To Shorter Wavelength	Hypsochromic
To Greater Absorbance	Hyperchromic
To Lower Absorbance	Hypochromic

Many other kinds of conjugated pi-electron systems act as chromophores and absorb light in the 200 to 800 nm region. These include unsaturated aldehydes and ketones and aromatic ring compounds. A few examples are displayed below. The spectrum of the unsaturated ketone (on the left) illustrates the advantage of a logarithmic display of molar absorptivity. The $\pi \rightarrow \pi^*$ absorption located at 242 nm is very strong, with an ε = 18,000. The weak $n \rightarrow \pi^*$ absorption near 300 nm has an ε = 100.

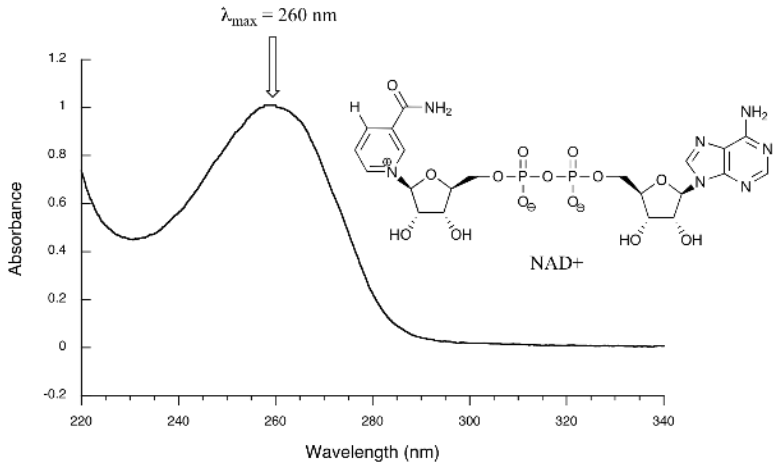


Benzene exhibits very strong light absorption near 180 nm (ε > 65,000) , weaker absorption at 200 nm (ε = 8,000) and a group of much weaker bands at 254 nm (ε = 240). Only the last group of absorptions are completely displayed because of the 200 nm cut-off characteristic of most spectrophotometers. The added conjugation in naphthalene, anthracene and tetracene causes bathochromic shifts of these absorption bands, as displayed in the chart below. All the absorptions do not shift by the same amount, so for anthracene (green shaded box) and tetracene (blue shaded box) the weak absorption is obscured by stronger bands that have experienced a greater red shift. As might be expected from their spectra, naphthalene and anthracene are colorless (with their absorptions in the UV range), but tetracene is orange (since its absorptions move into the visible range).

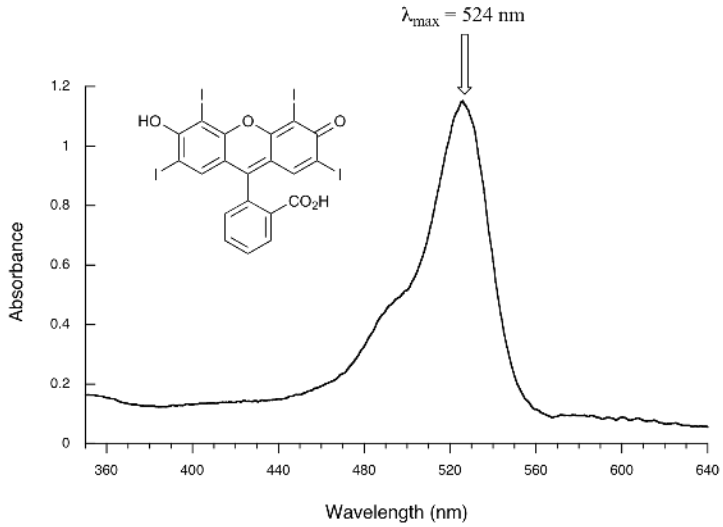


Looking at UV-Vis Spectra

Below is the absorbance spectrum of an important biological molecule called nicotinamide adenine dinucleotide, abbreviated NAD^+. This compound absorbs light in the UV range due to the presence of conjugated pi-bonding systems.

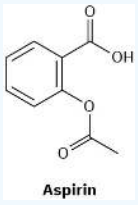
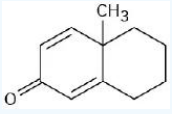
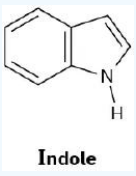


Below is the absorbance spectrum of the common food coloring Red #3. The extended system of conjugated pi bonds causes the molecule to absorb light in the visible range. Because the λ_{max} of 524 nm falls within the green region of the spectrum, the compound appears red to our eyes.



? Exercise 1.7.1

Which of the following compounds would you expect to show ultraviolet absorptions in the 200 to 400 nm range?

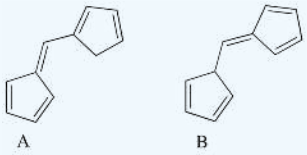
(a)  **(b)**  **(c)**  **(d)**  Aspirin **(e)**  **(f)**  Indole

Answer

All except **(a)** have UV absorptions.

Exercise 1.7.2

Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.



Answer

Molecule A has a longer system of conjugated pi bonds, and thus will absorb at a longer wavelength. Notice that there is an sp^3-hybridized carbon in molecule B which isolates two of the pi bonds from the other three.

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1.8: Conjugation, Color, and the Chemistry of Vision

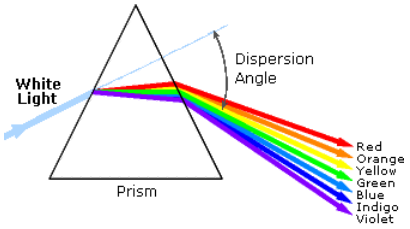
Objectives

After completing this section, you should be able to

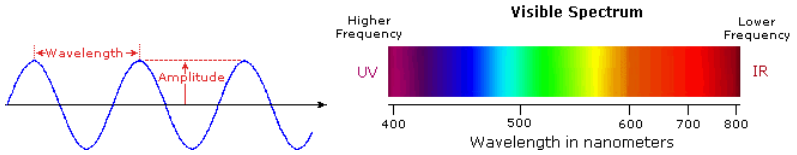
1. explain why some organic compounds have different colors based on compound structure and our perception of light.
2. state the relationship between frequency of light absorbed and the extent of conjugation in an extended pi electron system.

Introduction

An obvious difference between certain compounds is their color. Thus, quinone is yellow; chlorophyll is green; and aspirin is colorless. In this respect the human eye is functioning as a spectrometer analyzing the light reflected from the surface of a solid or passing through a liquid. Although we see sunlight (or white light) as uniform or homogeneous in color, it is actually composed of a broad range of radiation wavelengths in the ultraviolet (UV), visible and infrared (IR) portions of the spectrum. As shown on the image below, the component colors of the visible portion can be separated by passing sunlight through a prism, which acts to bend the light in differing degrees according to wavelength.

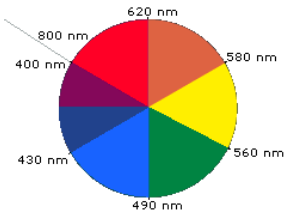


Visible wavelengths cover a range from approximately 400 to 800 nm. The longest visible wavelength is red and the shortest is violet. The wavelengths of what we perceive as particular colors in the visible portion of the spectrum are displayed and listed below.

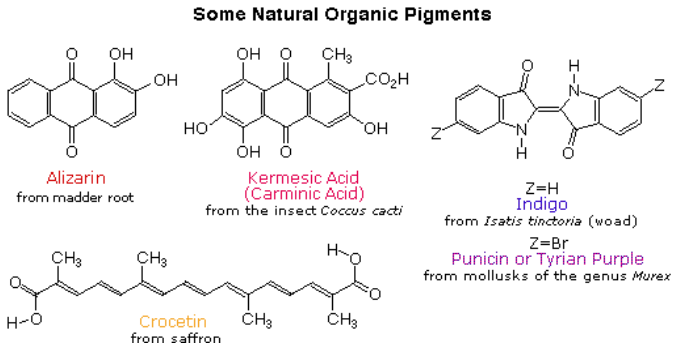


- **Violet:** 400 - 420 nm
- **Indigo:** 420 - 440 nm
- **Blue:** 440 - 490 nm
- **Green:** 490 - 570 nm
- **Yellow:** 570 - 585 nm
- **Orange:** 585 - 620 nm
- **Red:** 620 - 780 nm

When white light passes through or is reflected by a colored substance, a characteristic portion of the mixed wavelengths is absorbed. The remaining light will then assume the complementary color to the wavelength(s) absorbed. This relationship is demonstrated by the color wheel shown below. Here, complementary colors are diametrically opposite each other. Thus, absorption of violet (400-440 nm) light renders a substance yellow, and absorption of 490-560 nm (green) light makes it red. Green is unique in that it can be created by absorption close to 400 nm as well as absorption near 800 nm.



Early humans valued colored pigments, and used them for decorative purposes. Many of these were inorganic minerals, but several important organic dyes were also known. These included the crimson pigment, kermesic acid, the blue dye, indigo, and the yellow saffron pigment, crocetin. A rare dibromo-indigo derivative, punicin, was used to color the robes of the royal and wealthy. A common feature of all these colored compounds, displayed below, is a system of **extensively conjugated π-electrons**.



By understanding visible light, complementary colors, and adsorption the color of organic compounds can be understood. Beta-carotene, a compound found in carrots, is a deep orange color. Beta-carotene has 11 conjugated double bonds which places its λ_{max} at 455 nm which is within the blue region of the visible spectrum. The Beta-carotene compound absorbs blue from white light so it appears orange which is the the complementary color of blue. (Figure 1.8.1).

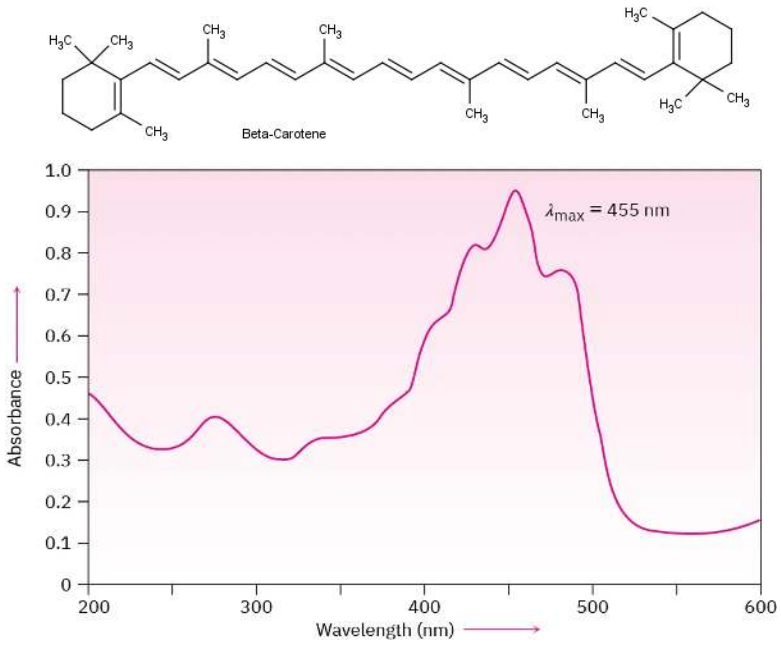
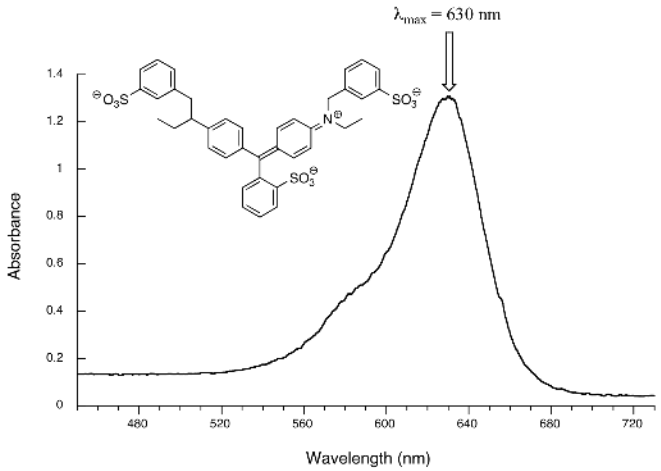


Figure 1.8.1: Ultraviolet spectrum of β-carotene, a conjugated molecule with 11 double bonds. The absorption occurs in the visible region.

Another example is seen in the absorption spectrum of another food coloring, Blue #1:



Blue #1 absorbs at a λ_{max} at 630 nm which is the color red in the visible spectrum. Blue is the complementary color of red.

Mechanism of Vision

Conjugation is also important in light sensitive compounds used for vision. Beta carotene, found in carrots and other natural products is cleaved into the liver and converted into Vitamin A, also known as retinol. Vitamin A is critical for vision because it is needed by the retina of eye. Retinol can be oxidized to an aldehyde called retinal which is also important for vision. (Figure 1.8.2).

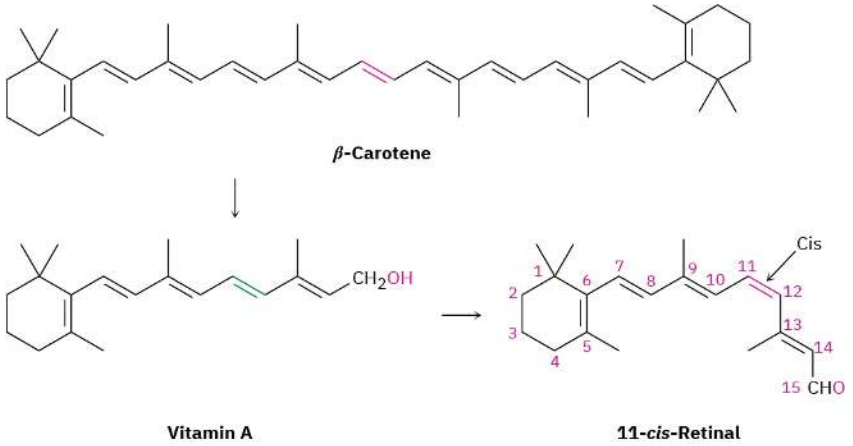
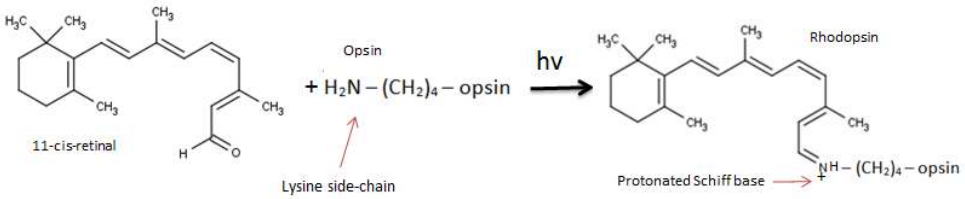


Figure 1.8.2: The key substance for vision is dietary *β*-carotene, which is converted to vitamin A by enzymes in the liver, oxidized to an aldehyde called 11-*trans*-retinal, and then isomerized by a change in geometry of the C11–C12 double bond to produce 11-*cis*-retinal.

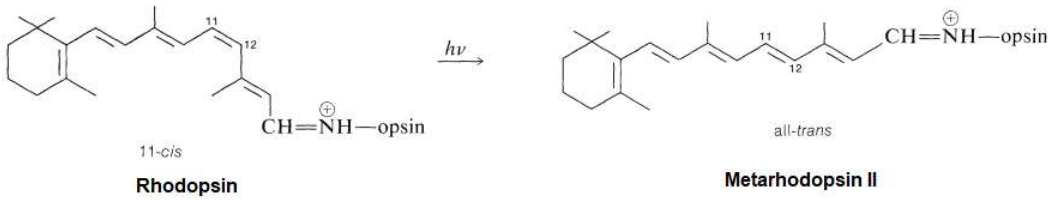
The eye is an extraordinarily sensitive instrument. Although its wavelength response is restricted to 400-800 nm, but its degree of sensitivity is such that a fully dark-adapted eye can clearly detect objects in light so dim as to correspond to a light input over the retina of only about 10,000 quanta per second - one light quantum per three minutes per receptor cell in the retina!

The retina is made up of two kinds of light-sensitive (photoreceptor) cells, known as rods and cones. The rods are the more sensitive and are responsible for vision in dim light. The cones are much fewer in number than the rods and provide detail and color vision in good light. The part of the retina that corresponds to the center of the visual field contains only cones. A red pigment called **rhodopsin** is the photosensitive substance in the rod cells of the retina. It absorbs most strongly in the blue-green region of the visible spectrum (λ_{max} = 500nm) and is essentially unaffected by the far-red end of the spectrum. Cone vision appears to involve a different pigment called **iodopsin**, which absorbs farther toward the red than does rhodopsin.

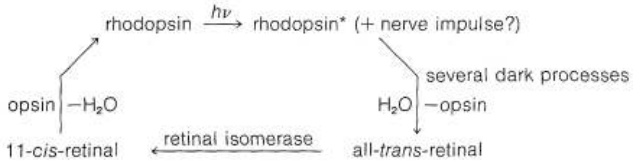
Rhodopsin, is made up of a protein (opsin) and retinal. Opsin does not absorb visible light, but when it is bonded with 11-cis-retinal to from rhodopsin, the new molecule has a very broad absorption band in the visible region of the spectrum. Rhodopsin is formed by an an imine (Schiff base) functional group formed between the aldehyde group of the retinal and the side-chain amino function of a lysine unit of opsin.



Opsin itself is colorless, whereas 11-cis-retinal absorbs strongly at 370 nm. The combination of opsin with 11-cis-retinal produces a remarkable shift of λ_{max} to longer wavelengths (430 nm to 620 nm, depending on the species). Light striking the retina changes the color of rhodopsin from red to yellow. The primary photochemical event in this process was established by G. Wald (Nobel Laureate in Physiology and Medicine, 1967), who showed that light absorption led to a change of configuration about the C_{11}-C_{12} double bond of the retinal moiety fo rhodopsin from *cis* to *trans* to form a compound called metarhodopsin II. The new form of trans-retinal does not fit as well into the opsin protein, and so a series of geometry changes in the protein begins. As the protein changes its geometry, it initiates a cascade of biochemical reactions that result in changes in charge so that a large potential difference builds up across the neuron membranes. This potential difference is passed along to an adjoining nerve cell as an electrical impulse. The nerve cell carries this impulse to the brain, where the visual information is interpreted.

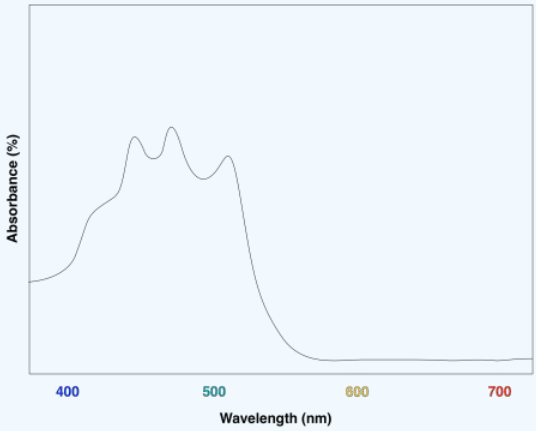


Metarhodopsin II can then be recycled back to rhodopsin by first cleaving to form all-*trans*-retinal and the isomerization back to 11-*cis*-retinal by the enzyme retinal isomerase. Finally, 11-*cis*-retinal is once again coupled with opsin to form rhodopsin.



Exercise 1.8.1

Lycopene is conjugated compound found in tomatoes. What colors correspond to the UV-Vis absorption maxima of lycopene? What color do we see when we look at lycopene?



Answer

The absorption maxima of lycopene are regions of blue and green in the visible spectrum. Lycopene would be expected to appears orange and red.

? Exercise 1.8.2

Aspirin has a λ_{max} of 220 nm. Briefly explain why Aspirin appears white.

Answer

Aspirin absorbs in the ultraviolet portion of the electromagnetic spectrum. Aspirin cannot remove any colors from white light by absorption so the compound itself appears white. Many compounds with a relatively small amount of conjugation appear white because they only absorb in the ultraviolet region and not the visible region.

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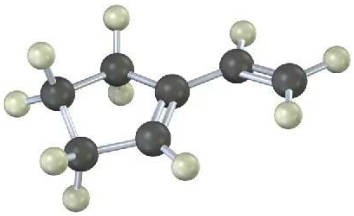
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1.9: Additional Problems

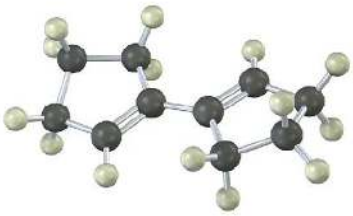
Additional Problems

Visualizing Chemistry

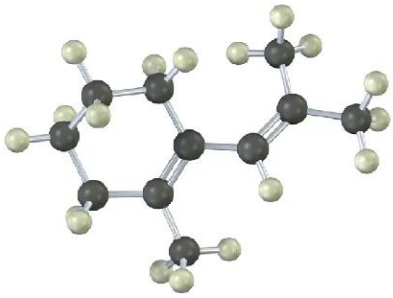
PROBLEM 1-16 Show the structures of all possible adducts of the following diene with 1 equivalent of HCl:



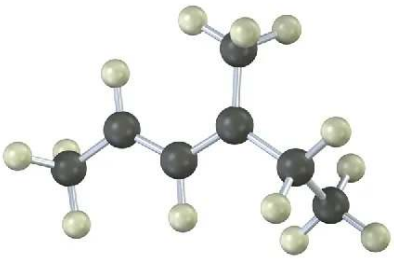
PROBLEM 1-17 Show the product of the Diels–Alder reaction of the following diene with 3-buten-2-one, $H_2C{=}CHCOCH_3$. Make sure you show the full stereochemistry of the reaction product.



PROBLEM 1-18 The following diene does not undergo Diels–Alder reactions. Explain.

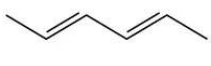


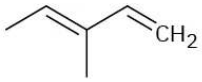
PROBLEM 1-19 The following model is that of an allylic carbocation intermediate formed by protonation of a conjugated diene with HBr. Show the structure of the diene and the structures of the final reaction products.

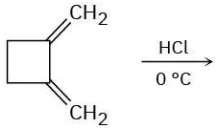


Mechanism Problems

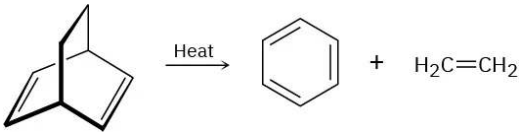
PROBLEM 1-20 Predict the major product(s) from the addition of 1 equivalent of HX and show the mechanism for each of the following reactions.

(a) 

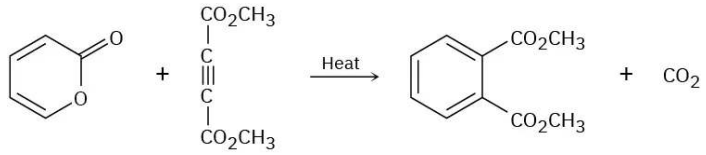
(b) 

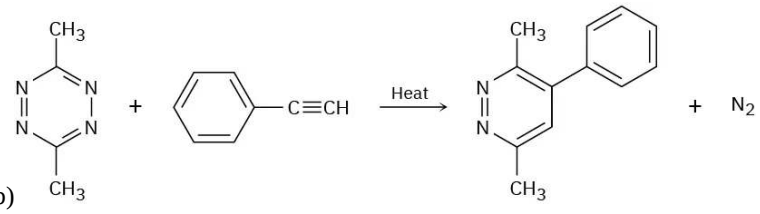
(c) 

PROBLEM 1-21 We've seen that the Diels–Alder cycloaddition reaction is a one-step, pericyclic process that occurs through a cyclic transition state. Propose a mechanism for the following reaction:

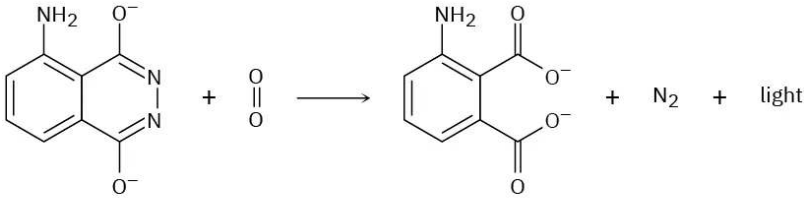


PROBLEM 1-22 In light of your answer to Problem 21 propose mechanisms for the following reactions.

(a) 

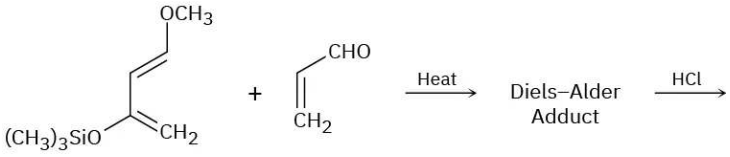
(b) 

PROBLEM 1-23 Luminol, which is used by forensic scientists to find blood, fluoresces as a result of Diels–Alder-like process. The dianion of luminol reacts with O_2 to form an unstable peroxide intermediate that then loses nitrogen to form a dicarboxylate and emit light. The process is similar to that in Problems 21 and 22. Propose a mechanism for this process.

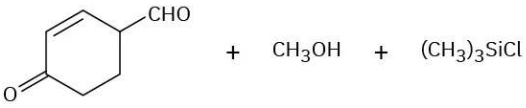


Luminol dianion

PROBLEM 1-24 A useful diene in the synthesis of many naturally occurring substances is known as Danishefsky's diene. It's useful because after the Diels–Alder reaction it can be converted into a product that can't be accessed by a typical Diels–Alder reaction. Show the Diels–Alder adduct and propose a mechanism that accounts for the final products.



Danishefsky's Diene



Conjugated Dienes

PROBLEM 1-25 Name the following compounds:

(a) $CH_3CH{=}C(CH_3){-}CH{=}CHCH_3$ (b) $H_2C{=}CH{-}CH{=}CH{-}CH{=}CHCH_3$

(c) $CH_3CH{=}C{=}CH{-}CH{=}CHCH_3$ (d) $CH_3CH{=}C(CH_2CH_2CH_3){-}CH{=}CH_2$

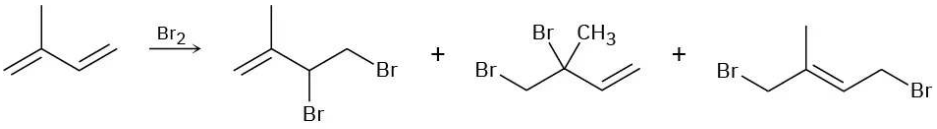
PROBLEM 1-26 Draw and name the six possible diene isomers of formula C_5H_8. Which of the six are conjugated dienes?

PROBLEM 1-27 What product(s) would you expect to obtain from the reaction of 1,3-cyclohexadiene with each of the following?

(a) 1 mol Br_2 in CH_2Cl_2 **(b)** O_3 followed by Zn **(c)** 1 mol HCl in ether **(d)** 1 mol DCl in ether

(e) 3-Buten-2-one ($H_2C{=}CHCOCH_3$) **(f)** Excess OsO_4, followed by $NaHSO_3$

PROBLEM 1-28 Electrophilic addition of Br_2 to isoprene (2-methyl-1,3-butadiene) yields the following product mixture:

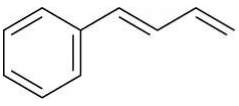


(3%) **(21%)** **(76%)**

Of the 1,2-addition products, explain why 3,4-dibromo-3-methyl-1-butene (21%) predominates over 3,4-dibromo-2-methyl-1-butene (3%).

PROBLEM 1-29 Propose a structure for a conjugated diene that gives the same product from both 1,2 and 1,4-addition of HBr.

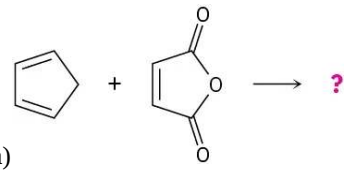
PROBLEM 1-30 Draw the possible products resulting from addition of 1 equivalent of HCl to 1-phenyl-1,3-butadiene. Which would you expect to predominate, and why?



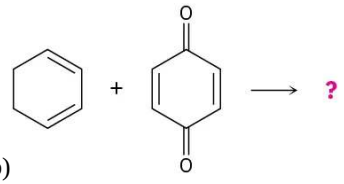
1-Phenyl-1,3-butadiene

Diels–Alder Reactions

PROBLEM 1-31 Predict the products of the following Diels–Alder reactions:

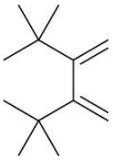


(a)



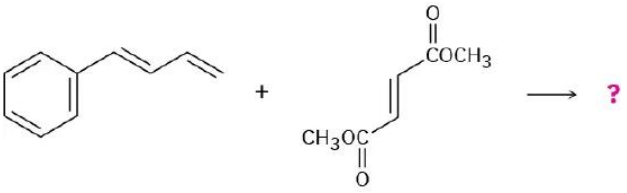
(b)

PROBLEM 1-32 2,3-Di-*tert*-butyl-1,3-butadiene does not undergo Diels–Alder reactions. Explain.



2,3-Di-*tert*-butyl-1,3-butadiene

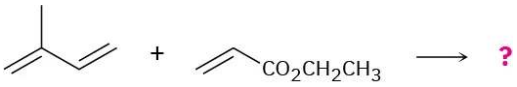
PROBLEM 1-33 Show the structure, including stereochemistry, of the product from the following Diels–Alder reaction:



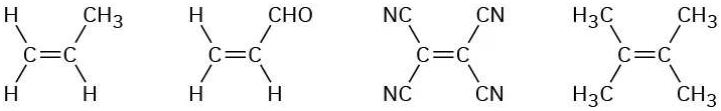
PROBLEM 1-34 How can you account for the fact that *cis*-1,3-pentadiene is much less reactive than *trans*-1,3-pentadiene in the Diels–Alder reaction?

PROBLEM 1-35 Would you expect a conjugated diyne such as 1,3-butadiyne to undergo Diels–Alder reaction with a dienophile? Explain.

PROBLEM 1-36 Reaction of isoprene (2-methyl-1,3-butadiene) with ethyl propenoate gives a mixture of two Diels–Alder adducts. Show the structure of both, and explain why a mixture is formed.



PROBLEM 1-37 Rank the following dienophiles in order of their expected reactivity in the Diels–Alder reaction.



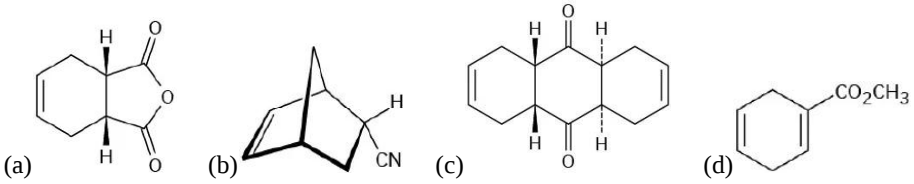
PROBLEM 1-38 1,3-Cyclopentadiene is very reactive in Diels–Alder cycloaddition reactions, but 1,3-cyclohexadiene is less reactive and 1,3-cycloheptadiene is nearly inert. Explain. (Molecular models are helpful.)

PROBLEM 1-39 1,3-Pentadiene is much more reactive in Diels–Alder reactions than 2,4-pentadienal. Why might this be?

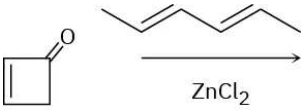


1,3-Pentadiene **2,4-Pentadienal**

PROBLEM 1-40 How could you use Diels–Alder reactions to prepare the following products? Show the starting diene and dienophile in each case.



PROBLEM 1-41 Show the product of the following reaction.



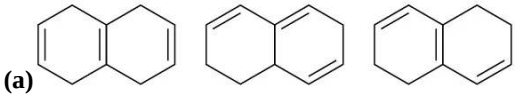
Diene Polymers

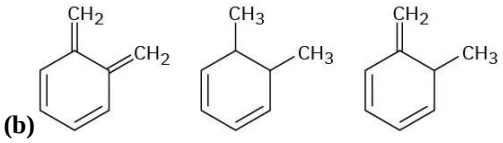
PROBLEM 1-42 Tires whose sidewalls are made of natural rubber tend to crack and weather rapidly in areas around cities where high levels of ozone and other industrial pollutants are found. Explain.

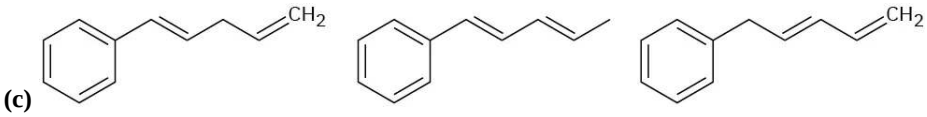
PROBLEM 1-43 1,3-Cyclopentadiene polymerizes slowly at room temperature to yield a polymer that has no double bonds except on the ends. On heating, the polymer breaks down to regenerate 1,3-cyclopentadiene. Propose a structure for the product.

UV Spectroscopy

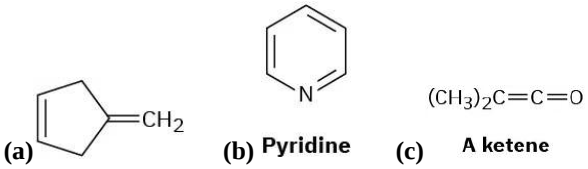
PROBLEM 1-44 Arrange the molecules in each of the following sets according to where you would expect to find their wavelength of maximum absorption in UV spectroscopy, from shortest to longest wavelength.







PROBLEM 1-45 Which of the following compounds would you expect to have a $\pi \rightarrow \pi^*$ UV absorption in the 200 to 400 nm range?



PROBLEM 1-46 Would you expect allene, $H_2C{=}C{=}CH_2$, to show a UV absorption in the 200 to 400 nm range? Explain.

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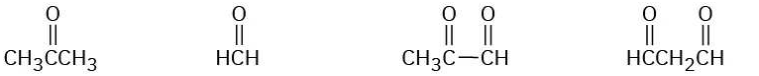
PROBLEM 1-47 The following ultraviolet absorption maxima have been measured:

Molecule	ultraviolet absorption maxima
1,3-Butadiene	217 nm
2-Methyl-1,3-butadiene	220 nm
1,3-Pentadiene	223 nm
2,3-Dimethyl-1,3-butadiene	226 nm
2,4-Hexadiene	227 nm
2,4-Dimethyl-1,3-pentadiene	232 nm
2,5-Dimethyl-2,4-hexadiene	240 nm

What conclusion can you draw about the effect of alkyl substitution on UV absorption maxima? Approximately what effect does each added alkyl group have?

PROBLEM 1-48 1,3,5-Hexatriene has λ_{max} = 258 nm. In light of your answer to Problem 14-47, approximately where would you expect 2,3-dimethyl-1,3,5-hexatriene to absorb?

PROBLEM 1-49 β-Ocimene is a pleasant-smelling hydrocarbon found in the leaves of certain herbs. It has the molecular formula $C_{10}H_{16}$ and a UV absorption maximum at 232 nm. On hydrogenation with a palladium catalyst, 2,6-dimethyloctane is obtained. Ozonolysis of β-ocimene, followed by treatment with zinc and acetic acid, produces the following four fragments:

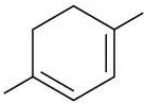
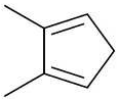


Acetone **Formaldehyde** **Pyruvaldehyde** **Malonaldehyde**

- (a) How many double bonds does β-ocimene have?
- (b) Is β-ocimene conjugated or nonconjugated?
- (c) Propose a structure for β-ocimene.
- (d) Write the reactions, showing starting material and products.

General Problems

PROBLEM 1-50 Draw the resonance forms that result when the following dienes are protonated. If the resonance forms differ in energy, identify the most stable one.

(a)  (b)  (c) 

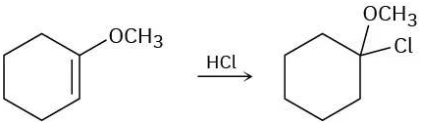
PROBLEM 1-51 Answer the following questions for 1,3,5-cycloheptatriene.

- (a) How many *p* atomic orbitals are in the conjugated system?
- (b) How many molecular orbitals describe the conjugated system?
- (c) How many molecular orbitals are bonding molecular orbitals?
- (d) How many molecular orbitals are anti-bonding molecular orbitals?
- (e) Which molecular orbitals are filled with electrons?
- (f) If this molecule were to absorb a photon of UV light an electron would move between which two molecular orbitals (be specific)?

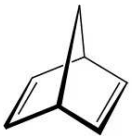
PROBLEM 1-52 Treatment of 3,4-dibromohexane with strong base leads to loss of 2 equivalents of HBr and formation of a product with formula C_6H_{10}. Three products are possible. Name each of the three, and tell how you would use ^1H and ^{13}C NMR

spectroscopy to help identify them. How would you use UV spectroscopy?

PROBLEM 1-53 Addition of HCl to 1-methoxycyclohexene yields 1-chloro-1-methoxycyclohexane as a sole product. Use resonance structures to explain why none of the other regioisomer is formed.



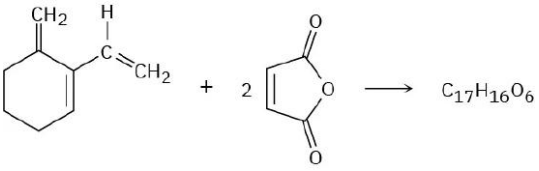
PROBLEM 1-54 Aldrin, a chlorinated insecticide now banned from use in most countries since 1990, can be made by Diels–Alder reaction of hexachloro-1,3-cyclopentadiene with norbornadiene. What is the structure of aldrin?



Norbornadiene

PROBLEM 1-55 Norbornadiene (Problem 54) can be prepared by reaction of chloroethylene with 1,3-cyclopentadiene, followed by treatment of the product with sodium ethoxide. Write the overall scheme, and identify the two kinds of reactions.

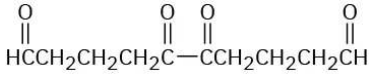
PROBLEM 1-56 The triene shown here reacts with 2 equivalents of maleic anhydride to yield a product with the formula $C_{17}H_{16}O_6$. Predict a structure for the product.



PROBLEM 1-57 Myrcene, $C_{10}H_{16}$, is found in oil of bay leaves and is isomeric with β-ocimene (Problem 49). It has an ultraviolet absorption at 226 nm and can be hydrogenated to yield 2,6-dimethyloctane. On ozonolysis followed by zinc/acetic acid treatment, myrcene yields formaldehyde, acetone, and 2-oxopentanedial:

Propose a structure for myrcene, and write the reactions, showing starting material and products.

PROBLEM 1-58 Hydrocarbon **A**, $C_{10}H_{14}$, has a UV absorption at λ_{max} = 236 nm and gives hydrocarbon **B**, $C_{10}H_{18}$, on hydrogenation. Ozonolysis of **A**, followed by zinc/acetic acid treatment, yields the following diketo dialdehyde:



An illustration shows the structure of diketo dialdehyde. It shows two carbonyl groups single bonded to each other. Each carbonyl group is bonded to a chain of three methylene groups and then to an aldehyde group.

- (a) Propose two possible structures for **A**.
- (b) Hydrocarbon **A** reacts with maleic anhydride to yield a Diels–Alder adduct. Which of your structures for **A** is correct?
- (c) Write the reactions, showing the starting material and products.

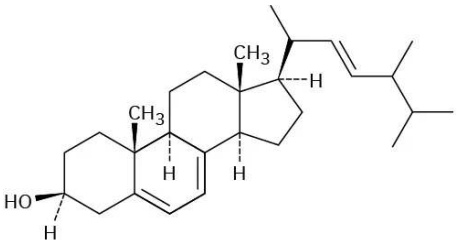
PROBLEM 1-59 Adiponitrile, a starting material used in the manufacture of nylon, can be prepared in three steps from 1,3-butadiene. How would you carry out this synthesis?



Adiponitrile

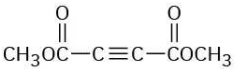
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PROBLEM 1-60 Ergosterol, a precursor of vitamin D, has λ_{max} = 282 nm and molar absorptivity ϵ = 11,900. What is the concentration of ergosterol in a solution whose absorbance A = 0.065 with a sample pathlength l = 1.00 cm?



Ergosterol ($C_{28}H_{44}O$)

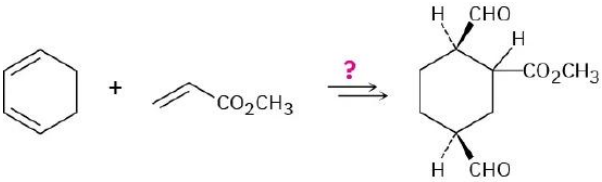
PROBLEM 1-61 Dimethyl butynedioate undergoes a Diels–Alder reaction with (2*E*,4*E*)-2,4-hexadiene. Show the structure and stereochemistry of the product.



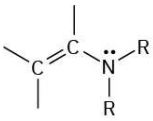
Dimethyl butynedioate

PROBLEM 1-62 Dimethyl butynedioate also undergoes a Diels–Alder reaction with (2*E*,4*Z*)-2,4-hexadiene, but the stereochemistry of the product is different from that of the (2*E*,4*E*) isomer (Problem 61). Explain.

PROBLEM 1-63 How would you carry out the following synthesis (more than one step is required)? What stereochemical relationship between the $–CO_2CH_3$ group attached to the cyclohexane ring and the –CHO groups would your synthesis produce?



PROBLEM 1-64 The double bond of an *enamine* (alk*ene* + *amine*) is much more nucleophilic than a typical alkene double bond. Assuming that the nitrogen atom in an enamine is sp^2-hybridized, draw an orbital picture of an enamine, and explain why the double bond is electron-rich.



An enamine

PROBLEM 1-65 Benzene has an ultraviolet absorption at λ_{max} = 204 nm, and para-toluidine has λ_{max} = 235 nm. How do you account for this difference?



Benzene
(λ_{max} = 204 nm)



***p*-Toluidine**
(λ_{max} = 235 nm)

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1.S: Conjugated Compounds and Ultraviolet Spectroscopy (Summary)

Concepts & Vocabulary

1.1 Introduction

- Dienes that consist of two double bonds separated by a single bond are conjugated.
- Dienes that have the double bonds separated by more than one single bond are isolated (non-conjugated)

1.2 Stability of Conjugated Dienes - Molecular Orbital Theory

- Conjugated dienes are more stable than non-conjugated dienes.
- Electrons in conjugated dienes are delocalized due to overlap of all 4 p-orbitals.
- Molecular orbitals show stability of dienes and allylic carbocations.

1.3 Electrophilic Additions to Conjugated Dienes - Allylic Carbocations

- Addition to conjugated dienes occur at multiple positions due to resonance of the allyl carbocation intermediate called 1,2 and 1,4 addition.

1.4 Kinetic vs. Thermodynamic Control of Reactions

- Lower transition states lead to kinetic products.
- More stable products lead to thermodynamic products.
- Kinetic reaction conditions favor 1,2 addition to conjugated dienes.
- Thermodynamic reaction conditions favor 1,4 addition to conjugated dienes.
- For some reactions, the kinetic and thermodynamic products are the same molecule.

1.5 The Diels-Alder Cycloaddition Reaction

- Cycloaddition reactions involve concerted bonding of two independent pi-electron systems for form a new ring.
- The Diels-Alder reaction is a widely used [4+2] cycloaddition that froms two new sigma bonds.

1.6 Characteristics of the Diels-Alder Reaction

- The Diels-Alder reaction is stereospecific with cis dienophiles yielding *cis* substitution and *trans* dienophiles generate trans substitution.
- The diene in a Diels-Alder reaction must be able to adopt an s-cis conformation.
- Diels-Alder reactions with cyclic dienes favor endo substituents.

1.7 Diene Polymers - Natural and Synthetic Rubbers

- Dienes can form polymers including natural examples such as rubber which is formed from isoprene monomers.

1.8 Ultraviolet Spectroscopy

- When UV and visible light is absorbed, electrons are excited from a bonding or non-bonding orbital to a nearby anti-bonding orbital.
- Colored organic molecules all include extensive conjugated pi electron systems.
- UV absorbance is higher energy than visible light, allowing for excitation of electrons without the low energy pi-bonding to pi anti-bonding transitions available in highly conjugated molecules.
- Chromophores are molecules or structural features that absorb light in the UV-Visible range.

1.9 Interpreting Ultraviolet Spectra: The Effect of Conjugation

- Conjugated pi systems lowers the energy gap for π -π^* transitions causing the molecule to absorb light of a longer wavelength.
- Many molecules absorb in the UV spectrum. As the energy gap becomes smaller, these absorbances move into the visible spectrum, starting with violet light which makes the resulting molecules appear yellow.

1.10 Conjugation, Color, and the Chemistry of Vision

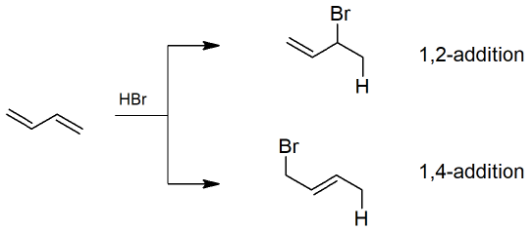
- Absorption of light causes chemical changes in the rods and cones in eyes leading to visual sensations.

Skills to Master

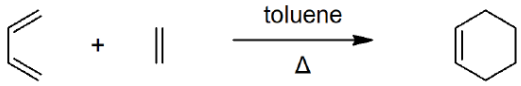
- Skill 1.1 Differentiate between conjugated and isolated dienes.
- Skill 1.2 Explain stability of conjugated dienes using Molecular Orbital Theory.
- Skill 1.3 Draw mechanisms for 1,2 and 1,4 addition to conjugated dienes.
- Skill 1.4 Predict kinetic and thermodynamic products of addition reactions to conjugated dienes.
- Skill 1.5 Explain kinetic and thermodynamic control of reactions.
- Skill 1.6 Identify dienes and dienophiles for Diels-Alder Cycloaddition reactions.
- Skill 1.7 Determine products of Diels-Alder Cycloaddition, including stereochemistry and endo/exo.
- Skill 1.8 Draw mechanisms for Diels-Alder Cycloaddition.
- Skill 1.9 Apply reactions of conjugated dienes to polymerization and natural rubber formation.
- Skill 1.10 Explain the electronic transitions that occur with absorption of UV-Visible light.
- Skill 1.11 Explain the effects of conjugation on wavelength of light absorbed in π -π* transitions.

Summary of Reactions

Electrophilic Addition



Diels−Alder Cycloaddition



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CHAPTER OVERVIEW

2: Benzene and Aromaticity

Learning Objectives

After you have completed Chapter 2, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. use the information presented in this chapter, along with material from earlier chapters, to solve problems, particularly road-map problems and those requiring an understanding of spectroscopy.
3. explain the concept of aromaticity and the stability of aromatic compounds.
4. define, and use in context, the key terms introduced.

In Chapter 1, we identified an aromatic compound as being a compound which contains a benzene ring (or phenyl group). It is now time to define aromaticity in a more sophisticated manner. In this chapter, we discuss the stability of benzene and other aromatic compounds, explaining it in terms of resonance and molecular orbital theory. You will study the nomenclature of aromatic compounds and the Hückel ($4n + 2$) rule for predicting aromaticity. The chapter concludes with a brief summary of the spectroscopic properties of arenes.

2.0: Introduction
2.1: Naming Aromatic Compounds
2.2: Acidity of Phenols
2.3: Basicity of Arylamines
2.4: Structure and Stability of Benzene
2.5: Aromaticity and the Hückel 4n + 2 Rule
2.6: Aromatic Ions
2.7: Aromatic Heterocycles
2.8: Polycyclic Aromatic Compounds
2.9: Reactions at the Benzylic Position
2.10: Spectroscopy of Aromatic Compounds
2.11: Additional Problems
2.S: Benzene and Aromaticity (Summary)

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2.0: Introduction

Objectives

After completing this section, you should be able to

1. explain what is meant by the term “aromatic compound.”
2. identify the aromatic portions present in naturally occurring compounds, given the necessary structures.

Key Terms

Make certain that you can define, and use in context, the key term below.

- aromatic

Study Notes

At this point in the course, we shall use the term *aromatic* to describe those compounds which contain a benzene ring. A broader definition of aromaticity will be given in Section 2.3.

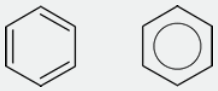


Figure 2.0.1: Two common ways of representing a benzene ring

The 100 Year Mystery of Benzene

It took humans over 100 years to determine and confirm the structure of benzene. Why did it take so long? Why was there such a curiosity? The 1:1 ratio of carbon to hydrogen in the empirical formula and low chemical reactivity of benzene were a paradox to chemists in the early 1800's.In 1825, Michael Faraday isolated an oily residue of gas lamps. Faraday called this liquid "bicarburet of hydrogen" and measured the boiling point to be 80°C. Additionally, Faraday determined the empirical formula to be CH. About nine years later, Eilhard Mitscherlich synthesized the same compound from benzoic acid and lime (CaO).

During the mid to late 1800's, several possible structures (shown below) were proposed for benzene.



It was not until the 1930's that Kekule's structure was confirmed by X-ray and electron diffraction. During the end of Kekule's career he revealed that the structure came to him in a vision after enjoying a glass or two of wine by the fire in his favorite chair. His inspiration for the structure of benzene was derived from an ouroboros in the flames.



Benzene, C_6H_6, is the simplest member of a large family of hydrocarbons, called aromatic hydrocarbons. These compounds contain ring structures and exhibit bonding that must be described using the resonance hybrid concept of valence bond theory or the delocalization concept of molecular orbital theory. (To review these concepts, refer to the earlier chapters on chemical bonding). The resonance structures for benzene, C_6H_6, are:

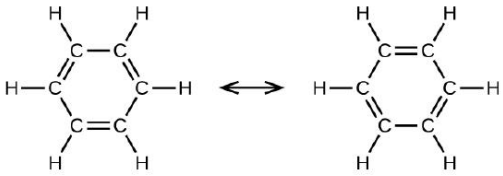


Figure 2.0.2: Kekulé's Model of Benzene.

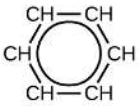
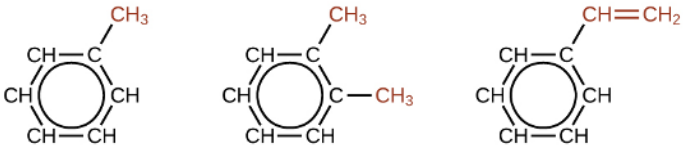


Figure 2.0.3: This condensed formula shows the unique bonding structure of Benzene.

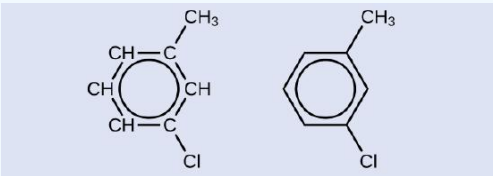
There are many derivatives of benzene. The hydrogen atoms can be replaced by many different substituents. Aromatic compounds more readily undergo substitution reactions than addition reactions; replacement of one of the hydrogen atoms with another substituent will leave the delocalized double bonds intact. The following are typical examples of substituted benzene derivatives:



Toluene and xylene are important solvents and raw materials in the chemical industry. Styrene is used to produce the polymer polystyrene.

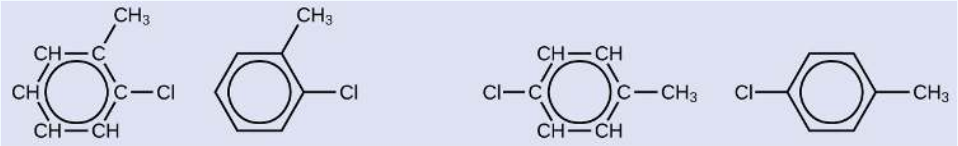
Structure of Aromatic Hydrocarbons

One possible isomer created by a substitution reaction that replaces a hydrogen atom attached to the aromatic ring of toluene with a chlorine atom is shown here. Draw two other possible isomers in which the chlorine atom replaces a different hydrogen atom attached to the aromatic ring:



Solution

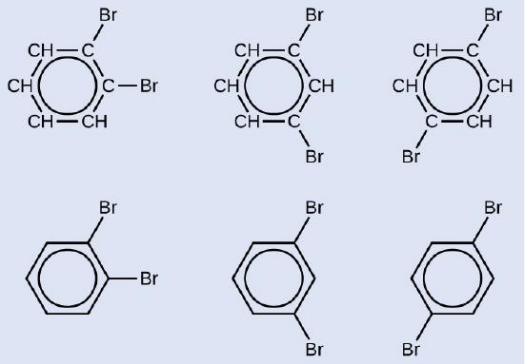
Since the six-carbon ring with alternating double bonds is necessary for the molecule to be classified as aromatic, appropriate isomers can be produced only by changing the positions of the chloro-substituent relative to the methyl-substituent:



Exercise 2.0.1

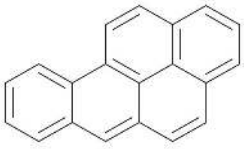
Draw three isomers of a six-membered aromatic ring compound substituted with two bromines.

Answer



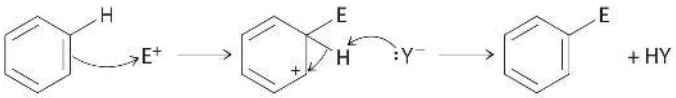
Most arenes that contain a single six-membered ring are volatile liquids, such as benzene and the xylenes, although some arenes with substituents on the ring are solids at room temperature. In the gas phase, the dipole moment of benzene is zero, but the presence of electronegative or electropositive substituents can result in a net dipole moment that increases intermolecular attractive forces and raises the melting and boiling points. For example, 1,4-dichlorobenzene, a compound used as an alternative to naphthalene in the production of mothballs, has a melting point of 52.7°C, which is considerably greater than the melting point of benzene (5.5°C).

Certain aromatic hydrocarbons, such as benzene and benz[a]pyrene, are potent liver toxins and carcinogens. In 1775, a British physician, Percival Pott, described the high incidence of cancer of the scrotum among small boys used as chimney sweeps and attributed it to their exposure to soot. His conclusions were correct: benz[a]pyrene, a component of chimney soot, charcoal-grilled meats, and cigarette smoke, was the first chemical carcinogen to be identified.



Benz[a]pyrene

Although arenes are usually drawn with three C=C bonds, benzene is about 150 kJ/mol more stable than would be expected if it contained three double bonds. This increased stability is due to the delocalization of the π electron density over all the atoms of the ring. Compared with alkenes, arenes are poor nucleophiles. Consequently, they do not undergo addition reactions like alkenes; instead, they undergo a variety of electrophilic aromatic substitution reactions that involve the replacement of –H on the arene by a group –E, such as $–NO_2$, $–SO_3H$, a halogen, or an alkyl group, in a two-step process. The first step involves addition of the electrophile (E) to the π system of benzene, forming a carbocation. In the second step, a proton is lost from the adjacent carbon on the ring:



The carbocation formed in the first step is stabilized by resonance.

> *Arenes undergo substitution reactions rather than elimination because of increased stability arising from delocalization of their π electron density.*

Many substituted arenes have potent biological activity. Some examples include common drugs and antibiotics such as aspirin and ibuprofen, illicit drugs such as amphetamines and peyote, the amino acid phenylalanine, and hormones such as adrenaline.

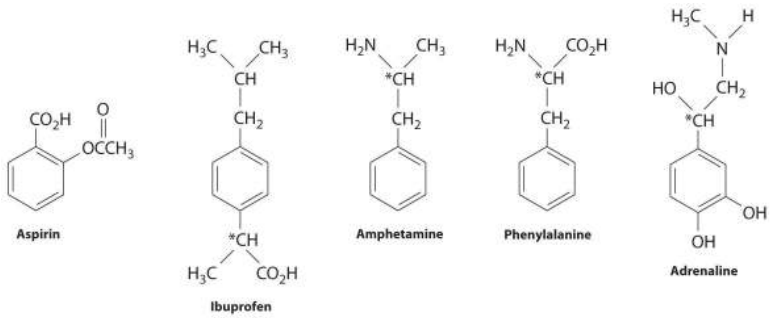


Figure 2.0.4*: Biologically Active Substituted Arenes*

Aspirin (antifever activity), ibuprofen (antifever and anti-inflammatory activity), and amphetamine (stimulant) have pharmacological effects. Phenylalanine is an amino acid. Adrenaline is a hormone that elicits the "fight or flight" response to stress. Chiral centers are indicated with an asterisk.

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2.1: Naming Aromatic Compounds

Objectives

After completing this section, you should be able to

1. draw the structure of each of the common aromatic compounds in Figure 3 (Common benzene derived compounds with various substituents), given their IUPAC-accepted trivial names.
2. write the IUPAC-accepted trivial name for each of the compounds in Figure 3, given the appropriate Kekulé, condensed or shorthand structure.
3. identify the ortho, meta and para positions in a monosubstituted benzene ring.
4. use the ortho/meta/para system to name simple disubstituted aromatic compounds.
5. draw the structure of a simple disubstituted aromatic compound, given its name according to the ortho/meta/para system.
6. provide the IUPAC name of a given aromatic compound containing any number of the following substituents: alkyl, alkenyl or alkynyl groups; halogens; nitro groups; carboxyl groups; amino groups; hydroxyl groups.
7. draw the structure of an aromatic compound containing any number of the substituents listed in Objective 6, above, given the IUPAC name.
8. provide the IUPAC name of a given aromatic compound in which the phenyl group is regarded as a substituent.
9. draw the Kekulé, condensed or shorthand structure of an aromatic compound in which the phenyl group is regarded as a substituent, given its IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- arene
- benzyl group
- phenyl group

Sources of Aromatic Compounds

Initially, aromatic compounds were isolated from coal tar. Coal tar, which is a distillate obtained when heating coal at 1000 ^{o}C in the absence of air, is a source of an amazing number of aromatic compounds. Many simple aromatic compounds, some of which includes nitrogen, oxygen, and sulfur, as well as hydrocarbons are obtained.

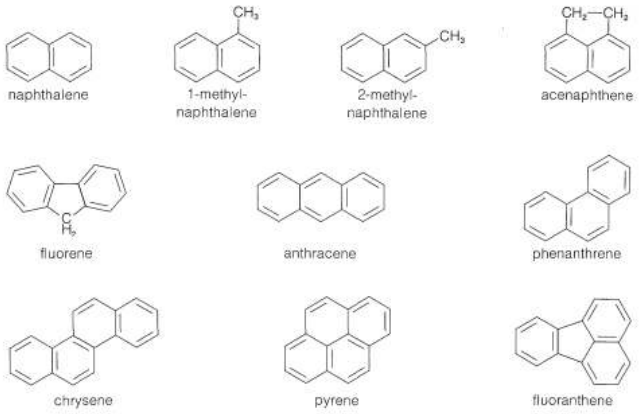
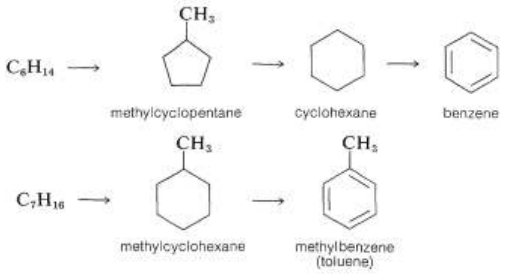


Figure 2.1.2: Some of the Aromatic Compounds Obtained from Coal Tar

Prior to World War II, coal tar was the only important source of aromatic hydrocarbons, but during the war the demand for benzene and toluene, a precursor to the explosive TNT, rose so sharply that other sources had to be found. Today, most of the benzene and almost all of the toluene produced in the United States are derived from petroleum. Although petroleum does contain some aromatic compound, it primarily made up of alkanes of various chain lengths. Aromatic compounds are synthesized from

petroleum the by a process referred to in the petroleum industry as catalytic re-forming or hydroforming. This involves heating a C6-C10 alkane fraction of petroleum with hydrogen in the presence of a catalyst to modify the molecular structure of its components. Some amazing transformations take place, and the C6-C7 alkanes can be converted to cycloalkanes, which, in turn, are converted to arenes. Benzene, and methylbenzene (toluene) are produced primarily in this way.



Nomenclature of Mono-Substituted Benzenes

Unlike aliphatic organics, nomenclature of benzene-derived compounds can be confusing because a single aromatic compound can have multiple possible names (such as common and systematic names) be associated with its structure. Common names are often used in the nomenclature of aromatic compounds. IUPAC still allows for some of the more widely used common name to be used. A partial list of these common name is shown in Figure 2.1.3 and there are numerous others. These common names take the place of the benzene base name. Methylbenzene is commonly known with the base name toluene, hydroxyphenol is known as phenol etc. It is very important to be able to identify these structures as they will be utilized in the nomenclature of more complex compounds.

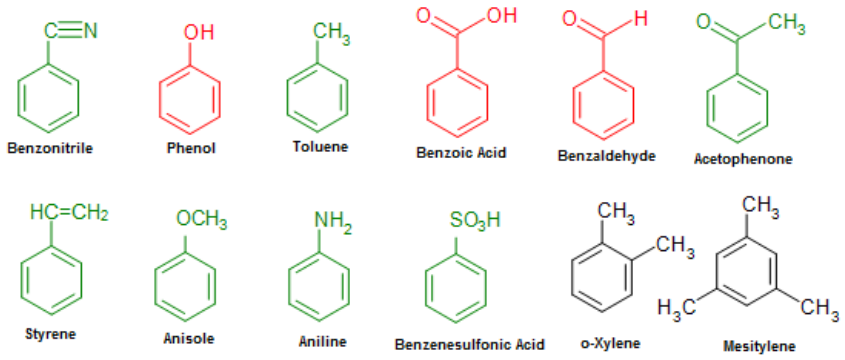
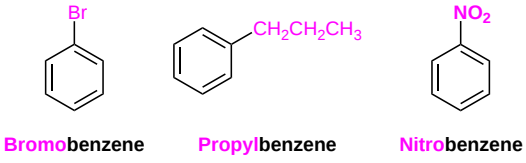


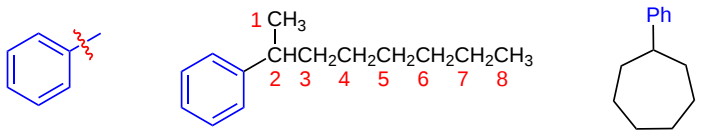
Figure 2.1.3: Common Names for Mono-Substituted Benzenes

Mono-substituted benzene rings, with a substituent not on the list above, are named with benzene being the parent name. These compounds are named as such: *Name of the substituent + Benzene.*



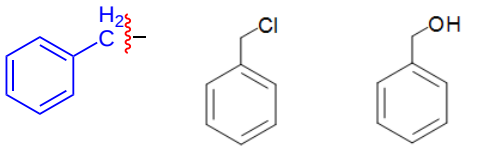
The use of Phenyl and Benzyl in Nomenclature

If the alkyl group attached to the benzene contains seven or more carbons the compounds is named as a phenyl substituted alkane. The name phenyl (C_6H_5-)is often abbreviated (Ph) and comes from the Greek word **pheno** which means "I bear light". This name commemorates the fact that benzene was first isolated by Michael Faraday in 1825 from the residue left in London street lamps which burned coal gas. If the alkyl substituent is smaller than the benzene ring (six or fewer carbons), the compound is named as an alkyl-substituted benzene following the rules listed above.



Phenyl group **2-Phenyloctane** **Phenylcycloheptane**

The benzyl group (abbv. Bn), similar to the phenyl group and can be written as $C_6H_5CH_2$-R, $PhCH_2$-R, or Bn-R. Nomenclature of benzyl group based compounds are very similar to the phenyl group compounds. For example, a chlorine attached to a benzyl group would simply be called benzyl chloride, whereas an OH group attached to a benzyl group would simply be called benzyl alcohol.

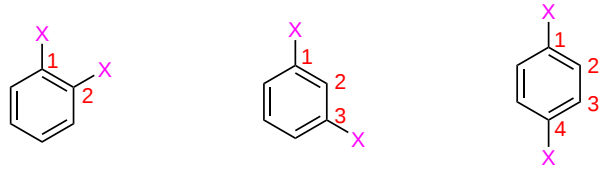


Benzyl group **Benzyl Chloride** **Benzyl Alcohol**

Nomenclature of Disubstituted Benzenes

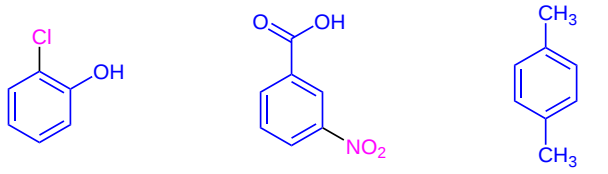
With disubstituted benzenes there are three distinct positional isomers which can occur and must be identified in the compounds name. Although numbering can be used to indicate the position of the two subsituents it is much more common for the compounds to be named using prefixes. These prefixes are italicized and are often abbreviated with a single letter. They are defined as the following:

- ***ortho*- *(o-):*** 1,2- (next to each other in a benzene ring)
- ***meta*- *(m-):*** 1,3- (separated by one carbon in a benzene ring)
- ***para*- *(p-):*** 1,4- (across from each other in a benzene ring)



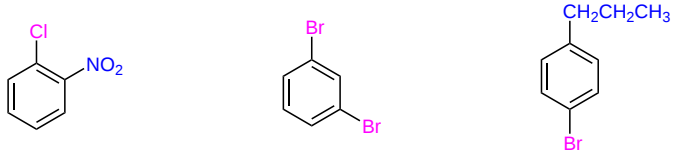
***ortho*-Disubstituted (1,2)** ***meta*-Disubstituted (1,3)** **para-Disubstituted (1,4)**

Figure 2.1.4: If any do appear then the compound is not named as a benzene but with a different parent name. These compounds are named as such: *Position prefix-Name of the substituent + Name of parent chain.*



ortho-Chlorophenol **meta-Nitrobenzoic acid** **para-Xylene**

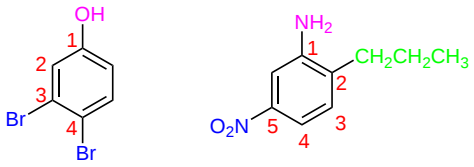
Figure 2.1.5: The compound is named as such: *Position prefix-Names of the substituents in alphabetical order + benzene.* Remember if two of the same substituent appears then the prefix *di-* is used before the substituent's name.



ortho-Chloronitrobenzene **meta-Dibromobenzene** **para-Bromopropylbenzene**

Nomenclature of Benzenes with Three or more Substituents

When three or more substituents are present the ortho, meta, para positional prefixes become inadequate and a numbering system for the ring must be applied. Here again it is important to check if any of the substituents are listed in **Figure** 2.1.2**.** If a substituent from **Figure** 2.1.2 is present it is given the parent name in the nomenclature. Also, this substituent is given position one in the numbering system. The other substituents are numbered such that they get the lowest possible sum. In the compound's name the subsituents are given their position number and listed alphabetically. Remember that di-, tri, tetra- prefixes are still used to indicate multiple of the same substituent being present but are ignored for alphabetical listing.



3,4-Dibromophenol **5-Nitro-2-propylaniline**

Figure 2.1.6, the benzene ring is name in the same fashion as cycloalkanes. The lowest possible number is given to the substituents present. This is best done by arbitrarily giving a substituent position one and then numbering the rest of the substituents. Then this process is repeated with the other substituents. Which ever iteration provides the lowest overall sum of numbers will be used in the compound's name. The substituents are assigned a location number, listed alphabetically and the suffix *-benzene* is added.

Study Notes

You should already know the names and structures of several hydrocarbons shown in Figure 2.2.1. A compound containing a benzene ring which has one or more alkyl substituents is called an arene.

A phenyl group consists of a benzene ring with one of its hydrogens removed.

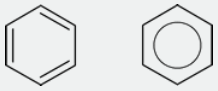
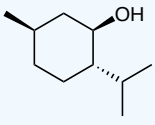


Figure 2.1.1: Two ways of representing a phenyl group

You should memorize the structures and formulas shown in Figure 3. You will meet these compounds frequently throughout the remainder of this course.

Note that the ortho/meta/para system cannot be used when more than two substituents are present in the benzene ring. The “numbering system” can be used instead of the ortho/meta/para system in most cases when only two substituents are present.

Exercise 2.1.1



(True/False) The following compound contains a benzene ring and thus is aromatic.

Answer

False, this compound does not contain a benzene ring in its structure.

Exercise 2.1.2

Benzene unusual stability is caused by how many conjugated pi bonds in its cyclic ring? ____

Answer

3

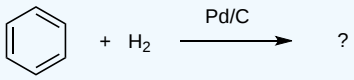
Exercise 2.1.3

Menthol, a topical analgesic used in many ointments for the relief of pain, releases a peppermint aroma upon exposure to the air. Based on this conclusion, can you imply that a benzene ring is present in its chemical structure? Why or why not?

Answer

No, a substance that is fragrant does not imply a benzene ring is in its structure. See camphor example (figure 1)

Exercise 2.1.4



Answer

No reaction, benzene requires a special catalyst to be hydrogenated due to its unusual stability given by its three conjugated pi bonds.

Exercise 2.1.5

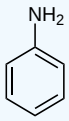
At normal conditions, benzene has ___ resonance structures.

Answer

2

Exercise 2.1.6

Which of the following name(s) is/are correct for the following compound?



a. nitrohydride benzene b. phenylamine c. phenylamide d. aniline e. nitrogenhydrogen benzene f. All of the above is correct

Answer

b, d

Exercise 2.1.7

Convert 1,4-dimethylbenzene into its common name.

Answer

p-Xylene

Exercise 2.1.8

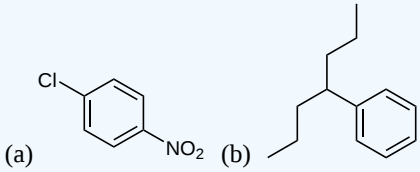
TNT's common name is: _____. Draw the Structure.

Answer

2,4,6-trinitrotoluene

Exercise 2.1.9

Name the following compounds:



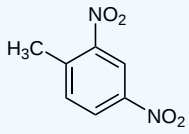
Answer

(a) p-chloronitrobenzene. (b)4-phenylheptane.

Exercise 2.1.10

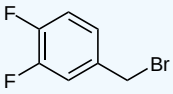
Draw the structure of 2,4-dinitrotoluene.

Answer



Example 2.1.11

Which of the following is the correct name for the following compound?



a. 3,4-difluorobenzyl bromide
b. 1,2-difluorobenzyl bromide
c. 4,5-difluorobenzyl bromide
d. 1,2-difluoroethyl bromide
e. 5,6-difluoroethyl bromide
f. 4,5-difluoroethyl bromide

Solution

a

Exercise 2.1.12

(True/False) Benzyl chloride can be abbreviated Bz-Cl.

Answer

False, the correct abbreviation for the benzyl group is Bn, not Bz. The correct abbreviation for Benzyl chloride is Bn-Cl.

Exercise 2.1.13

Benzoic Acid has what R group attached to its phenyl functional group?

Answer

COOH

Exercise 2.1.14

(True/False) A single aromatic compound can have multiple names indicating its structure.

Answer

True. TNT, for example, has the common name 2,4,6-trinitrotoluene and its systematic name is 2-methyl-1,3,5-trinitrobenzene.

Exercise 2.1.15

List the corresponding positions for the OMP system (o-, m-, p-).

Answer

Ortho - 1,2 ; Meta - 1,3 ; Para - 1,4

Exercise 2.1.16

A scientist has conducted an experiment on an unknown compound. He was able to determine that the unknown compound contains a cyclic ring in its structure as well as an alcohol (-OH) group attached to the ring. What is the unknown compound?

a. Cyclohexanol
b. Cyclicheptanol
c. Phenol
d. Methanol
e. Bleach
f. Cannot determine from the above information

Answer

The correct answer is f). We cannot determine what structure this is since the question does not tell us what kind of cyclic ring the -OH group is attached on. Just as cyclohexane can be cyclic, benzene and cycloheptane can also be cyclic.

Exercise 2.1.17

Which of the following statements is **false** for the compound, phenol?

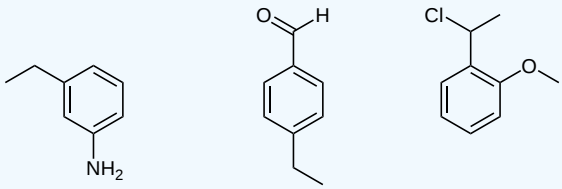
a. Phenol is a benzene derived compound.
b. Phenol can be made by attaching an -OH group to a phenyl group.
c. Phenol is highly toxic to the body even in small doses.
d. Phenol can be used as a catalyst in the hydrogenation of benzene into cyclohexane.
e. Phenol is used as an antiseptic in minute doses.
f. Phenol is amongst one of the three common names retained in the IUPAC nomenclature.

Answer

d

Exercise 2.1.18

State wither the following is para, meta, or ortho substituted.



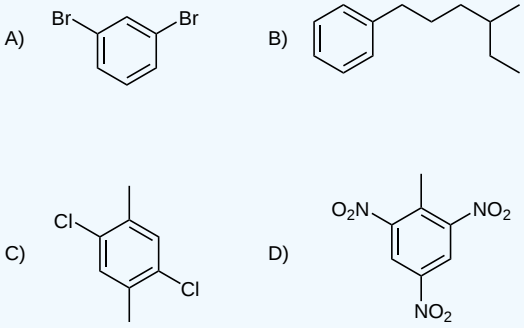
A B C

Answer

A – meta; B – para; C – ortho

Exercise 2.1.19

Name the following compounds.



Answer

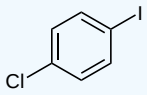
- a. 1,3-Dibromobenzene
- b. 1-phenyl-4-methylhexane
- c. 1,4-Dichloro-2,5-dimethylbenzene
- d. 2-methyl-1,3,5-trinitrobenzene. (Also known as trinitrotoluene, or TNT)

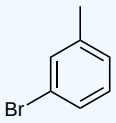
Exercise 2.1.20

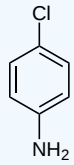
Draw the following structures

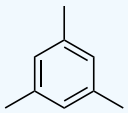
a. p-chloroiodobenzene
b. m-bromotoluene
c. p-chloroaniline
d. 1,3,5-trimethylbenzene

Answer

A) 

C) 

B) 

D) 

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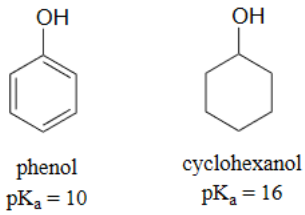
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2.2: Acidity of Phenols

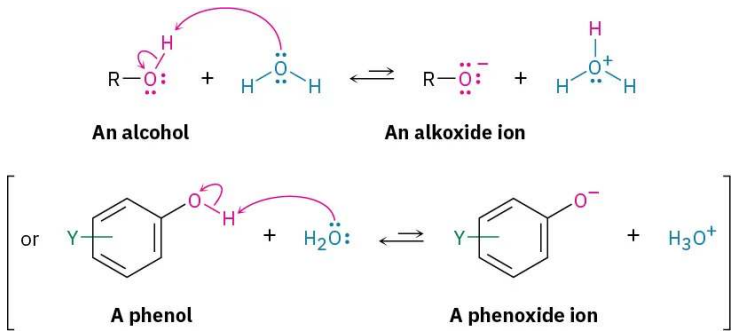
In aqueous solutions, phenols are weakly acidic and lower the pH of a solution. Sodium hydroxide can be used to fully deprotonate a phenol.

Phenols are about a million times more acidic than alcohols (Table 2.2.1). The reason for this increasing acidity is the stability of the conjugate base through resonance effects. An excellent example of this effect is seen in phenol, which is roughly a million times more acidic than cyclohexanol.

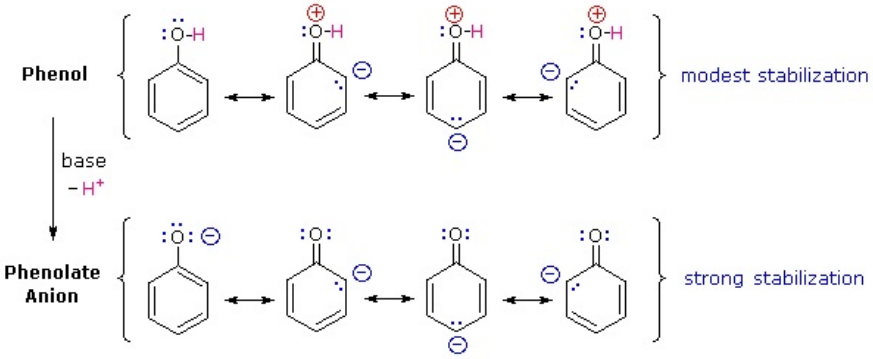


Acidity of Phenols

Compounds like alcohols and phenol, which contain an -OH group attached to a hydrocarbon, are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even if it is still a very weak acid. A hydrogen ion can break away from the -OH group and transfer to a base. For example, in a solution in water:

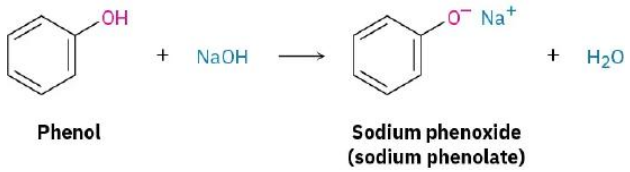


Phenols are more acidic than alcohols because the phenoxide anion is resonance-stabilized. The increased acidity of phenol is caused by the negative charge and a set of lone pair electrons from the phenoxide's oxygen atom being delocalized by resonance to three different carbons on the aromatic ring. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread throughout the whole ion, allowing it to be highly stabilized.



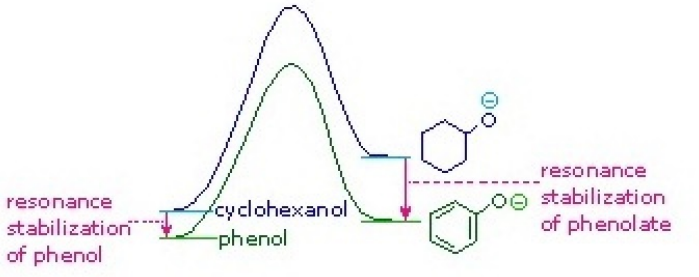
Phenol is acidic enough to be deprotonated by weaker bases, such as sodium hydroxide (NaOH), to form the phenoxide ion. They are therefore soluble in dilute aqueous NaOH and can often be separated from a mixture simply by basic extraction into aqueous

solution, followed by re-acidification.



Comparing the Acidity of Alcohols with Phenols

Why is phenol a much stronger acid than cyclohexanol? To answer this question, we must evaluate how an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. Formulas illustrating this electron delocalization will be displayed when the "Resonance Structures" button beneath the previous diagram is clicked. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.

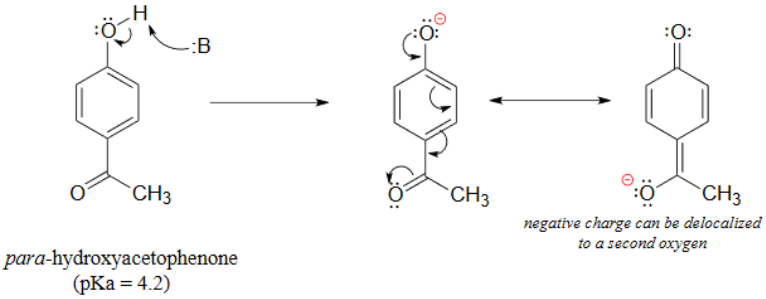


The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds is similar to that of water. An energy diagram showing the effect of resonance on cyclohexanol and phenol acidities is shown on the right. Since the resonance stabilization of the phenolate conjugate base is much greater than the stabilization of phenol itself, the acidity of phenol relative to cyclohexanol is increased. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.

Acidity of Substituted Phenols

Substituted phenols can be either more acidic or less acidic than phenol itself, depending on whether the substituent is electron-withdrawing or electron-donating. Phenols with an electron-donating substituent are less acidic because these substituents concentrate the charge.

Phenols with an electron-withdrawing substituent, such as a nitro or carbonyl on the aromatic ring, are more acidic because these substituents delocalize the negative charge. For the conjugate base of the phenol derivative below, an additional resonance contributor can be drawn in which the negative formal charge is placed on the carbonyl oxygen.



para-hydroxyacetophenone
(pKa = 4.2)

Now the negative charge on the conjugate base can be spread out over two oxygens (in addition to three aromatic carbons). The phenol acid therefore has a pK_a similar to that of a carboxylic acid, where the negative charge on the conjugate base is also delocalized to two oxygen atoms. The ketone group on the aromatic ring is acting as an electron-withdrawing group and 'pulling' electron density towards itself, through both inductive and resonance effects.

The acidifying effect of an electron-withdrawing substituent is particularly noticeable in phenols with a nitro group at the ortho or para position.

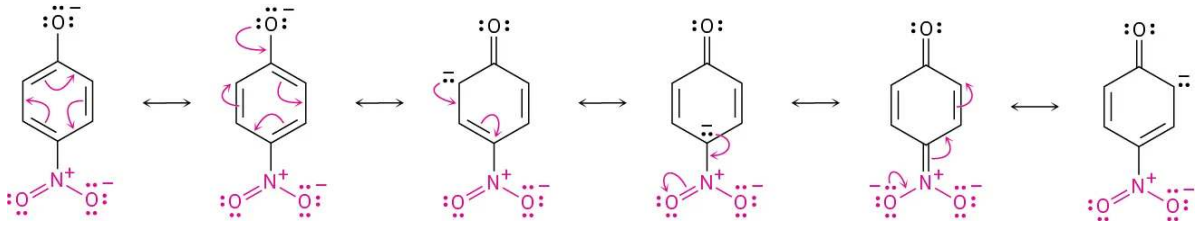
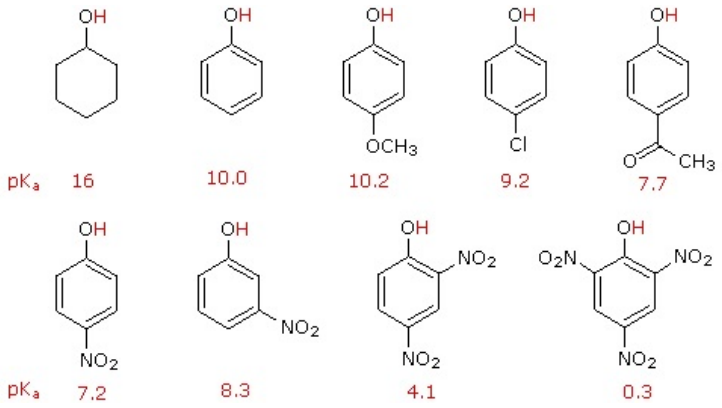


Figure 2.2.4: The resonance-stabilized phenoxide ion is more stable than expected because the negative charge and a set of lone pair electrons from the phenoxide's oxygen atom are delocalized by resonance to three different carbons on the aromatic ring and an additional oxygen on the nitro group, increasing the acidity of the phenol.

It is noteworthy that the influence of a nitro substituent is over ten times stronger in the *para*-location than it is meta, despite the fact that the latter position is closer to the hydroxyl group. This occurs since nitro groups at the meta position cannot accept the negative charge through resonance. Furthermore additional nitro groups have an additive influence if they are positioned *ortho* or *para* locations to the hydroxide. The trinitro compound shown at the lower right is a very strong acid called picric acid.

Lastly, if an electron donating group is attached to aromatic ring, as in *p*-methoxyphenol, the phenoxide ion is destabilized which causes a decrease in acidity in the corresponding phenol.



Worked Example 2.2.1: Predicting the Relative Acidity of a Substituted Phenol

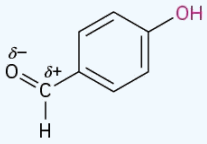
Is *p*-hydroxybenzaldehyde more acidic or less acidic than phenol?

Strategy

Identify the substituent on the aromatic ring, and decide whether it is electron-donating or electron-withdrawing. Electron-withdrawing substituents make the phenol more acidic by stabilizing the phenoxide anion, and electron-donating substituents make the phenol less acidic by destabilizing the anion.

Solution

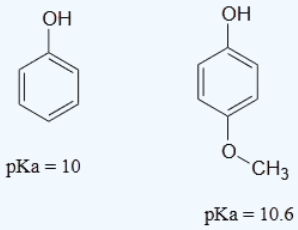
We saw in Section 16.4 that a carbonyl group is electron-withdrawing. Thus, *p*-hydroxybenzaldehyde is more acidic (pK_a = 7.9) than phenol (pK_a = 9.89).



***p*-Hydroxybenzaldehyde**
(pK_a = 7.9)

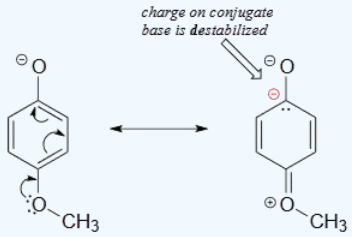
Worked Example 2.2.2

Using resonance structures, please explain why 4-methoxyphenol is less acidic than phenol.



Answer

The methoxy group is an electron-donating group by resonance. A resonance contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.



Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making the corresponding phenol less acidic.

Exercises

Exercise 2.2.1

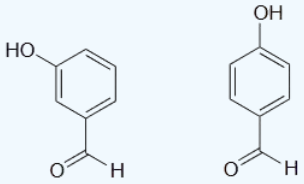
Predict which compound is more soluble in water and explain your reasoning: Phenol or cyclohexanol.

Answer

Phenol is more soluble in water than cyclohexanol because of the more polar character of its ring. Phenol is able to interact with water better than cyclohexanol due to the conjugated pi-system of electrons in its ring, which gives it a more ionic character.

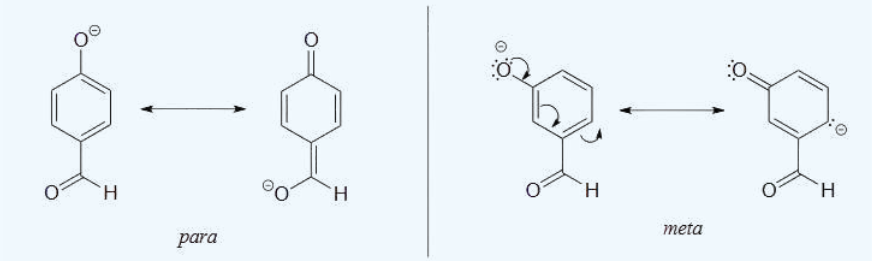
Exercise 2.2.2

The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



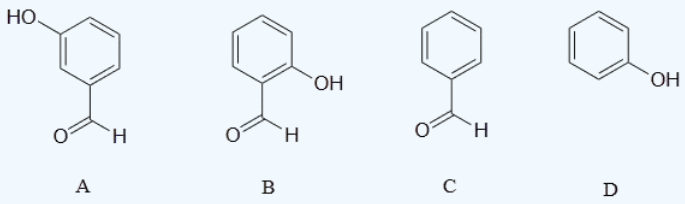
Answer

The para-substituted phenol is more acidic because the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. This is not possible when the aldehyde group is in the meta position.



Exercise 2.2.3

Rank the four compounds below from most acidic to least.



Answer

Compound B is the strongest acid due to electron-withdrawing resonance effects-the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. Compound A is the 2nd strongest acid -while the negative charge on the conjugate base cannot be delocalized to the aldehyde oxygen due to the *meta*-position, the aldehyde none the less has a stabilizing, electron-withdrawing inductive effect. Compound D is ranked #3 -it is phenol, and does not have any electron-withdrawing substituents on the ring as do B and A. Compound C is the least acidic -neither the phenyl group nor the aldehyde are even slightly acidic.

Exercise 2.2.4

Rank the following substances in order of increasing acidity:

a. $(CH_3)_2CHOH$, $HC{\equiv}CH$, $(CF_3)_2CHOH$, CH_3OH
b. Phenol, p-methylphenol, p-(trifluoromethyl)phenol
c. Benzyl alcohol, phenol, p-hydroxybenzoic acid

Answer

1. $HC{\equiv}CH < (CH_3)_2CHOH < CH_3OH < (CF_3)_2CHOH$
2. p-Methylphenol < Phenol < p-(Trifluoromethyl)phenol
3. Benzyl alcohol < Phenol < p-Hydroxybenzoic acid

? Exercise 2.2.5

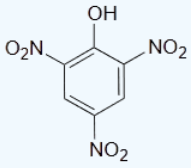
p-Nitrobenzyl alcohol is more acidic than benzyl alcohol, but *p*-methoxybenzyl alcohol is less acidic. Explain.

Answer

The electron-withdrawing nitro group stabilizes an alkoxide ion, but the electron-donating methoxyl group destabilizes the anion.

? Exercise 2.2.6

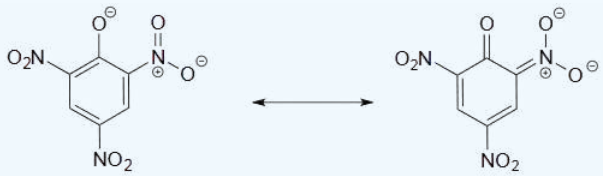
Use a resonance argument to explain why picric acid has such a low pKa.



picric acid
pKa = 0.25

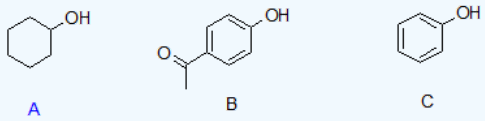
Answer

The negative charge on the conjugate base of picric acid can be delocalized to oxygen atoms on all threeof the nitro groups. One such resonance contributor is shown below. This extensive delocalization means that the conjugate base is very stable, and the conjugate acid is thus a very strong acid.



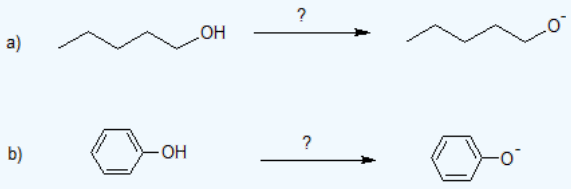
Exercise \(\PageIndex{7}\)

1. Arrange the following compounds in order of decreasing acidity when they are in solution.



A B C

2. Specify the base needed to deprotonate each reactant.



Answer

1. B > C > A
2. a) NaH or $NaNH_2$ b) NaOH, KOH, or LiOH

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2.3: Basicity of Arylamines

Objectives

After completing this section, you should be able to

1. use the concept of resonance to explain why arylamines are less basic than their aliphatic counterparts.
2. arrange a given series of arylamines in order of increasing or decreasing basicity.
3. discuss, in terms of inductive and resonance effects, why a given arylamine is more or less basic than aniline.

Study Notes

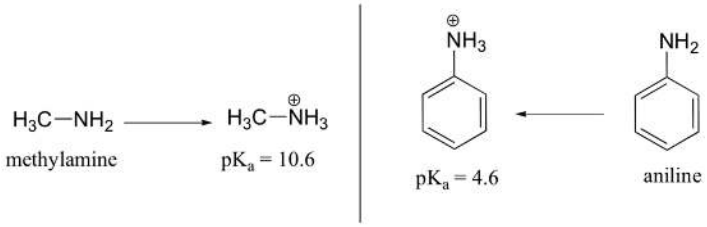
With reference to the discussion of base strength, the traditional explanation for the base-strengthening effect of electron-releasing (I) substituents is that such substituents help to stabilize the positive charge on an arylammonium ion more than they stabilize the unprotonated compound, thereby lowering $\Delta G°$.

The electron-withdrawing (i.e., deactivating) substituents decrease the stability of a positively charged arylammonium ion.

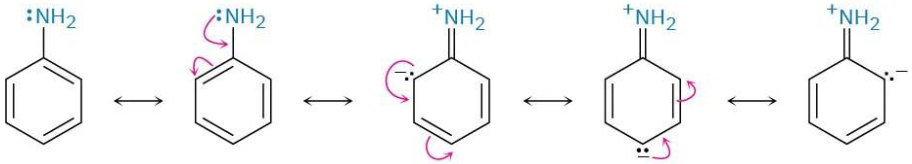
Note that the arylammonium ion derived from aniline, $PhNH_3^+$, is commonly referred to as the anilinium ion.

Basicity of Aniline

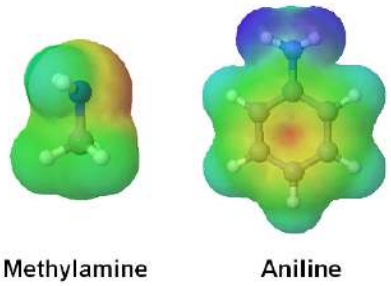
Aniline is substantially less basic than methylamine, as is evident by looking at the pK_a values for their respective ammonium conjugate acids (remember that the lower the pKa of the conjugate acid, the weaker the base).



This difference in basicity can be explained by the observation that, in aniline, the lone pair of electrons on the nitrogen are delocalized by the aromatic p system, making it less available for bonding to H^+ and thus less basic. The lone pair electrons of aniline are involved in four resonance forms, making them more stable and, therefore, less reactive relative to alkylamines.



The delocalization effect can be seen when viewing the electrostatic potential maps of aniline and methyl amine. The nitrogen of methyl amine has a significant amount of electron density on its nitrogen, shown as a red color, which accounts for its basicity compared to aniline. Meanwhile, the electron density of aniline's nitrogen is delocalized in the aromatic ring, making it less basic.



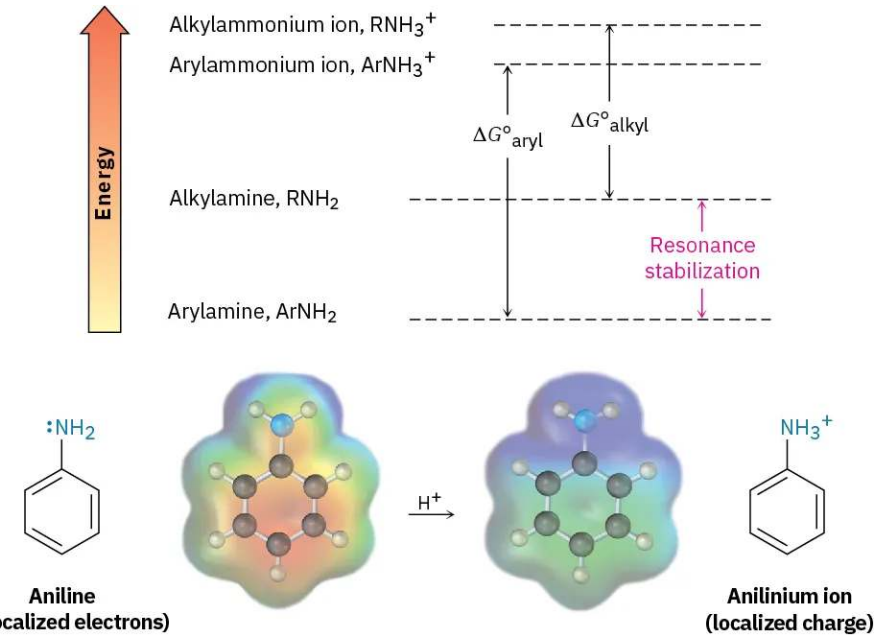
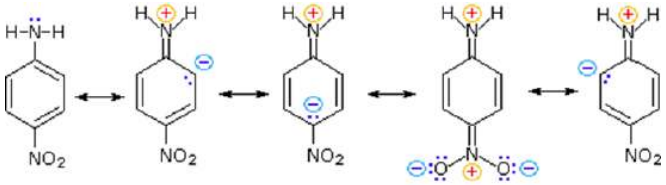


Figure 2.3.1: Arylamines have a larger positive $\Delta G°$ for protonation and are therefore less basic than alkylamines, primarily because of resonance stabilization of the ground state. Electrostatic potential maps show that lone-pair electron density is delocalized in the amine but the charge is localized in the corresponding ammonium ion.

Basicity of Substituted Arylamines

The addition of substituents onto the aromatic ring can make arylamines more or less basic. Substituents which are electron-withdrawing (-Cl, $-CF_3$, -CN, $-NO_2$) decrease the electron density in the aromatic ring and on the amine making the arylamine less basic. In particular, the nitro group of *para*-nitroaniline allows for an additional resonance form to be drawn, which further stabilizes the lone pair electrons from the nitrogen, making the substituted arylamine less basic than aniline. This effect is analogous to the one discussed for the acidity of substituted phenols in **Section 2.7.**



Reduced Basicity of *para*-Nitroaniline due to Electron Pair Delocalization

Substituents which are electron-donating ($-CH_3$, $-OCH_3$, $-NH_2$) increase the electron density in the aromatic ring and on the amine making the arylamine more basic. In the case of *para*-methoxyaniline, the lone pair on the methoxy group donates electron density to the aromatic system, and a resonance contributor can be drawn in which a negative charge is placed on the carbon adjacent to the nitrogen, which makes the substituted arylamine more basic than aniline.

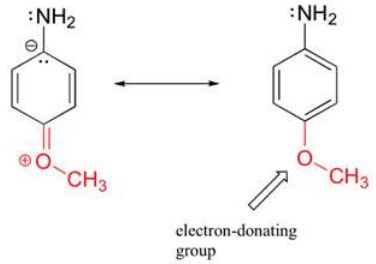


Figure 2.3.2:Increased Basicity of para-Methoxyaniline due to Electron-Donation

Table 2.3.2 considers only *p*-substituted anilines, but similar trends are observed for ortho and meta derivatives.

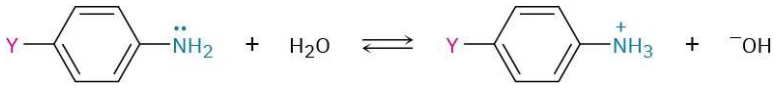
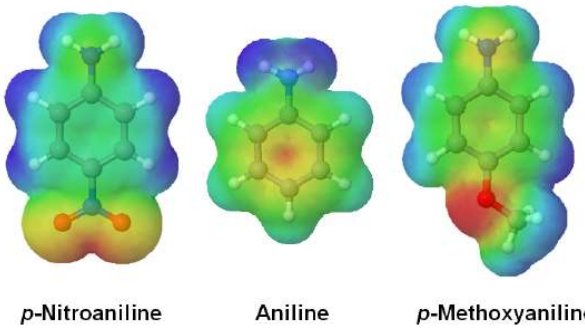


Table 2.3.2 Base Strength of Some *p*-Substituted Anilines

	Substituent, Y	pK_a	
Stronger base	–NH_2	6.15	Activating groups
	–OCH_3	5.34	
	–CH_3	5.08	
	–H	4.63	
	–Cl	3.98	Deactivating groups
	–Br	3.86	
	–CN	1.74	
Weaker base	–NO_2	1.00	

The shifting electron density of aniline, *p*-nitroaniline, and *p*-methoxyaniline are seen in their relative electrostatic potential maps. For *p*-Nitroaniline virtually all of the electron density, shown as a red/yellow color. is pulled toward the electron-withdrawing nitro group. In *p*-methoxyaninline the electron donating methoxy group donates electron density into the ring. The amine in p-methoxyaniline is shown to have more electron density, shown as a yellow color, when compared to the amine in aniline.



? Exercise 2.3.1

Using the knowledge of the electron donating or withdrawing effects of subsituents gained in Section 16.6, rank the following compound in order of decreasing basicity.

a. *p*-Nitroaniline, methyl p-aminobenzoate, *p*-chloroaniline
b. *p*-Bromoaniline, *p*-Aminobenzonitrile, *p*-ethylaniline
c. p-(Trifluoromethyl)aniline, *p*-methoxyaniline, *p*-methylaniline

Answers

a. *p*-Chloroaniline, methyl p-aminobenzoate, *p*-nitroaniline
b. *p*-Ethylaniline, *p*-Bromoaniline, *p*-aminobenzonitrile
c. *p*-Methoxyaniline, *p*-methylaniline, *p*-(trifluoromethyl)aniline

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2.4: Structure and Stability of Benzene

Objectives

After completing this section, you should be able to

1. compare the reactivity of a typical alkene with that of benzene.
2. Use the heat of hydrogenation data to show that benzene is more stable than might be expected for “cyclohexatriene.”
3. state the length of the carbon-carbon bonds in benzene, and compare this length with those of bonds found in other hydrocarbons.
4. describe the geometry of the benzene molecule.
5. describe the structure of benzene in terms of resonance.
6. describe the structure of benzene in terms of molecular orbital theory.
7. draw a molecular orbital diagram for benzene.

Key Terms

Make certain that you can define, and use in context, the key term below.

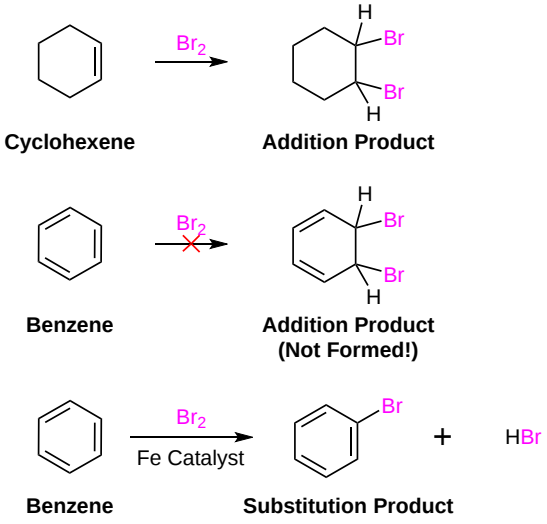
- degenerate

Study Notes

Note that the figure showing the molecular orbitals of benzene has two bonding (ψ_2 and ψ_3) and two anti-bonding (ψ_4* and ψ_5*) orbital pairs at the same energy levels. Orbitals with the same energy are described as degenerate orbitals.

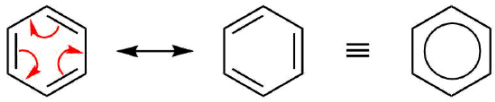
Structure of Benzene

When benzene (C_6H_6) was first discovered its low hydrogen to carbon ratio (1:1) led chemists to believe it contained double or triple bonds. Since double and triple bonds rapidly add bromine (Br_2), this reaction was applied to benzene. Surprisingly, benzene was entirely unreactive toward bromine. In addition, if benzene is forced to react with bromine through the addition of a catalyst, it undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. These experiments suggested that the six-carbon benzene core is unusually stable for chemical reactions.

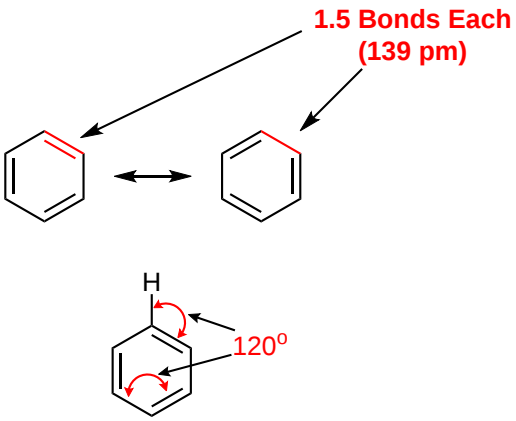


The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of benzene as a hexagonal, planar ring of carbons with alternating single and double bonds was adopted, and the exceptional chemical stability of

this system was attributed to special resonance stabilization of the conjugated cyclic triene. No single structure provides an accurate representation of benzene as it is a combination of two structurally and energetically equivalent resonance forms representing the continuous cyclic conjugation of the double bonds. In the past, the benzene resonance hybrid was represented by a hexagon with a circle in the center to represent the benzene's pi-electron delocalization. This method has largely been abandoned because it does not show the pi electrons contained in benzene. Currently, the structure of benzene is usually represented by drawing one resonance form with the understanding that it does not completely represent the true structure of benzene.



The six-membered ring in benzene is a perfect hexagon with all carbon-carbon bonds having an identical length of 139 pm[1]. The 139 pm bond length is roughly in between those of a C=C double bond (134 pm) and a C-C single (154 pm) which agrees with the benzene ring being a resonance hybrid made up of 1.5 C-C bonds. Each carbon in the benzene ring is sp^2 hybridized which makes all the C-C-C and H-C-C bond angles in benzene 120° and makes the overall molecule planar.



The High Stability of Benzene

In previous polyalkene, examples the electron delocalization described by resonance enhanced the stability of the molecule. However, benzene's stability goes beyond this. Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. The addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 118 kJ/mol. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a 1,3-cyclohexadiene to release 236 kJ/mol on complete hydrogenation, but the actual value is 230 kJ/mol, a bit less than twice that for cyclohexene because conjugated dienes are more stable than isolated dienes.

Carrying the process one step further, we might expect $\Delta H^\circ_{\text{hydrog}}$ for “cyclohexatriene” (benzene) to be a bit less than 3 × 118 = 354 kJ/mol, or three times the cyclohexene value. The actual value, however, is –206 kJ/mol, some 148 kJ/mol (35.4 kcal/mol) less than expected. Because of this difference in actual and expected energy released during hydrogenation, benzene must have 148 kJ/mol less energy to begin with. In other words, benzene is more stable than expected by 148 kJ/mol.

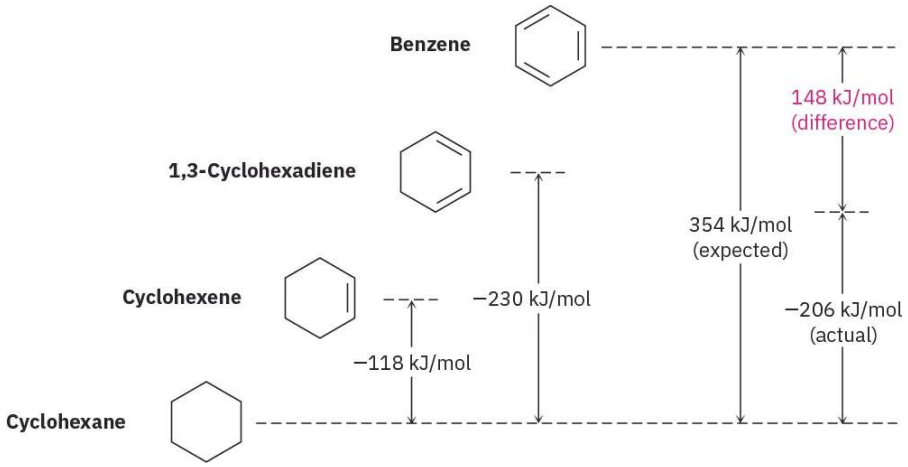


Figure 2.4.1: A comparison of the heats of hydrogenation for cyclohexene, 1,3-cyclohexadiene, and benzene. Benzene is 148 kJ/mol (35.4 kcal/mol) more stable than might be expected for "cyclohexatriene."

These **heats of hydrogenation** would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. **Benzene, however, is an extraordinary 36 kcal/mole more stable than expected**. This sort of stability enhancement is called **aromaticity** and molecules with aromaticity are called aromatic compounds. Benzene is the most common aromatic compound but there are many others. Aromatic stabilization explains benzene's lack of reactivity compared to typical alkenes.

Atomic Orbitals of Benzene

Also, each of benzene's six carbon atoms are sp^2 hybridized and have an unhybrized p orbital perpendicular to plane of the ring. Because each of the six carbon atoms and their corresponding p orbitals are equivalent, it is impossible for them to only overlap with one adjacent p orbital to create three defined double bonds. Instead each p orbital overlaps equally with both adjacent orbitals creating a cyclic overlap involving all six p orbitals. This allows the p orbitals to be delocalized in molecular orbitals that extend all the way around the ring allowing for more overlap than would be obtained from the linear 1,3,5-hexatriene equivalent.

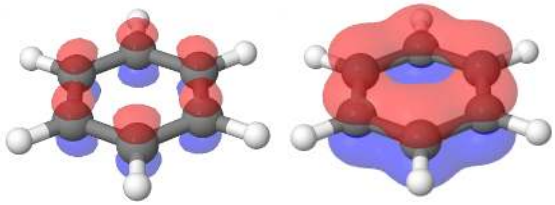


Figure 2.4.2: Each carbon in the benzene ring is sp2 hybrized with a p orbital perpendicular to the ring plane (Left) Being planar and cyclic allows benzene's p orbitals to undergo cyclic overlap (Right)

For this to happen, of course, the ring must be planar – otherwise the *p* orbitals couldn't overlap properly and benzene is known to be a flat molecule. An electrostatic potential map of benzene, shown below, shows that the pi electrons are evenly distributed around the ring and that every carbon equivalent.

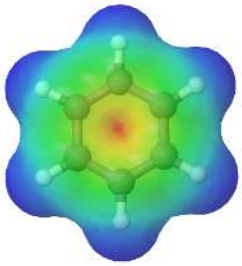


Figure 2.4.3: An electrostatic potential map of benzene

The Molecular Orbitals of Benzene

A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). The three low-energy molecular orbitals, denoted ψ_1, ψ_2, and ψ_3, are bonding combinations, and the three high-energy orbitals are antibonding.

When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals having the greatest overlap (e.g. ψ_1) being the lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6 electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or **closed shell**, that gives the benzene ring its thermodynamic and chemical stability, just as a filled valence shell octet confers stability on the inert gases.

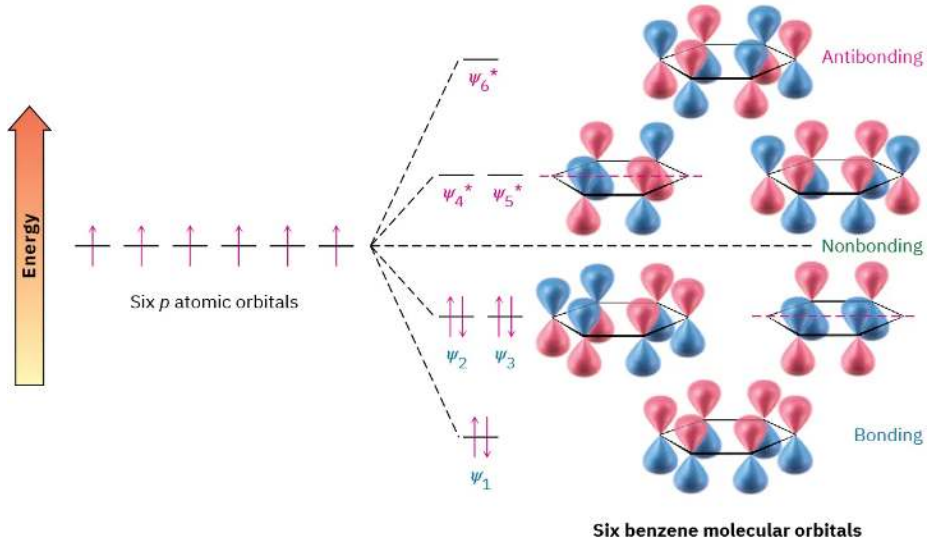
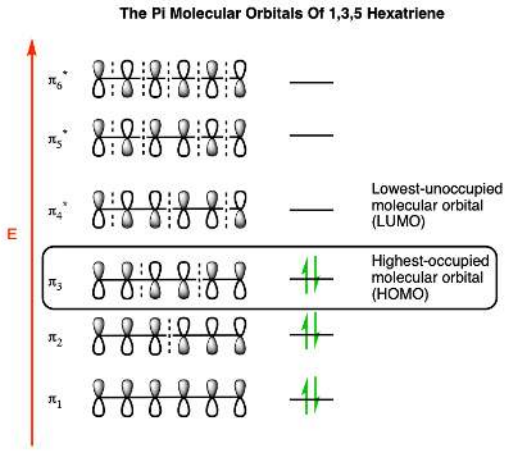


Figure 2.4.4: The six benzene π molecular orbitals. The bonding orbitals ψ_2 and ψ_3 have the same energy and are said to be degenerate, as are the antibonding orbitals ψ_4* and ψ_5*. The orbitals ψ_3 and ψ_4* have no π electron density on two carbons because of a node passing through these atoms.

Note that the two bonding orbitals ψ_2 and ψ_3 have the same energy, as do the two antibonding orbitals ψ_4* and ψ_5* . Such orbitals with the same energy are said to be degenerate. Note also that the two orbitals ψ_3 and ψ_4* have nodes passing through ring carbon atoms, thereby leaving no π electron density on these carbons. The six *p* electrons of benzene occupy the three bonding molecular orbitals and are delocalized over the entire conjugated system, leading to the observed 150 kJ/mol stabilization of benzene.

To better see source of the stabilizing aromaticity effect created by the cyclic p orbitals of benzene, the molecular orbitals of 1,3,5-hexatriene must be investigated. The molecule 1,3,5-hexatriene contains six p orbitals which all overlap but in a linear fashion. As with benzene, this overlap creates 3 stabilized bonding molecular which are completely filled with six p electron. As expected, the conjugation creates a marked increase of stability in 1,3,5-hexatriene but not as much as in benzene.





The main difference in stability can be seen when comparing the lowest energy molecular orbital of 1,3,5-hexatriene and benzene: pi_1. In pi_1 molecular orbital of 1,3,5-hexatriene there are 5 stabilizing bonding interactions where there are 6 stabilizing bonding interactions in the pi_1 of benzene. The sixth bonding interaction is made possible by benzene's p orbitals being in a ring. Because benzene's pi_1 molecular orbital has more stabilizing bonding interactions it is lower in energy than the pi_1 molecular orbital of 1,3,5-hexatriene. This gives benzene the additional aromatic stability not seen in the acyclic 1,3,5-hexatriene.

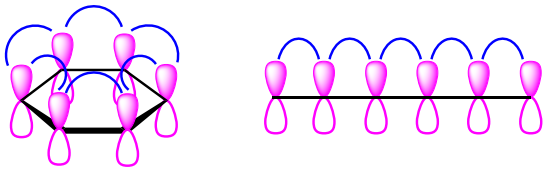
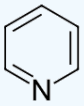


Figure 2.4.5: The pi_1 molecular orbital of benzene (Left) has 6 stabilizing bonding interaction where 1,3,5-hexatriene's (Right) only has 5.

Exercises

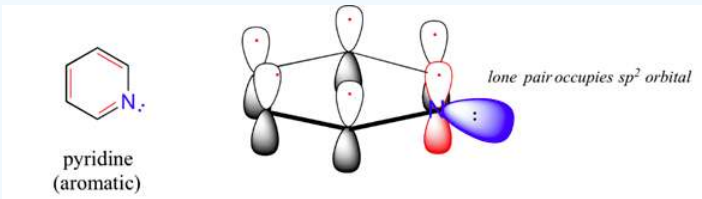
Exercise 2.4.1

The molecule, pyridine, is planar with bond angles of 120°. Pyridine has many other characteristics similar to benzene. Draw a diagram showing the p orbitals in pyridine and use it to explain its similarity to benzene.



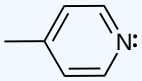
Answer

The nitrogen and each carbon in the pyridine ring is sp^2 hybridized. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair electrons. The unhybridized *p* orbital contains a single electron, which is part of the 6 pi-electron system delocalized around the ring. Pyridine is most likely aromatic which gives it its planar shape and 120° bond angles.

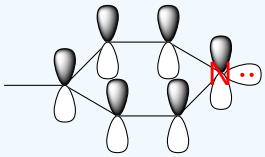


Exercise 2.4.2

The molecule shown, *p*-methylpyridine, has similar properties to benzene (flat, 120° bond angles). Draw the pi-orbitals for this compound.



Answer



References

https://royalsocietypublishing.org/d...rspa.1964.0092 "A crystallographic study of solid benzene by neutron diffraction" G.E. Bacon, N. A. Curry, and S.A. Wilson, 1964

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2.5: Aromaticity and the Hückel 4n + 2 Rule

Objectives

After completing this section, you should be able to

1. define aromaticity in terms of the Hückel 4*n* + 2 rule.
2. use the Hückel 4*n* + 2 rule to determine whether or not a given polyunsaturated cyclic hydrocarbon should exhibit aromatic properties.
3. describe the difference in properties between an aromatic hydrocarbon, such as benzene, and a non-aromatic polyunsaturated cyclic hydrocarbon, such as cyclobutadiene or cyclooctatetraene.
4. draw molecular orbital diagrams for aromatic species, such as benzene, the cyclopentadienyl anion and pyridine, and compare these diagrams with those obtained for non-aromatic species, such as cyclobutadiene and the cyclopentadienyl cation.

Study Notes

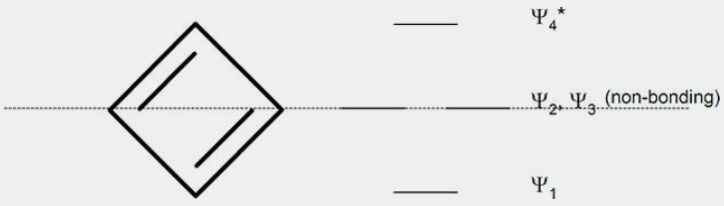
The following mnemonic device will help you establish the approximate energy levels for the molecular orbitals of various organic ring systems.

Whatever the size of the ring, place one point of the ring down to the bottom. The corners of the ring, where the carbons are located, will roughly approximate the location and pattern of the molecular orbital energy levels. Cut the ring exactly in half. The energy levels in the top half will be anti-bonding (Ψ^*) orbitals and those in the bottom will be bonding (Ψ) orbitals. If the carbons fall directly in the centre of the ring (e.g., four-membered rings) the energy levels there are non-bonding.

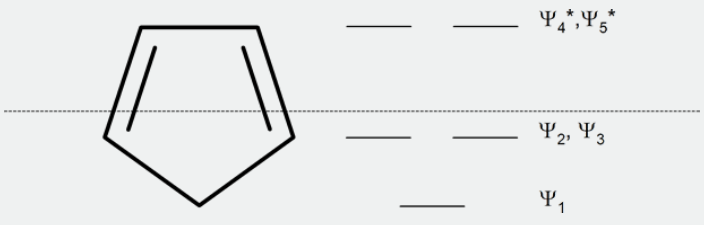
cyclopropenyl ring (three-membered ring)



cyclobutadienyl ring (four-membered ring)



cyclopentadienyl ring (five-membered ring)



In 1931, German chemist and physicist Erich Hückel proposed a theory to help determine if a planar ring molecule would have aromatic properties. His rule states that if a cyclic, planar molecule has $4n + 2\ \pi$ electrons, it is considered aromatic. This rule would come to be known as **Hückel's Rule**.

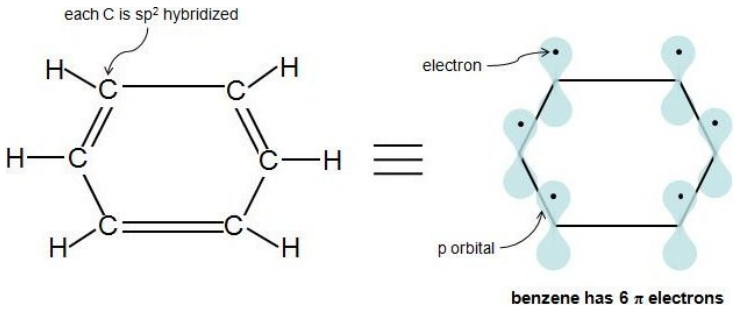
Four Criteria for Aromaticity

When deciding if a compound is aromatic, go through the following checklist. If the compound does not meet all the following criteria, it is likely not aromatic.

1. The molecule is cyclic (a ring of atoms)
2. The molecule is planar (all atoms in the molecule lie in the same plane)
3. The molecule is fully conjugated (p orbitals at every atom in the ring)
4. The molecule has 4n+2 π electrons (n=0 or any positive integer)

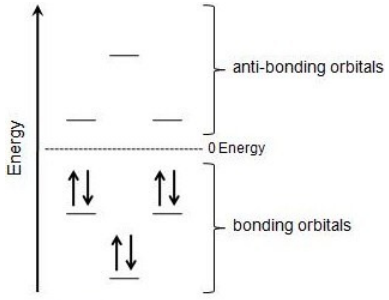
Counting pi Electrons

Perhaps the toughest part of Hückel's Rule is figuring out which electrons in the compound are actually π electrons. Once this is figured out, the rule is quite straightforward. Pi electrons lie in the p orbitals and sp^2 hybridized atoms have 1 of these p orbitals each. When looking at a C=C double bond we know that there is one sigma bond and one pi bond. The pi bond is formed by the overlap of 1 p orbital from each carbon in the double bond. Each p orbital contains one electron so when the two p orbitals overlap the two electrons become a pi bond and are thus called pi electrons. Because aromaticity deals directly with double bonds and conjugation it is simpler to just count the number pi electrons in a compound. Each double bond (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 π electrons.



Why 4n+2 π Electrons?

According to Hückel's Molecular Orbital Theory, a compound is particularly stable if all of its bonding molecular orbitals are filled with paired electrons. This is true of aromatic compounds, meaning they are quite stable. With aromatic compounds, 2 electrons fill the lowest energy molecular orbital, and 4 electrons fill each subsequent energy level (the number of subsequent energy levels is denoted by n), leaving all bonding orbitals filled and no anti-bonding orbitals occupied. This gives a total of 4n+2 π electrons. You can see how this works with the molecular orbital diagram for the aromatic compound, benzene, below. Benzene has 6 π electrons. Its first 2 π electrons fill the lowest energy orbital, and it has 4 π electrons remaining. These 4 fill in the orbitals of the succeeding energy level. Notice how all of its bonding orbitals are filled, but none of the anti-bonding orbitals have any electrons.



molecular orbital diagram for benzene

To apply the 4n+2 rule, first count the number of π electrons in the molecule. Then, set this number equal to 4n+2 and solve for n. If is 0 or any positive integer (1, 2, 3,...), the rule has been met. For example, benzene has six π electrons:

$$4n + 2 = 6 \quad (2.5.1)$$
$$4n = 4 \quad (2.5.2)$$
$$n = 1 \quad (2.5.3)$$

For benzene, we find that $n = 1$, which is a positive integer, so the rule is met.

With Hückel's theory we can assume that if a molecule meets the other criteria for aromaticity and also has 2, 6, 10, 14, 18 ect. pi electrons it will most likely be aromatic.

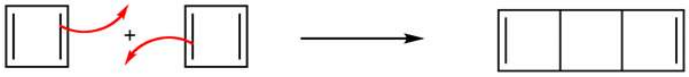
Antiaromaticity

More than 100 years ago, chemists recognized the possible existence of other conjugated cyclic polyalkenes, which at least superficially would be expected to have properties like benzene. The most interesting of these are cyclobutadiene, whose shape and alignment of p orbitals suggested it should have substantial electron-delocalization energies.



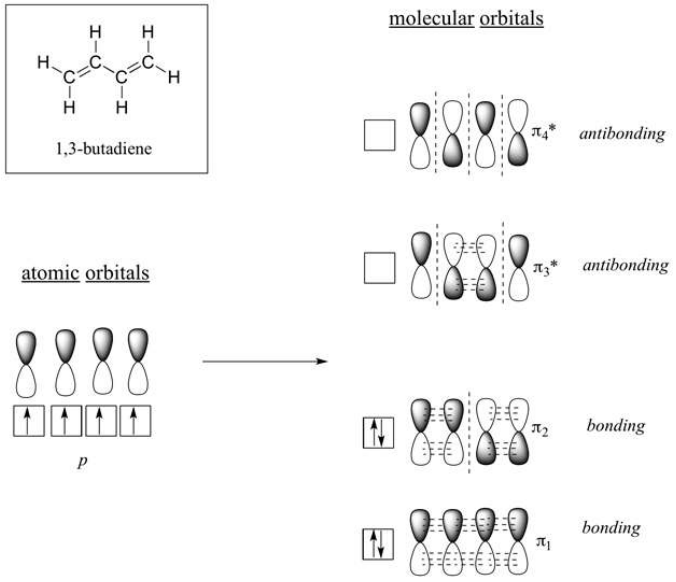
Cyclobutadiene

However, cyclobutadiene was found to be an extremely unstable molecules. In fact, cyclobutadiene is even more reactive than most alkenes. The synthesis of cyclobutadiene eluded chemists for almost 100 years. As more work was done, it became increasingly clear that the molecule, when formed in reactions, was immediately converted to something else. Finally, cyclobutadiene was captured in an essentially rigid matrix of argon at 8K. On warming to even 35K , it dimerizes through a Diels Alder reaction to yield a tricyclicdiene.



Due to the square ring, cyclobutadiene was expected to have some degree of destabilization associated with ring strain. However, estimations of the strain energies, though substantial, did not account for cyclobutadiene's high degree of instability. Also, why was it not being stabilized through cyclic conjugation in the same way as benzene. The answer can be seen in the molecular orbitals.

We considering the molecular orbitals diagram of the analogous 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two antibonding pi* orbitals. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.

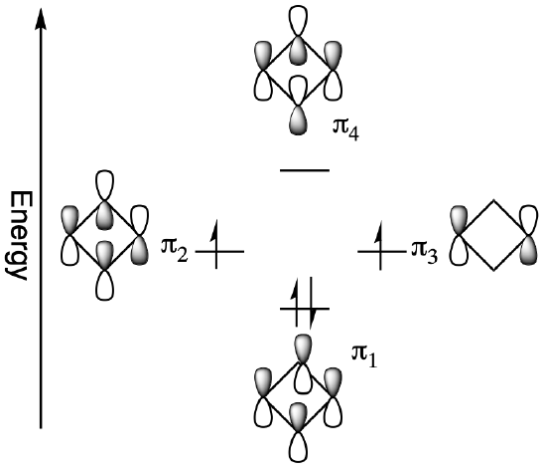


Cyclobutadiene

However, when placed into a ring the molecular orbitals undergo a significant change. The four p orbitals of cyclobutadiene combine to form the following 4 molecular orbitals:

- a bonding molecular orbital which is lower in energy than the atomic orbitals
- two degenerate non-bonding molecular orbitals which are of equivalent energy to the atomic orbitals
- one antibonding molecular orbital which is higher in energy

The non-bonding orbitals represent that there is no direct interaction between adjacent atoms. When adding cyclobutadiene's 4 pi electrons to the molecular orbital diagram, the bonding orbital is filled and both non-bonding orbitals are singly occupied. If cyclobutadiene's double bonds were delocalized, all the pi electrons would be in low energy bonding orbitals. However, only two of the pi electrons are in bonding orbitals; the other two are non-bonding. In addition, the molecular orbital diagram shows that two of the electrons are unpaired, a situation called a triplet state, which usually makes organic molecules very reactive. For cyclobutadiene cyclic conjugation has made the molecule less stable. This unexpected instability in 4n π-electron cyclic conjugated compounds is termed **antiaromaticity** and the compounds are called antiaromatic.



Antiaromaticity gives cyclobutadiene some interesting structural features. Cyclobutadiene's single and double bonds have different bond lengths, 158 pm and 135 pm respectively which give it a rectangular shape. If the double bonds were conjugated, there would only be one average bond length, like benzene, and shape would be square. In fact, cyclobutadiene's double bonds are not conjugated but locked into position.

Cyclooctatetraene

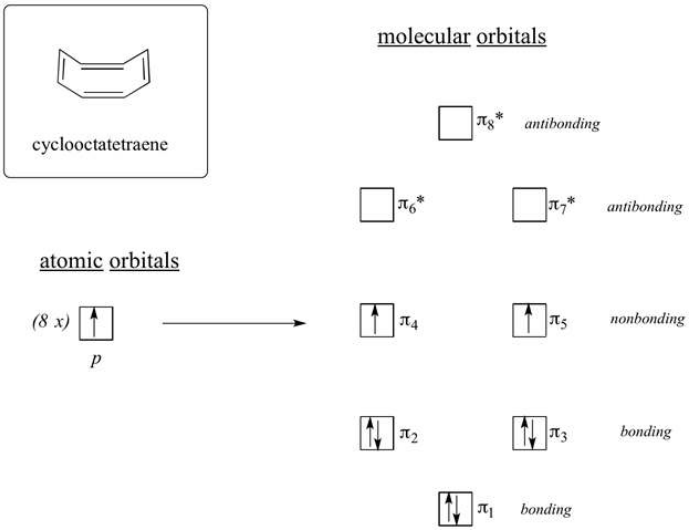
Just like 4n + 2 rule with aromaticity, compounds which are flat, cyclic, have a p orbital at every member of the ring, and 4n pi electrons should be antiaromatic. Another potentially antiaromatic molecule is 1,3,5,7-cyclooctatetraene.

Cyclooctatetraene was first synthesized in 1911 by a German chemist, R. Willstatter (Nobel Prize 1915), who reported an extraordinary thirteen-step synthesis of cyclooctatetraene from a rare alkaloid called pseudopelletierine isolated from the bark of pomegranate trees. However, during the Second World War, the German chemist W. Reppe found that cyclooctatetraene can be made in reasonable yields by the tetramerization of ethyne under the influence of a nickel cyanide catalyst:



If cyclooctatetraene was flat it would have all the requirements to be antiaromatic. It is cyclic, has a p orbital in every member of the ring, and has 8 pi electrons. When looking at the molecular orbital diagram of cyclooctatetraene we see it shares certain characteristics in common with cyclobutadiene. Two of the molecular orbitals are degenerate non-bonding orbitals. When the

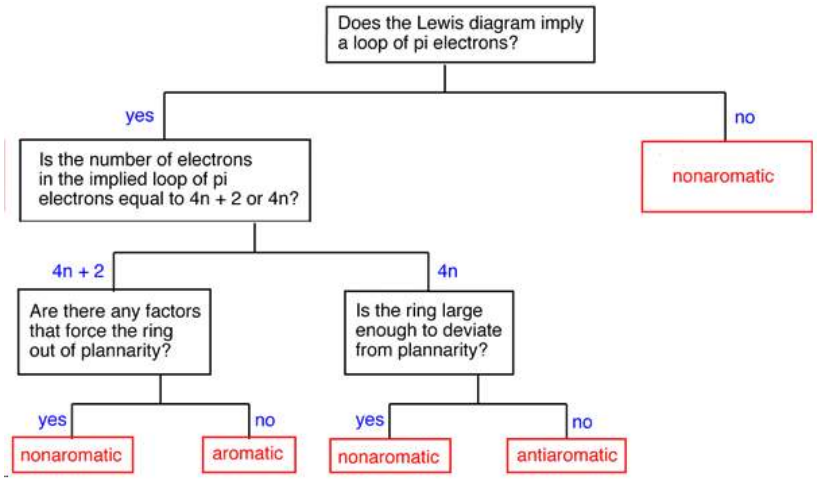
molecular orbitals are fill with cyclooctatetraene's 8 pi electrons the last two electrons are unpaired in the two nonbonding orbitals creating a triplet state. Based off the molecular orbital diagram cyclooctatetraene should be antiaromatic.



However, cyclooctatetraene is easily prepared and relatively stable. Also, it undergoes addition reactions typical of alkenes. In reality, cyclooctatetraene is not flat but has a tub-like shape. By assuming this shape, the p orbtials between double bond are out of alignment for overlap. Because the double bonds are not conjugated, cyclooctatetraene escapes the destabilizing effects of antiaromaticity. This makes its its pi bonds react like 'normal' alkenes. Because cyclooctatetraene is not flat nor conjugated it is properly defined as non-aromatic. In general, if an antiaromatic compound has the ability to form a non-planar shape it will do so to avoid destabilization by becoming non-aromatic.

Determining if a Compound is Aromatic, Antiaromatic, or Nonaromatic

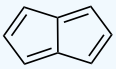
To make this determination it is important to first as if the compound has the possibility of cyclic conjugation. This requires that the compound be cyclic and have a p orbital at every atom in the ring. If the compound does not have both of these criteria it cannot be aromatic or antiaromatic and must therefore be nonaromatic. Next the number of pi electrons in the ring is determined to see if it follows the count of aromaticity (4n + 2) or antiaromaticity (4n). Before making the final determination, it is vital to know the actual geometry of the molecule. Despite the number of pi electrons, a compound cannot be aromatic or antiaromatic if its geometry is not planar to allow for p orbital overlap.



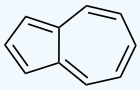
Example 2.5.1



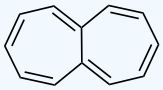
Cyclopentadiene (planar)
4 p Electrons
Nonaromatic



Pentalene (planar)
8 p Electrons
Antiaromatic



Azulene (planar)
10 p Electrons
Aromatic



Heptalene (planar)
12 p Electrons
Antiaromatic

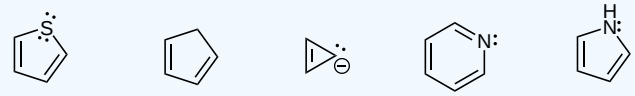
A Common Misconception

A very common misconception is that hybridization can be used to predict the geometry, or that hybridization somehow involves an energy cost associated with 'promoting' electrons into the hybrid orbitals. **This is entirely wrong.** Hybridization is always determined by geometry. You can only assign hybridization states to an atom if you already know its geometry, based on some experimental or theoretical evidence. The geometry of the oxygen in furan is trigonal planar and therefore the hybridization must be sp^2.

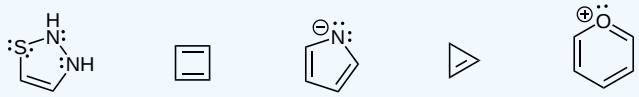
The *specific* rule is that if you have an sp^2 conjugated system, the lone pair will be involved ***if it makes the system more stable.*** In this case, conferring Hückel 4n+2 aromaticity. For furan with *two* lone pairs on the oxygen atom, if we count electrons from the carbon atoms, we have 4 (one per carbon). So adding two electrons from one of the lone pairs will give 6 = 4(1)+2, so the Hückel rule is applicable, and furan is aromatic.

Exercise 2.5.1

Using the criteria for aromaticity, determine if the following molecules are aromatic:



a) b) c) d) e)



f) g) h) i) j)

Answer

- a) Aromatic - only 1 of S's lone pairs counts as π electrons, so there are 6 π electrons, n=1
- b) Not aromatic - not fully conjugated, top C is sp^3 hybridized
- c) Not aromatic - top C is sp^2 hybridized, but there are 4 π electrons, n=1/2
- d) Aromatic - N is using its 1 p orbital for the electrons in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1
- e) Aromatic - there are 6 π electrons, n=1
- f) Not aromatic - all atoms are sp^2 hybridized, but only 1 of S's lone pairs counts as π electrons, so there 8 π electrons, n=1.5
- g) Not aromatic - there are 4 π electrons, n=1/2
- h) Aromatic - only 1 of N's lone pairs counts as π electrons, so there are 6 π electrons, n=1
- i) Not aromatic - not fully conjugated, top C is sp^3 hybridized
- j) Aromatic - O is using its 1 p orbital for the elections in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1

Exercise 2.5.2

To be aromatic, a molecule must be planar conjugated, and obey the 4n+2 rule. The following is the following molecule aromatic?



Answer

No, it is not. It does not obey the 4n+2 rule. Also, it is not planar.

References

1. Vollhardt, Peter, and Neil E. Schore. "Organic Chemistry: Structure and Function". 5th ed. New York: W. H. Freeman & Company, 2007.
2. Berson, Jerome. "Chemical Creativity: Ideas from the Work of Woodward", Hückel, Meerwein, and Others. New York: Wiley-VCH, 1999.
3. Badger, G.M. "Aromatic Character and Aromaticity". London, England: Cambridge University Press, 1969.
4. Lewis, David and David Peters. "Facts and Theories of Aromaticity". London, England: Macmillan Press, 1975.

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2.6: Aromatic Ions

Objectives

After completing this section, you should be able to

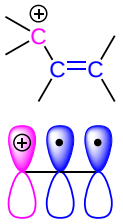
1. use the Hückel 4*n* + 2 rule to explain the stability of the cyclopentadienyl anion, the cycloheptatrienyl cation and similar species.
2. use the Hückel 4*n* + 2 rule to determine whether or not a given unsaturated cyclic hydrocarbon anion or cation is aromatic.
3. draw the resonance contributors for the cyclopentadienyl anion, cation and radical, and similar species.

Aromatic Ions

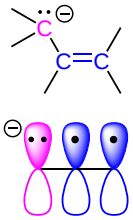
As previously, noted a ring must be fully conjugated to have the potential to be aromatic. This means that every atom in the ring must have a *p* orbital, which can overlap with adjacent *p* orbitals. Until now, the atoms providing the *p* orbitals have been neutral *sp2* hybridized carbons. However, it is also possible for *sp2* hybridized carbons to have a charge. There are several examples of cationic and anionic compounds with unexpected stabilities that suggest that they are aromatic. It is important to understand how charged carbons in these compounds will affect the determination of aromaticity.

There are two main situations which need to be considered: The conjugation of a carbocation and the conjugation of a carbanion. A carbocation carbon is surrounded by three electron groups giving it sp^2 hybridization. The remaining unhybridized *p* orbital holds the carbocation's positive charge and is vacant of pi electrons. Although a carbocation is capable of extending conjugation it does not add to the compound's pi electron count.

A carbanion carbon is surrounded by four electron groups and would normally be sp^3 hybridized. However, to obtain the stabilizing effects of conjugation, carbanion carbons can becomes sp^2 hybridized, putting the set of lone pair electrons into the unhybridized *p* orbital. Because the carbanion's *p* orbital contains two electrons in the form of a set of lone pair electrons, it increases a compound's pi electron count by 2.



2 p Electrons Total
The carbocation adds
0 p Electrons



4 p Electrons Total
The carbanion adds
2 p Electrons

Cyclopentadiene Ion

One of the most well know examples of an aromatic ion is the 1,3-cyclopentadiene ion. 1,3-Cyclopentadiene is nonaromatic due to the presence of an intervening sp^3 hybridized -CH_2- carbon atom which prevents pi electrons from delocalizing about the entire ring. Also, it only has 4 pi electrons which does not follow Hückel's 4n + 2 rule. However, if a proton is removed form the CH_2 group to form the cyclopentadienyl anion, the carbon atom becomes sp^2 hybridized and the two electrons of the resulting lone pair occupy the newly produced *p* orbital. This increases the number of pi electrons in the cyclopentadienyl anion to 6 which follows the 4n +2 rule. Moreover, this new *p* orbital overlaps with the *p* orbitals already present allowing for cyclic delocalization of pi electrons about the entire ring.

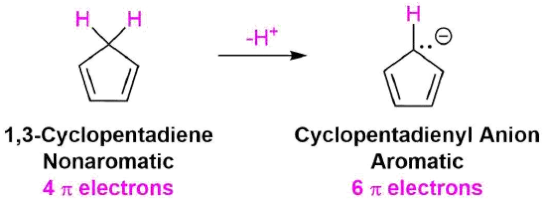
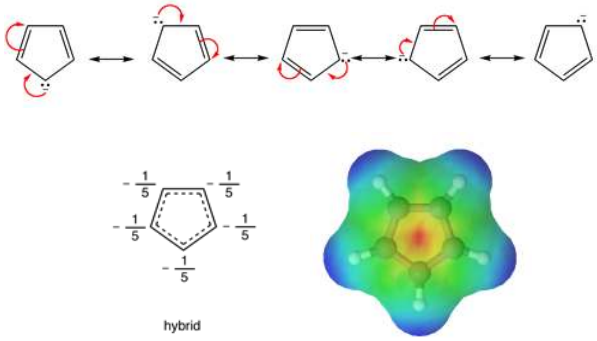
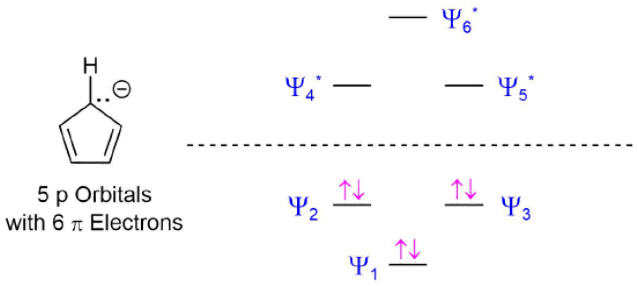


Figure 2.6.1: The aromatic six-π-electron cyclopentadienyl anion. The anion can be formed by removing a hydrogen ion (H^+) from the CH_2 group of 1,3-cyclopentadiene.

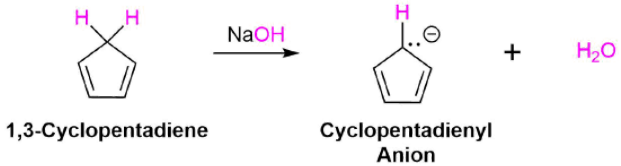
The lone pair electrons and the negative charge are conjugated about the entire ring making each carbon in the cyclopentadienyl anion equivalent with 1/5 the negative charge. The resonance hybrid can be shown by drawing a series of five resonance form. Also, the electrostatic potential map of the cyclopentadienyl anion show the negative charge, seen in red/yellow is distributed over the entire ring. The fact that the red/yellow color is held in the center of the ring indicates that the extra electrons of the ion are involved in the aromatic p-electron system.



The reason why the 4n +2 rule still works for a 5 p orbital ring system can be seen by looking the molecular orbital diagram of the cyclopentadienyl anion. As discussed in **Section 15.3**, the molecular orbital diagram of a 5 p orbital system is made up of 3 bonding MO's and 2 antibonding MO's. The 6 pi electrons gained by forming an anion is enough to completely fill the bonding MO's in the diagram giving the cyclopentadienyl anion aromaticity.



One of the effects of the aromaticity of the cyclopentadienyl anion is that the acidity of 1,3-cyclopentadiene is unusually strong. As previously discussed, stabilizing the conjugate base increases the acidity of the corresponding acid. In this case, the conjugate base of 1,3-cyclopentadiene, the cyclopentadienyl anion, is stabilized through aromaticity. This makes 1,3-cyclopentadiene one of the most acidic hydrocarbons known with a pK_a of 16. This is almost 10^{30} times more acidic than cyclopentane. Because of its acidity, cyclopentadiene can be deprotonated by moderately strong bases such as NaOH.



Tropylium ion

The molecule 1,3,5-cycloheptatriene has six pi electrons but is nonaromatic due the presence of an sp^3 hybridized -CH_2- group which prevents cyclic delocalization. When 1,3,5-cycloheptatriene is reacted with a reagent that can remove a hydride ion ($H:^-$), the 1,3,5-cycloheptatrienyl cation, which is commonly known as the tropylium cation, is formed with unexpected ease. Despite the presence of an electron deficient carbocation, the tropylium cation, is unusually stable and can be isolated as a salt.

Removal of a hydride from the -CH_2- group in 1,3,5-cycloheptatriene creates an sp^2 hybridized carbocation with a vacant *p* orbital. The new *p* orbital allows for cyclic conjugation to occur among the seven *p* orbitals in the tropylium cation. The vacant *p* orbital does not change the pi electron count so the tropylium cation has 6 pi electrons which obeys the 4n + 2 rule for aromaticity.

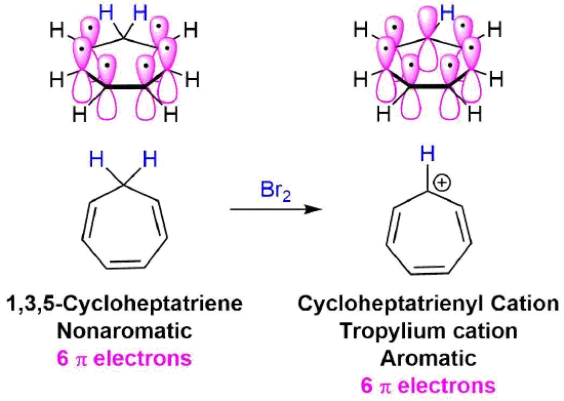
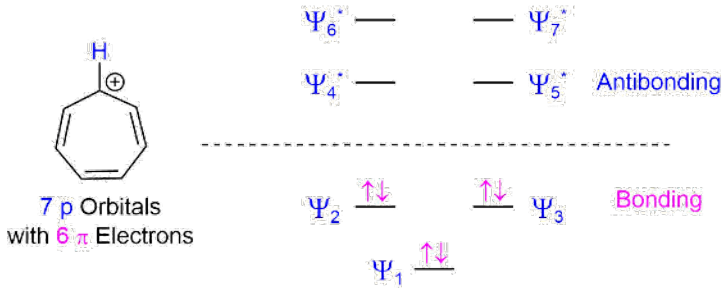
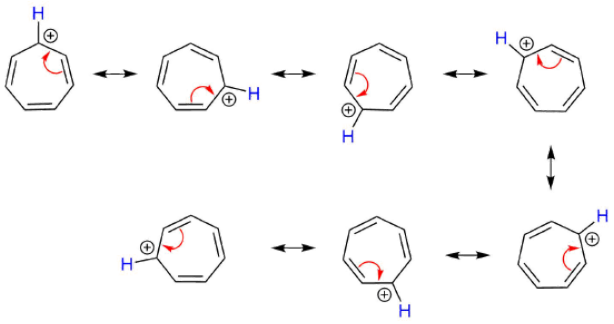


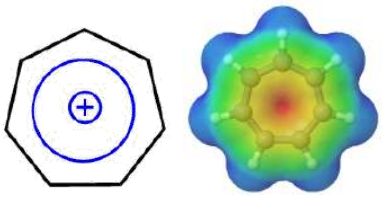
Figure 2.6.2: The aromatic six-*π*-electron cycloheptatrienyl cation. The cation can be generated by removing a hydride ion ($H:^-$) from the CH_2 group of 1,3,5-cycloheptatriene.

The molecular orbital diagram for the 7 *p* orbitals in the tropylium cation has three bonding MO's and 4 antibonding MO's. The tropylium cation's 6 pi electrons completely fill the bonding molecular orbitals which is consistent with the tropylium cation being aromatic and therefore unusually stable.



As predicted with aromaticity, the positive charge is completely conjugated about the entire ring giving each carbon +1/7 charge. The true resonance hybrid can be depicted by drawing a series of seven resonance form. Also, the electrostatic potential map of the tropylium cation shows the positive charge is evenly distributed over the entire ring. The equivalency of the carbons in the seven membered ring is experimentally supported by an ^1H NMR spectrum of the tropylium cation which contains one peak showing that all seven protons are equivalent.





Antiaromatic Ions

In a similar fashion, cyclically conjugated ions with 4n pi electrons can be predicted to be antiaromatic and therefore highly unstable. An excellent example is the cyclopentadienyl cation. Above, the cyclopentadienyl anion was shown to be aromatic, however, the formation of a carbocation produces a different result. Although the vacant *p* orbital provided by the carbocation allows for cyclic conjugation to occur the compound only has 4 pi electrons.

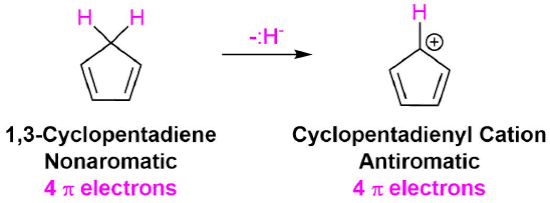
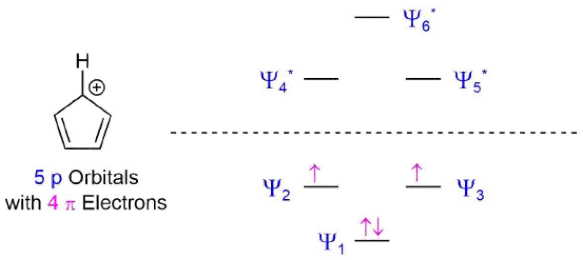
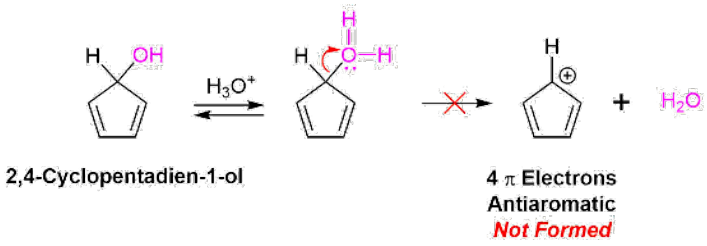


Figure 2.6.3: The aromatic six-π-electron cyclopentadienyl cation. The cation can be formed by removing a hydronium ion (H^-) from the CH_2 group of 1,3-cyclopentadiene.

After placing these 4 pi electrons into the molecular orbital for a cyclic 5 *p* orbital species the bonding molecular orbitals remain unfilled. Two of the pi electrons are unpaired in degenerate molecular orbitals creating the highly unstable triplet state. As predicted by Hückel's Rule, the cyclopentadienyl cation has 4n pi electrons and should be anitaromatic and very unstable.



Although there is some discussion as to whether the cyclopentadienyl cation is truly antiaromatic, there is experimental evidence which shows it is usually unstable. In particular, the compound 2,4-cyclopentadien-1-ol is usually resistant to S_N1 reactions with acid halides. The carbocation intermediate created during the mechanism of this reaction would be expected to easily form due to the resonance stabilization provided by the two double bonds. Because the carbocation intermediate is antiaromatic it does not form so the reaction does not occur.



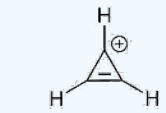
Exercises

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Exercise 2.6.1

1) Are all bonds equivalent cyclopentadienyl anion? How many lines (signals) would you expect to see in a ^{1}H and ^{13}C NMR spectrum?

2) Is the cyclopropenium ion aromatic? Use the 4n + 2 rule and the MO diagram for a 3 p orbital ring system to explain your answer.

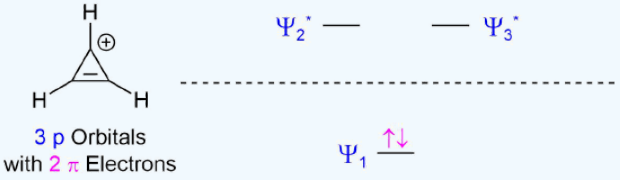


Cyclopropenium Ion

Answer

1) Due to the cyclopentadienyl anion being fully conjugated a protons and carbons are equivalent. Both the ^{1}H and ^{13}C NMR spectrum would only have one signal.

2) The cyclopropenium ion has 2 pi electrons which follows the 4n + 2 rule when n = 0. When considering the molecular orbital diagram for a 3 p orbital ring system the is one bonding MO and two antibonding MO's. The two pi electrons completely fill the bonding MO allowing for aromaticity.

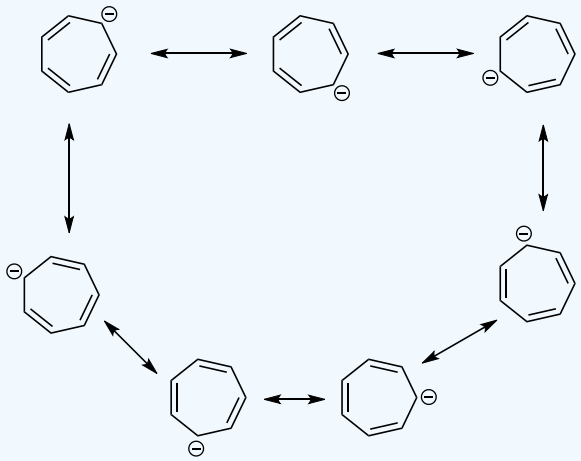


Exercise 2.6.2

Draw the resonance structures for cycloheptatriene anion. Are all bonds equivalent? How many lines (signals) would you see in a H^{1} NMR? C^{13} NMR?

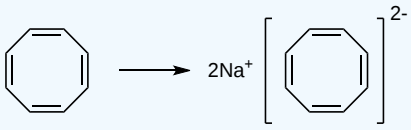
Answer

All protons and carbons are the same, so therefore each spectrum will only have one signal each in the proton NMR and carbon NMR.



Exercise 2.6.3

The following reaction occurs readily. Propose a reason why this occurs?



Answer

The addition of two electrons gives the ring system 10 pi electrons which follows the 4n+2 rule making the dianion aromatic. When looking at the MO diagram for an 8 p orbital ring system, 10 pi electrons completely fills the three bonding MO's and the two nonbonding MO's allowing for aromaticity.

The ring becomes aromatic with the addition of two electrons. Thereby obeying the 4n+2 rule.

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2.7: Aromatic Heterocycles

Objectives

After completing this section, you should be able to

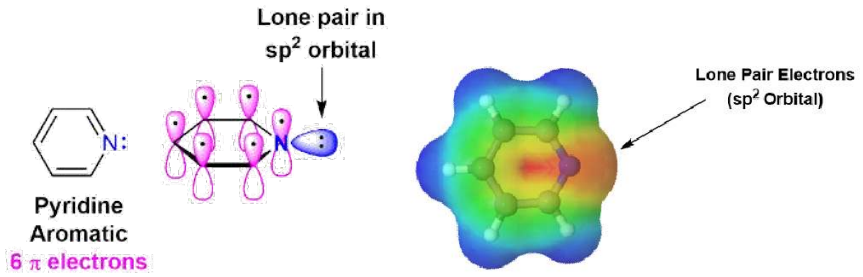
1. define heterocycles
2. draw the structure of the common aromatic heterocycles pyridine and pyrrole.
3. use the Hückel 4*n* + 2 rule to explain the aromaticity on heterocycles.
4. draw a diagram to show the orbitals involved in forming the conjugated six-pi-electron systems present in aromatic heterocycles such as pyridine, pyrrole, etc.

Aromatic Heterocycles

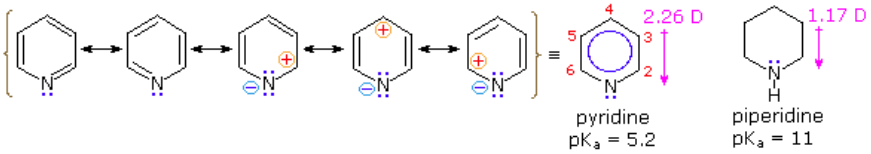
Many cyclic compounds have an element other than carbon present in the ring. Cyclic compounds that include one or more elements other than carbon are called a heterocycle. The most common heterocyclic compounds contain carbon along with nitrogen, oxygen, or sulfur. Because some heterocyclic compounds are aromatic, it is important to discuss how the inclusion of non-carbon atoms affects the determination of aromaticity. The reactivity and general physical properties of aromatic nitrogen heterocycles will be discussed in greater detail in Chapter 10.

Pyridine

Pyridine is an example of a six-membered aromatic heterocycle and has an electronic structure similar to benzene. In the bonding picture of pyridine the five carbons and single nitrogen are all sp^2 hybridized. All six of these atoms have a p orbital perpendicular to the plane of the ring and each contains one pi electron which allows the ring to be fully conjugated. This makes the pi electron count for pyridine 6 pi electrons. In much the same fashion as benzene, the 6 pi electrons follow the 4n + 2 rule and completely fill the bonding molecular orbitals which fulfills the electronic requirement for aromaticity. The lone pair electrons on pyridine's nitrogen are contained in a sp^2 orbital that lies in the same plane as the ring and does not overlap with the p orbitals of the ring. The lone pair electrons are not part of the aromatic system and do not affect the p electron count. Pyridine's electrostatic potential map shows that the lone pair electrons, shown in a yellow/red color, are locked onto the nitrogen and not distributed around the ring.



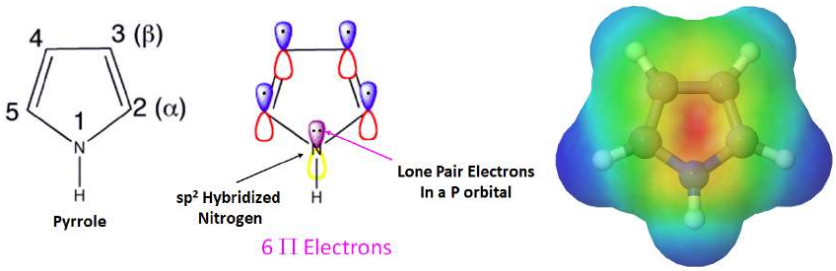
The lack of involvement of pyridine's nitrogen lone pair electrons in the aromatic conjugation creates charge separated structures not normally found for benzene. The combination of the resonance forms creates an overall charge separation which increases the electron density around the ring's nitrogen and decreases the electron density on the ring carbons. This causes pyridine to have a larger dipole moment (2.26 D) than its non-aromatic equivalent piperidine where the dipole moment (1.17 D). In both cases the dipole moment points towards the ring nitrogen.

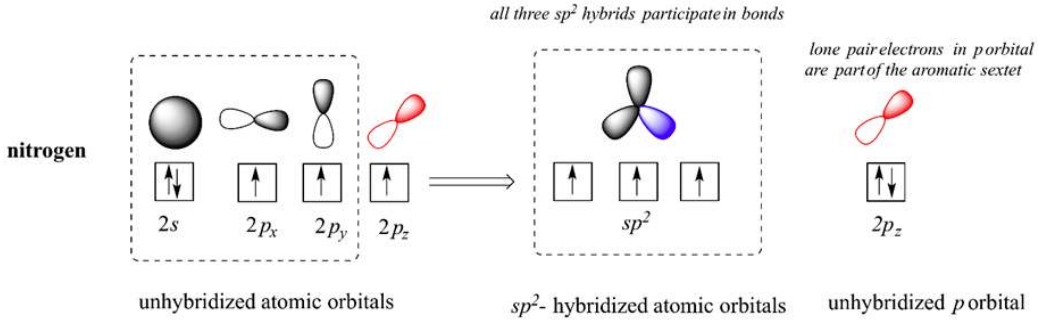


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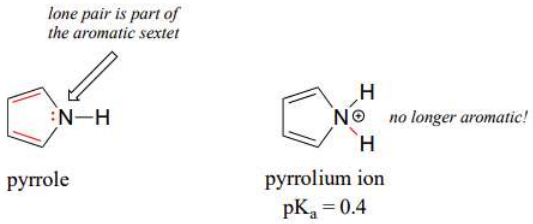
Pyrrole

Pyrrole is a five-membered heterocyclic ring which has 5 p orbitals and six pi electrons contributing to its aromaticity. Each carbon in pyrrole contributes one p orbital and pi electron. The nitrogen in pyrrole contributes two pi electrons by becoming sp^2 hybridized and placing its lone pair electrons into a p orbital. The electrostatic potential map of pyrrole show the nitrogen's lone pair electrons are distributed in the ring.

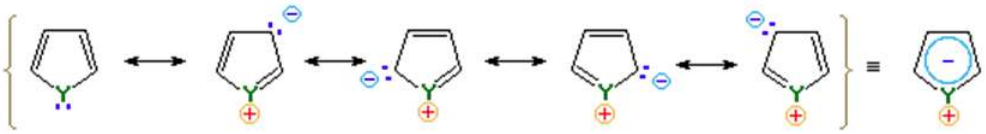




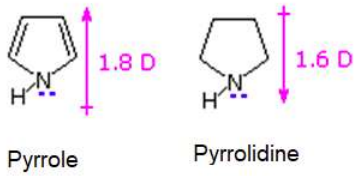
Because the nitrogen lone pair *is* part of the aromatic sextet the electrons are very stable and are much less available for bonding to a proton (and if they *do* pick up a proton, the molecule loses aromaticity). Pyrrole is a very weak base: the conjugate acid, the pyrrolium ion, is a strong acid with a pK_a of 0.4.



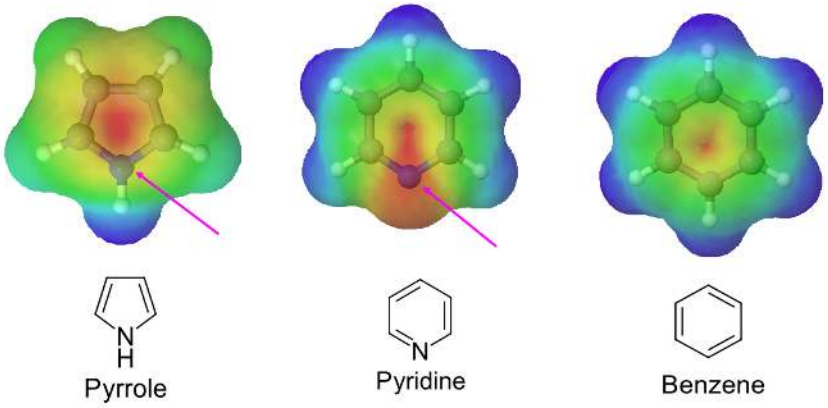
The involvement of the nitrogen lone pair electrons in pyrrole's aromatic conjugation creates charge separated structures not normally found for benzene. The combination of these resonance forms creates an overall separation of charge which increases the electron density around the ring carbons and decreases the electron density on the nitrogen. This effect has a number of ramifications. First is that pyrrole has a large dipole moment (1.8 D) pointing away from the ring nitrogen. This is in sharp contrast to the non-aromatic heterocycle pyrrolidine where the dipole moment (1.5 D) points towards the ring nitrogen.



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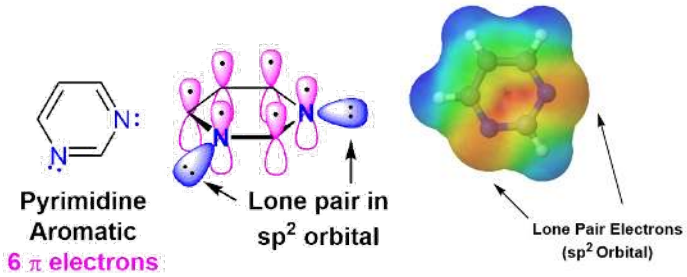


Due to the resonance forms, pyridine has more electron density around its nitrogen than in a typical alkyl amine. The electrostatic potential map of pyridine (Shown Below) shows more electron density (shown as a red color) on the ring nitrogen of pyridine when compared to pyrrole. The map of pyridine also shows that the resonance forms decrease the electron density of pyridine's ring carbons (Show as a blue/green color) when compared to those of benzene. The involvement of the nitrogen's lone pair electrons in the aromaticity of pyridine makes the ring deactivated towards electrophilic aromatic substitution.



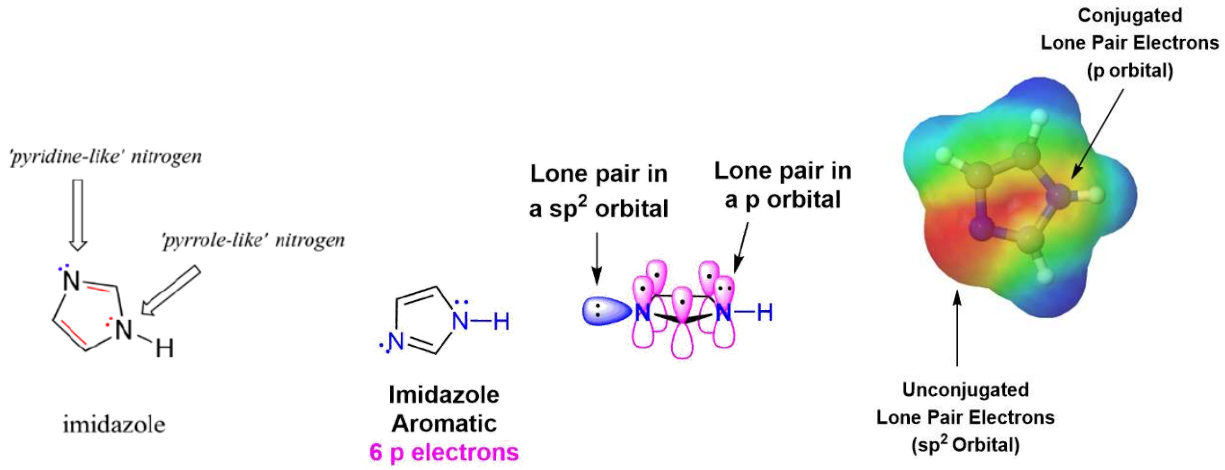
Pyrimidine

Pyrimidine is an another six-membered aromatic heterocycle that is analogous to pyridine. Pyrimidine has four carbons atoms and two nitrogen atoms that are sp^2 hybridized. Each of these atoms contributes a p orbital and a pi election allowing pyrimidine to be fully conjugated and aromatic. Both of the nitrogens in pyrimidine have lone pair electrons contained in a sp^2 orbitals and are not involved in the aromatic system. An electrostatic potential map of pyrimidine shows that neither set of lone pair electrons is distributed around the ring.



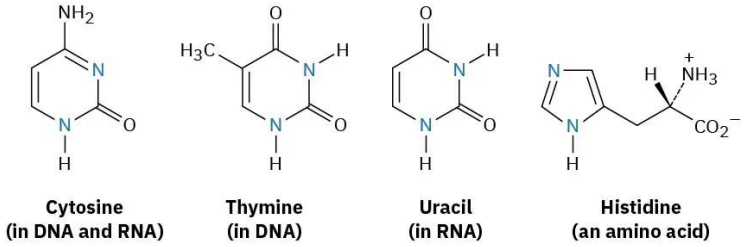
Imidazole

Imidazole is another five-membered heterocyclic ring which has 6 pi electrons and is aromatic. Both of the nitrogen atoms are sp^2 hybridized. One nitrogen is pyridine-like because it is part of a double bond and adds one pi electron to the aromatic pi ring. The other nitrogen is not part of a double bond making it pyrrole-like allowing it to contribute 2 pi electrons from it lone pair electrons. When looking at the electrostatic potential map of imidazole, the lone pair electrons on the pyrrole-like nitrogen are distributed around the ring while the lone pair electrons on the pyridine-like nitrogen are non-conjugated and locked into place.



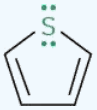
Biological Chemistry

Pyrimidine and imidazole rings are particularly important in biological chemistry. Pyrimidine, for instance, is the parent ring system in cytosine, thymine, and uracil, three of the five heterocyclic amine bases found in nucleic acids. An aromatic imidazole ring is present in histidine, one of the amino acids found in proteins.



Worked Example 2.7.1: Accounting for the Aromaticity of a Heterocycle

Thiophene, a sulfur-containing heterocycle, undergoes typical aromatic substitution reactions rather than addition reactions. Why is thiophene aromatic?



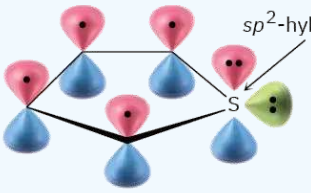
Thiophene

Strategy

Recall the requirements for aromaticity—a planar, cyclic, conjugated molecule with $4n + 2$ π electrons—and see how these requirements apply to thiophene.

Solution

Thiophene is the sulfur analog of pyrrole. The sulfur atom is sp^2-hybridized and has a lone pair of electrons in a p orbital perpendicular to the plane of the ring. Sulfur also has a second lone pair of electrons in the ring plane.



Thiophene

Exercises

Exercise 2.7.1

Determine if furan is aromatic. Draw an orbital diagram to support your answer.

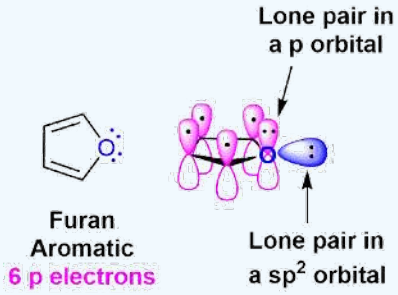


Furan

Answer

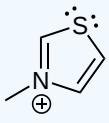
For a molecule to be aromatic it must: Be cyclic, be planar, be fully conjugated, and have 4n+2 π electrons.

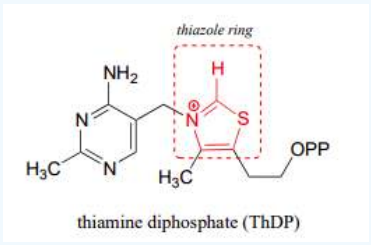
Furan is cyclic and can be assumed to be planar due to the constrains of having a five membered ring with two double bonds. To be fully conjugated each atom in the ring must have a p orbital. Although the oxygen has 4 electron groups and appears to be sp^3 hybridized, it will become sp^2 hybridized to gain the stability of conjugation. Becoming sp^2 hybridized allows the oxygen atom to put a set of lone pair electrons into a p orbital allowing it to be part of the cyclic conjugation. These two pi electrons along with the 4 pi electrons provided by the two double bonds gives furan 6 pi electrons total. This follows the 4n + 2 rule making furan aromatic.



Exercise 2.7.2

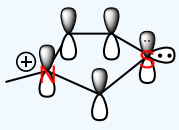
The thiazolium ring is a five-membered sulfur containing aromatic ring system which is found in biological systems, such as thiamine diphosphate (ThDP). Describe how thiazolium ring is aromatic.

thiazolium ring: 



Answer

Similar to the last question, the drawing shows that there are only 6 electrons in the pi-system.



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2.8: Polycyclic Aromatic Compounds

Objectives

After completing this section, you should be able to draw the resonance contributors for polycyclic aromatic compounds, such as naphthalene, anthracene, etc.

Key Terms

Make certain that you can define, and use in context, the key term below.

- polycyclic aromatic compounds

Polycyclic Aromatic Compounds

Hückel's 4n +2 rule for aromaticity does not only apply to mono-cyclic compounds. Benzene rings may be joined together (fused) to give larger polycyclic aromatic compounds. A few examples are drawn below, together with the approved numbering scheme for substituted derivatives. The peripheral carbon atoms (numbered in all but the last three examples) are all bonded to hydrogen atoms. Unlike benzene, all the C-C bond lengths in these fused ring aromatics are not the same, and there is some localization of the pi-electrons. The six benzene rings in coronene are fused in a planar ring; whereas the six rings in hexahelicene are not joined in a larger ring, but assume a helical turn, due to the crowding together of the terminal ring atoms (in the structure below, note that the top right and center right rings are not attached to one another). This helical configuration renders the hexahelicene molecule chiral, and it has been resolved into stable enantiomers.

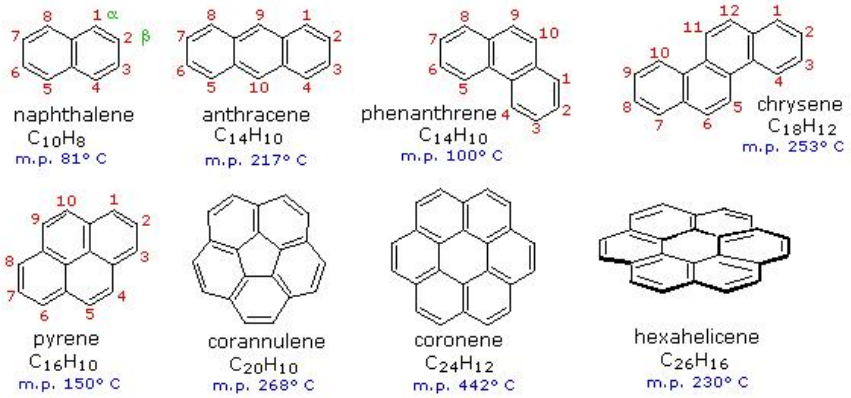
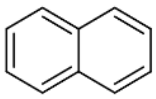
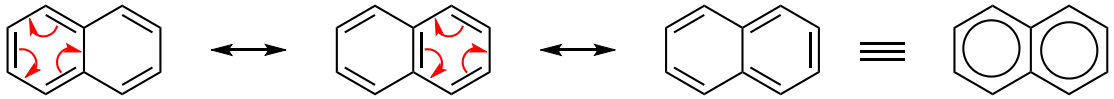


***Figure 1**: Examples of Polycyclic Aromatic Hydrocarbons (PAHs).*

Probably the most well know polycyclic aromatic compound which only contains carbon is naphthalene ($C_{10}H_8$). Naphthalene shares many of the same characteristic as benzene. Naphthalene is cyclic and known to be flat. Each carbon in naphthalene is sp^2 hybridized so it is completely conjugated. The true structure of naphthalene is a combination of three resonance hybrids.

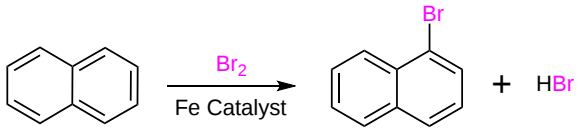


Naphthalene



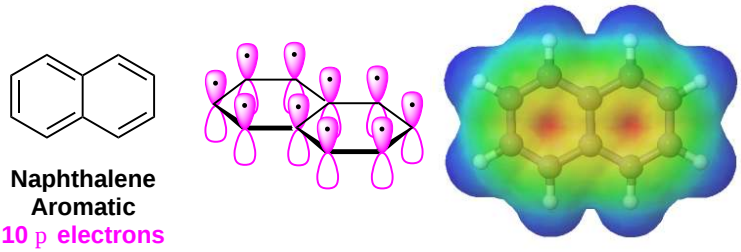
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Heat of hydrogenation experiments with naphthalene shows an unusual "aromatic" stabilization energy. Also, naphthalene prefers to react with electrophiles to give substitution products rather than the typical double bond addition products.



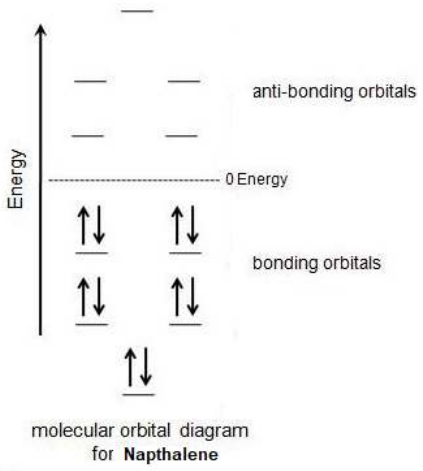
Naphthalene **1-Bromonaphthalene Substitution Product**

Every carbon in naphthalene is sp^2 hybridized so there is conjugated p orbital overlap over the entire ring system. The electrostatic potential map shows that pi electrons in naphthalene are evenly distributed making each carbon equivalent.



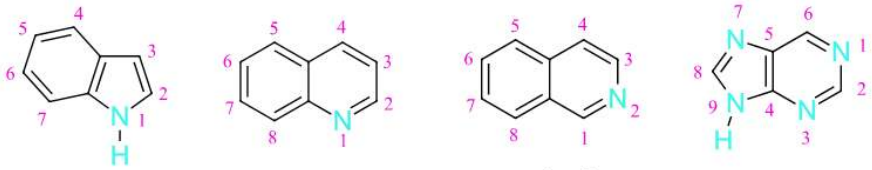
Naphthalene
Aromatic
10 p electrons

Lastly, naphthalene has 10 pi electrons which fulfills Hückel's rule. The importance of the 4n + 2 rule can be seen when considering the molecular orbital diagram of naphthalene. Naphthalene has 10 p orbitals which is 4 more than benzene. In the molecular orbital diagram of naphthalene, the 4 additional p orbitals become 2 bonding orbitals and two anti-bonding orbitals. The two additional bonding orbitals require 4 additional pi electrons to be filled so naphthalene needs 10 pi electrons in total to fill all of the bonding molecular orbitals.

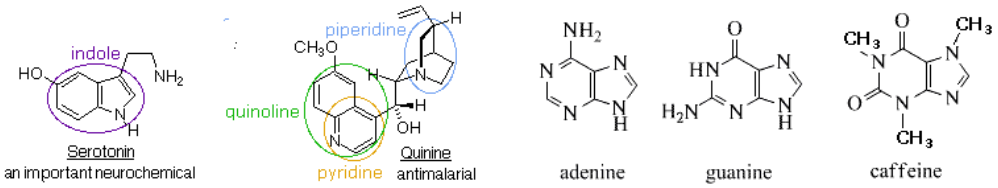


Polycyclic Aromatic Heterocycles

There is a wide variety of polycyclic aromatic heterocycles, many of which contain nitrogen, oxygen, or sulfur. Some of the biologically important structures, are the nitrogen containing polycyclic aromatic heterocycles indole, quinoline, isoquinoline, and purine which are all polycyclic aromatic heterocycles commonly found in nature. Notice that these compound all have 10 pi electrons.



Indole, quinoline, and isoquinoline all contain a hetrocyclic ring fused to benzene. Purine is made up to two heterocyclic rings, imidazole and pyrimidine, fused together. Quinoline is found in the antimalarial drug quinine. Indole is found in the neurotransmitter serotonin. The purine ring structure is found in adenine and guanine, two important parts of DNA and in the stimulant caffeine.



Study Notes

As their name indicates, *polycyclic aromatic hydrocarbons* are aromatic hydrocarbons which contain more than one benzenoid (i.e., benzene-like) ring. This section deals only with those compounds in which the benzenoid rings are fused together; in other words, compounds in which at least one carbon-carbon bond is common to two aromatic rings. Another type of polycyclic aromatic hydrocarbon contains two or more benzenoid rings joined by a carbon-carbon single bond. The simplest compound of this type is biphenyl, the compound from which PCBs (polychlorinated biphenyls) are derived.

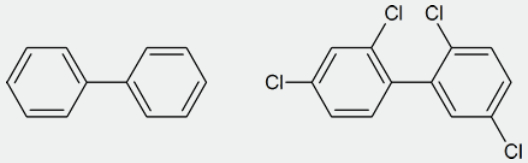
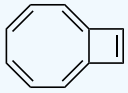


Figure 2: Structures of biphenyl and a typical PCB

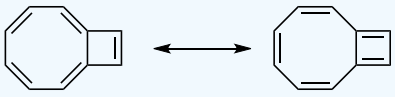
Exercise 2.8.1

This is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.



Answer

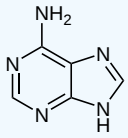
Yes, It has 10 pi electrons which follows the 4n+2 rule making it aromatic



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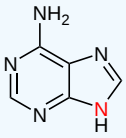
Exercise 2.8.2

The following molecule is adenine. It has a purine core. How many electrons are donated to the pi system from the nitrogen in the core?



Answer

There is only one nitrogen of the core that contributes a set of lone pair electrons as 2 pi electrons (in red). All of the other nitrogens are sp2 hybrized and contribute 1 pi electron each. In total, the core is aromatic with 10 electrons in the pi-system.



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2.9: Reactions at the Benzylic Position

Objectives

After completing this section, you should be able to

- write an equation to describe the oxidation of an alkylbenzene to a carboxylic acid.
- identify the reagents required to oxidize a given alkylbenzene to a carboxylic acid.
- identify the product formed from the side-chain oxidation of a given alkylbenzene.
- identify the aromatic compound needed to produce a given carboxylic acid through side-chain oxidation.
- write the equation for the bromination of an alkylbenzene side chain.
- identify the reagents and conditions necessary to bring about bromination in the side chain of an alkylbenzene.
- identify the product formed when a given alkylbenzene undergoes side-chain bromination.
- identify the alkylbenzene needed to prepare a given benzylic bromide by radical substitution.
- write the mechanism for the radical substitution at the benzylic position of an alkylbenzene.
- explain the stability of benzylic radicals in terms of resonance, and draw the resonance contributors of a given benzyl radical.
- explain, and illustrate with appropriate examples, the importance of benzylic bromides as intermediates in organic syntheses.
- arrange a given series of radicals (including benzylic type radicals) in order of increasing or decreasing stability. (Review Section 10.3 if necessary.)

Key Terms

Make certain that you can define, and use in context, the key terms below.

- benzylic oxidation
- benzylic position
- side-chain oxidation

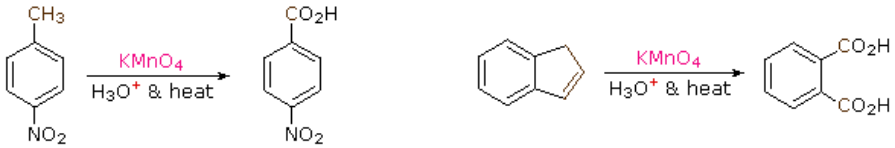
Oxidation of Alkyl Side-Chains

Despite its unsaturation, the benzene ring is inert to strong oxidizing agents such as $KMnO_4$, which will cleave alkene carbon–carbon bonds (Section 8.8). It turns out, however, that the presence of the aromatic ring has a dramatic effect on the reactivity of alkyl side chains. These side chains react rapidly with oxidizing agents and are converted into carboxyl groups, $–CO_2H$.The net effect is conversion of an alkylbenzene into a benzoic acid, **Ar–R** → **Ar**–CO2HAr–R → Ar–CO2H. Butylbenzene is oxidized by aqueous $KMnO_4$ to give benzoic acid, for instance.



Butylbenzene **Benzoic acid (85%)**

Two other examples of this reaction are given below, and illustrate its usefulness in preparing substituted benzoic acids.



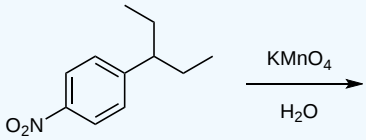
The mechanism of side-chain oxidation is complex and involves reaction of C–H bonds at the position next to the aromatic ring to form intermediate benzylic radicals. *tert*-Butylbenzene has no benzylic hydrogens, however, and is therefore inert.

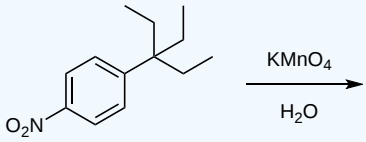


***tert*-Butylbenzene**

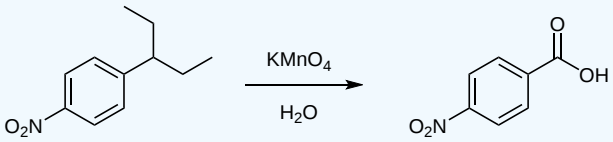
Exercise 2.9.1

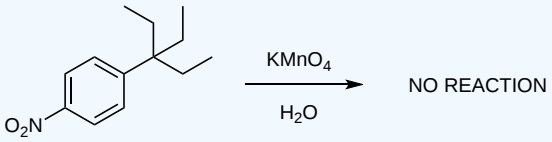
Predict the products of the following two reactions.





Answer

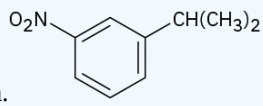


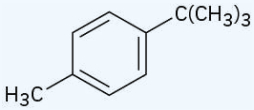


It one leads to no reaction because it requires a hydrogen just off the phenyl ring.

Exercise 2.9.2

What aromatic products would you obtain from the $KMnO_4$ oxidation of the following substances?

a. 

b. 

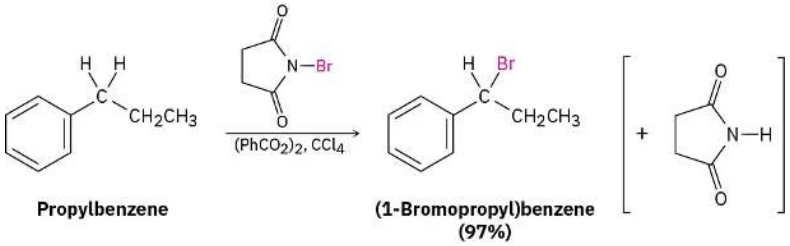
Answer

a. *m*-Nitrobenzoic acid

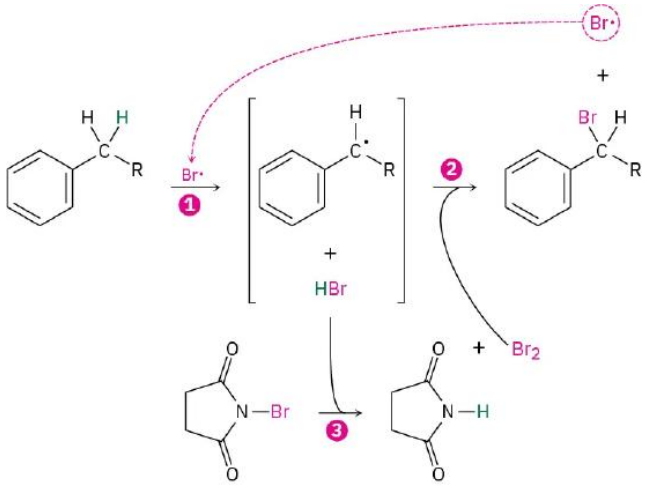
b. *p*-*tert*-Butylbenzoic acid

Bromination of the Benzylic Carbon

Side-chain bromination at the benzylic position occurs when an alkylbenzene is treated with *N*-bromosuccinimide (NBS). For example, propylbenzene gives (1-bromopropyl)benzene in 97% yield on reaction with NBS in the presence of benzoyl peroxide, $(PhCO_2)_2$, as a radical initiator. Bromination occurs exclusively in the benzylic position next to the aromatic ring and does not give a mixture of products.



The mechanism of benzylic bromination is similar to that discussed in Section 10.3 for allylic bromination of alkenes. Abstraction of a benzylic hydrogen atom first generates an intermediate benzylic radical, which then reacts with Br_2 in step 2 to yield product and a **Br**· radical, which cycles back into the reaction to carry on the chain shown below as a summary. The Br_2 needed for reaction with the benzylic radical is produced in step 3 by a concurrent reaction of HBr with NBS.



Reaction occurs exclusively at the benzylic position because the benzylic radical intermediate is stabilized by resonance. Figure **2.9.1** shows how the benzyl radical is stabilized by overlap of its *p* orbital with the ringed π electron system.

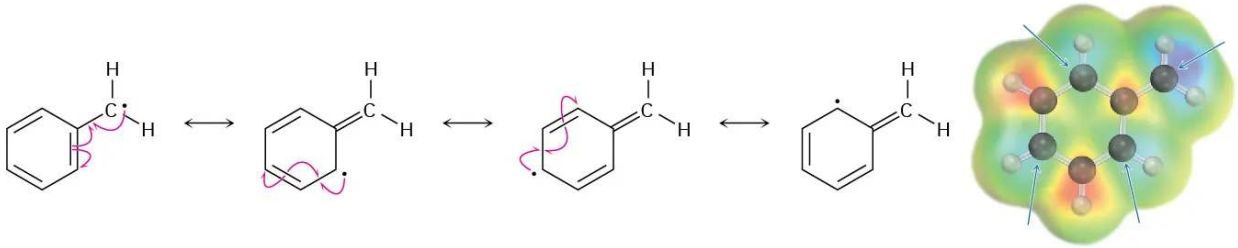


Figure **2.9.1**: A resonance-stabilized benzylic radical. The spin-density surface shows that the **unpaired electron** is shared by the carbons in ortho and para positions.

Study Notes

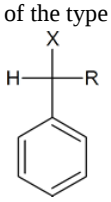
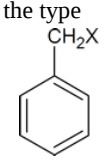
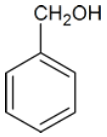
As you can see from the examples, no matter what the length of the alkyl group in the arene substrate, the product is always a one-carbon carboxyl group. Thus, the benzylic carbon atom has been oxidized and the term *benzylic oxidation* is appropriate. The term *side-chain oxidation* is also commonly used.

In alkylbenzenes, the carbon atom which is attached to the aromatic ring is particularly reactive. Reactions taking place at this carbon atom are said to occur at the *benzylic position*.

You may wish to review allylic bromination using N-bromosuccinimide from CHEM 231.

Benzylic halides undergo the typical reactions of alkyl halides, so they are frequently used in multistep syntheses.

Note that we have adopted the terminology given below.

Any compound of the type  (where X = halogen) will be referred to as a "benzylic halide."	Compounds of the type  are actually called benzyl chloride, benzyl bromide, etc.	The compound  is called benzyl alcohol.

? Exercise 2.9.3

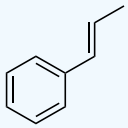
Consider a benzyl radical. Would it be more stable than an alkyl radical? Explain.

Answer

Yes, it would be more stable than an alkyl radical. The benzyl radical is stabilized through several resonance structures where the radical is moved through the ring via the pi system there.

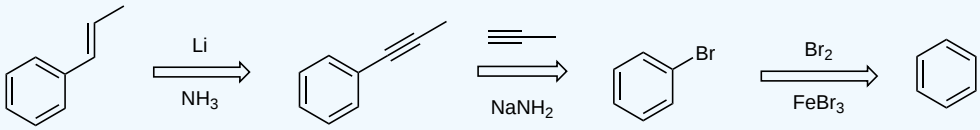
? Exercise 2.9.4

How would you make the following molecule?



Answer

The following is just one possibility.



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2.10: Spectroscopy of Aromatic Compounds

Objectives

After completing this section, you should be able to

1. determine whether an unknown compound contains an aromatic ring by inspection of its infrared spectrum, given a table of characteristic infrared absorptions.
2. state the approximate chemical shift of aryl protons in a proton NMR spectrum.
3. explain why signals resulting from the presence of aryl protons are found downfield from those caused by vinylic protons in a proton NMR spectrum.
4. propose possible structures for an unknown aromatic compound, given its proton NMR spectrum, other spectroscopic data (such as a ^{13}C NMR or infrared spectrum), or both.

Key Terms

Make certain that you can define, and use in context, the key term below.

- ring current

Study Notes

It is not necessary that you memorize detailed spectroscopic data. In the laboratory, on assignments and when writing examinations, you will be provided with a table of characteristic infrared absorptions to assist you in interpreting infrared spectra.

The important points to note about the proton NMR of aromatic compounds are the approximate chemical shifts of such protons and the complex splitting pattern that is sometimes observed. You are advised not to spend too long trying to understand why the signal for an aryl proton is found downfield from the signal for a vinylic proton. In general, we want you to be able to interpret NMR spectra, and leave the underlying theory for subsequent chemistry courses.

The chemical shifts of aromatic protons

Some protons resonate much further downfield than can be accounted for simply by the deshielding effect of nearby electronegative atoms. Vinylic protons (those directly bonded to an alkene carbon) and aromatic (benzylic) protons are dramatic examples.

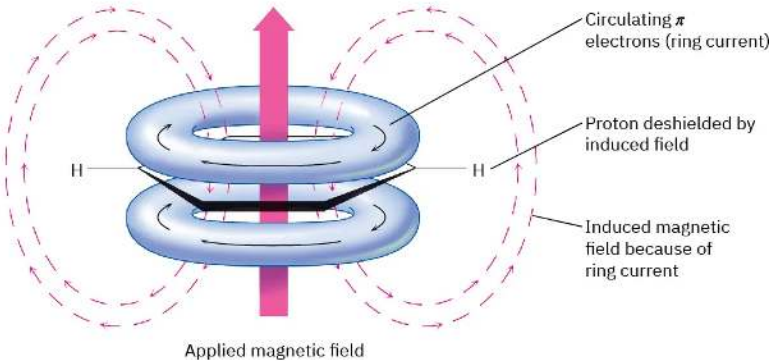


Figure 2.10.1: The origin of aromatic ring-current. Aromatic protons are deshielded by the induced magnetic field caused by delocalized π electrons circulating around the aromatic ring.

We'll consider the aromatic proton first. Recall that in benzene and many other aromatic structures, a sextet of p electrons is delocalized around the ring. When the molecule is exposed to B_0, these p electrons begin to circulate in a **ring current**, generating their own induced magnetic field that opposes B_0. In this case, however, the induced field of the p electrons does not shield the

benzylic protons from B_0 as you might expect– rather, it causes the protons to experience a *stronger* magnetic field in the direction of B_0 – in other words, it *adds* to B_0 rather than subtracting from it.

To understand how this happens, we need to understand the concept of **diamagnetic anisotropy** (anisotropy means `non-uniformity`). So far, we have been picturing magnetic fields as being oriented in a uniform direction. This is only true over a small area. If we step back and take a wider view, however, we see that the lines of force in a magnetic field are actually anisotropic. They start in the 'north' direction, then loop around like a snake biting its own tail.

If we are outside the ring in the figure above, we feel a magnetic field pointing in a northerly direction. If we are inside the ring, however, we feel a field pointing to the south.

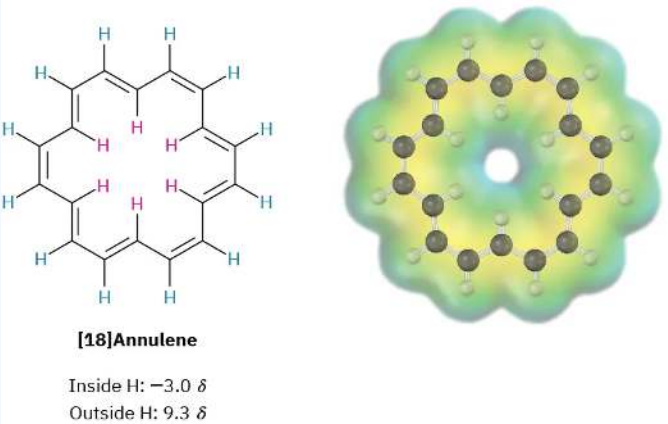
In the induced field generated by the aromatic ring current, the benzylic protons are outside the ring – this means that the induced current in this region of space is oriented in the *same* direction as B_0.

In total, the benzylic protons are subjected to three magnetic fields: the applied field (B_0) and the induced field from the electrons pointing in one direction, and the induced field of the non-aromatic electrons pointing in the opposite (shielding) direction. The end result is that benzylic protons, due to the anisotropy of the induced field generated by the ring current, appear to be highly de-shielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

The presence of anisotropy effects is often used to indicate aromaticity in a molecule. An example is the nonaromatic 8 pi electron cyclooctatetraene. In order to avoid anti-aromatic destabilization, the molecule takes a non-planar conformation which prevents conjugation and ring currents. Consequently, the molecule's protons absorbed at 5.8 ppm which is within the alkene region of ^{1}H NMR.

? Exercise 2.10.1

The ^{1}H-NMR spectrum of [18] annulene has two peaks, at 8.9 ppm and -1.8 ppm (upfield of TMS!) with an integration ratio of 2:1. Explain the unusual chemical shift of the latter peak.

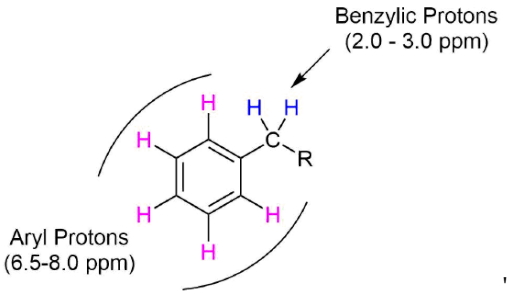


Answer

The molecule contains two groups of equivalent protons: the twelve pointing to the outside of the ring, and the six pointing into the center of the ring. The molecule is aromatic, as evidenced by the chemical shift of the 'outside' protons' (and the fact that there are 18 p electrons - a Hückel number). The inside protons are *shielded* by the induced field of the aromatic ring current, because *inside the ring this field points in the opposite direction of B_0*. This is the source of the unusually low (negative relative to TMS) chemical shift for these protons.

Characteristic ^{1}H NMR Absorptions of Aromatic Compounds

Protons directly attached to an aromatic ring, commonly called aryl protons, show up about 6.5-8.0 PPM. This range is typically called the aromatic region of an ^{1}H NMR spectrum. Protons on carbons directly bonded to an aromatic ring, called benzylic protons, show up about 2.0-3.0 PPM.



For the ^{1}H NMR spectrum of p-bromotoluene, the absorption for the benzylic protons appears as a strong singlet at 2.28 ppm. Due to the molecule's symmetry, the aryl protons appear as two doublets at 6.96 & 7.29 ppm.

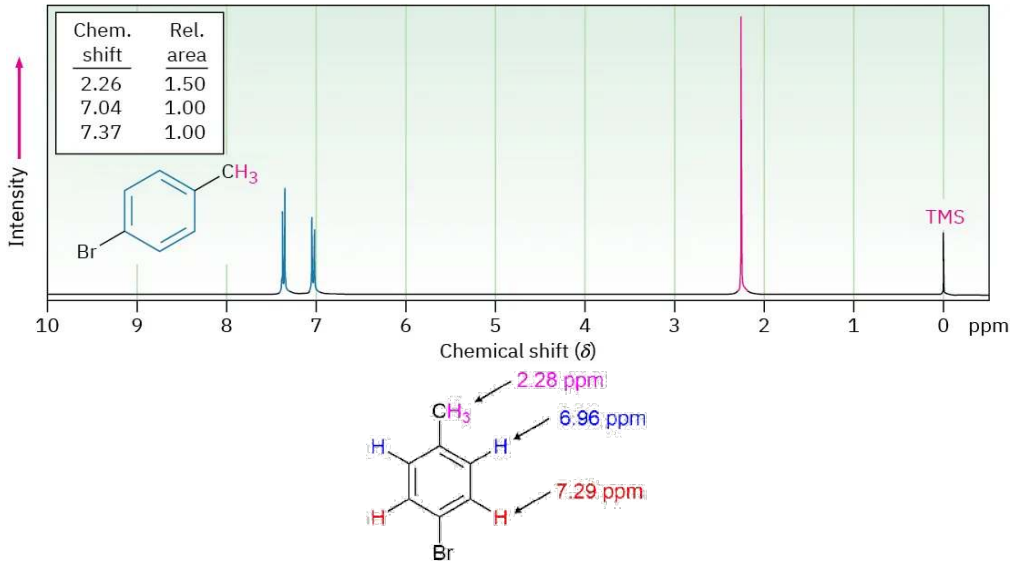


Figure 2.10.2: The ^{1}H NMR spectrum of *p*-bromotoluene.

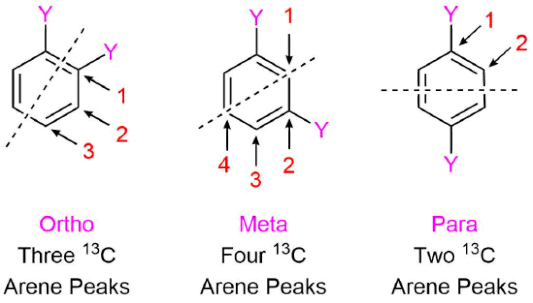
Characteristic ^{13}C NMR Absorptions of Aromatic Compounds

Carbons in an aromatic ring absorb in the range of 120-150 ppm in a ^{13}C NMR spectrum. This is virtually the same range as nonaromatic alkenes (110-150 ppm) so peaks in this region are not definitive proof of a molecule's aromaticity.

Due to the decoupling in ^{13}C NMR, the number of absorptions due to aromatic carbons can easily be observed. This can be used to determine the relative positions (*ortho*, *meta*, or *para*) for di-substituted benzenes. Peak assignments can be simplified by noting that ^{13}C peaks tend to be larger if two carbons contribute to the absorption.

Symmetrical Di-substituted Benzenes

Benzenes substituted with two identical groups have a relatively high amount of symmetry. In all three configurations, there is a plane of symmetry that reduces the number of distinct aryl carbon absorptions to less than six. The *ortho* configuration has a plane of symmetry which mirrors each carbon in the benzene ring causing only three ^{13}C aryl absorptions to occur. The *meta* configuration's plane of symmetry mirrors two carbons of the benzene ring allowing for four aryl absorptions to occur. The *para* configuration actually has two planes of symmetry (one vertical and one horizontal on the structure below) through the benzene ring, which only allows two distinct aryl absorptions to occur.



Asymmetrical Di-substituted Benzenes

The lack of a plane of symmetry in asymmetrical di-substituted benzenes makes each carbon in the *ortho* and *meta* configuration unique. Consequently, their ^{13}C NMR spectra show six arene absorptions. However, the *para* configuration has a plane of symmetry drawn through the two substituents which mirrors two carbons of the benzene ring causing only 4 arene absorptions to appear.

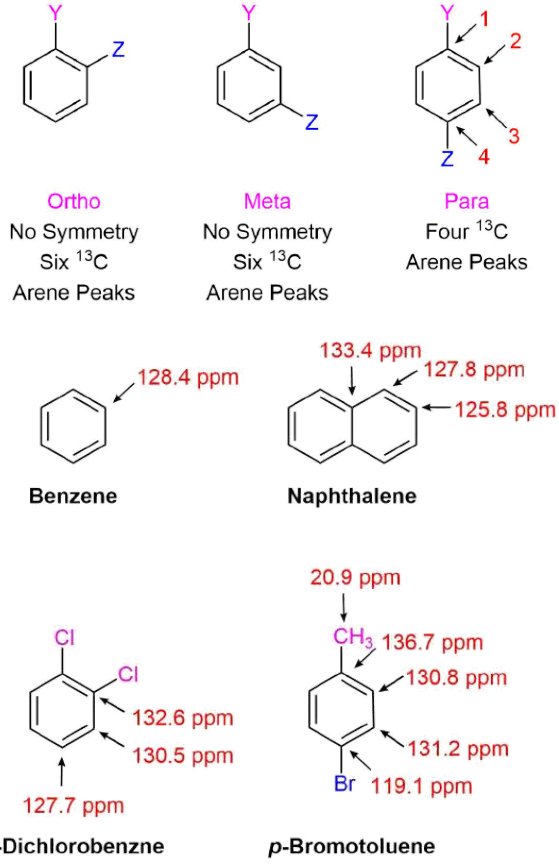


Figure 2.10.3: Some ^{13}C NMR absorptions of aromatic compounds (δ units).

Characteristic IR Absorption of Benzene Derivatives

Arenes have absorption bands in the 650-900 cm^{-1} region due to the bending of the C–H bond out of the plane of the ring. The exact placement of these absorptions can indicate the pattern of substitution on a benzene ring. However, this is beyond the scope of introductory organic chemistry. Arenes also possess a characteristic absorption at about 3030-3100 cm^{-1} as a result of the aromatic C–H stretch. It is somewhat higher than the alkyl C–H stretch (2850–2960 cm^{-1}), but falls in the same region as olefinic compounds. Two bands (1500 and 1660 cm^{-1}) caused by C=C in-plane vibrations are the most useful for characterization as they are intense and are likely observed.

In aromatic compounds, each band in the spectrum can be assigned:

- C–H stretch from 3100-3000 cm^{-1}
- overtones, weak, from 2000-1665 cm^{-1}
- C–C stretch (in-ring) from 1600-1585 cm^{-1}
- C–C stretch (in-ring) from 1500-1400 cm^{-1}
- C–H "oop" from 900-675 cm^{-1}

Note that this is at a slightly higher frequency than the –C–H stretch in alkanes. This is a very useful tool for interpreting IR spectra. Only alkenes and aromatics show a C–H stretch slightly higher than 3000 cm^{-1}.

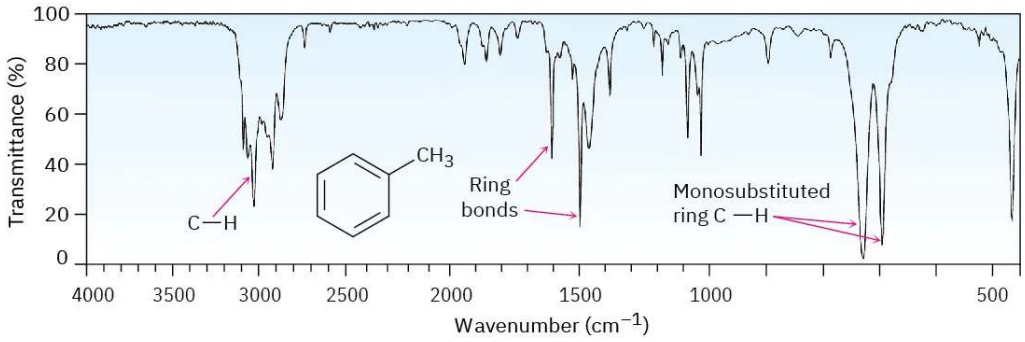
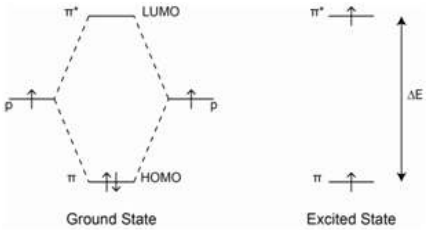


Figure 2.10.4: Infrared Spectrum of Toluene

Ultraviolet Spectroscopy

The presence of conjugated π bonds makes aromatic rings detectable in a UV/Vis spectrum. Benzene primarily absorbs through a be a π-π* transition over the range from 160-208 nm with a λ_{max} value of about 178 nm.



Benzene shows a less intense absorption in 230-276 nm range. These absorptions are due to the vibrational fine structure often displayed by rigid molecules such as benzene and other aromatic compounds.

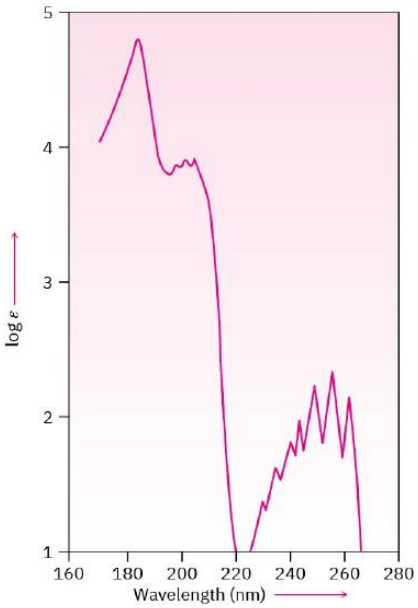


Figure 2.10.5: Ultraviolet spectrum of benzene. There are primary bands at 184 and 202 nm and secondary (fine-structure) bands at 255 nm.

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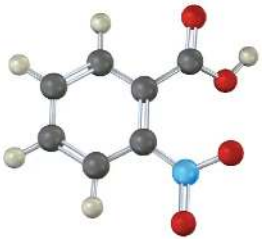
2.11: Additional Problems

2 • Additional Problems

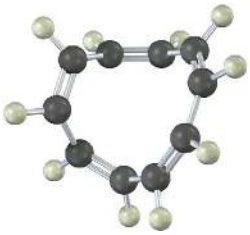
Visualizing Chemistry

PROBLEM 2-13 Give IUPAC names for the following substances (red = O, blue = N):

(a) 

(b) 

PROBLEM 2-14 All-cis cyclodecapentaene is a stable molecule that shows a single absorption in its ^{1}H NMR spectrum at 5.67 δ. Tell whether it is aromatic, and explain its NMR spectrum.



PROBLEM 2-15 1,6-Methanonaphthalene has an interesting ^{1}H NMR spectrum in which the eight hydrogens around the perimeter absorb at 6.9 to 7.3 δ, while the two CH_2 protons absorb at –0.5 δ. Tell whether it is aromatic, and explain its NMR spectrum.

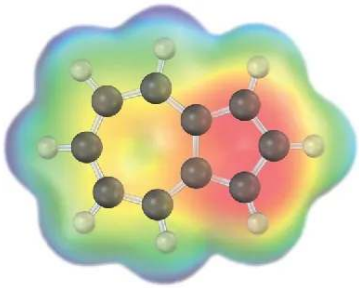


1,6-Methanonaphthalene

PROBLEM 2-16 The following molecular model is that of a carbocation. Draw two resonance structures for the carbocation, indicating the positions of the double bonds.



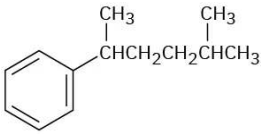
PROBLEM 2-17 Azulene, an isomer of naphthalene, has a remarkably large dipole moment for a hydrocarbon (μ = 1.0 D). Explain, using resonance structures.

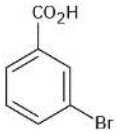


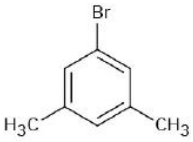
Azulene

Naming Aromatic Compounds

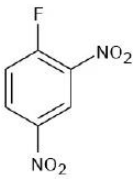
PROBLEM 2-18 Give IUPAC names for the following compounds:

(a) 

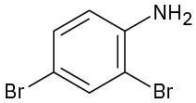
(b) 

(c) 

(d) 

(e) 

(f) 

(g). 

PROBLEM 2-19 Draw structures corresponding to the following names:

(a) 3-Methyl-1,2-benzenediamine (b) 1,3,5-Benzenetriol (c) 3-Methyl-2-phenylhexane

(d) *o*-Aminobenzoic acid (e) *m*-Bromophenol (f) 2,4,6-Trinitrophenol (picric acid) (g) *N*,*N*-Dimethylaniline

PROBLEM 2-20 Draw and name all possible isomers of the following:

(a) Dinitrobenzene (b) Bromodimethylbenzene (c) Trinitrophenol

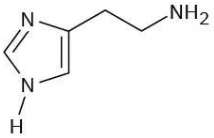
PROBLEM 2-21 Draw and name all possible aromatic compounds with the formula C_7H_7Cl.

PROBLEM 2-22 Draw and name all possible aromatic compounds with the formula C_8H_9Br. (There are 14.)

Amine Basicity

Problem 2-aa Although pyrrole is a much weaker base than most other amines, it is a much stronger acid ($pK_a \approx 15$ for the pyrrole versus 35 for diethylamine). The N–H hydrogen is readily abstracted by base to yield the pyrrole anion, $C_4H_4N^-$. Explain.

Problem 2-ab Histamine, whose release in the body triggers nasal secretions and constricted airways, has three nitrogen atoms. List them in order of increasing basicity and explain your ordering.



Histamine

Problem 2-ac Account for the fact that *p*-nitroaniline ($pK_a = 1.0$) is less basic than *m*-nitroaniline ($pK_a = 2.5$) by a factor of 30. Draw resonance structures to support your argument. (The pK_a values refer to the corresponding ammonium ions.)

Problem 2-ad Oxazole is a five-membered aromatic heterocycle. Would you expect oxazole to be more basic or less basic than pyrrole? Explain.



Oxazole

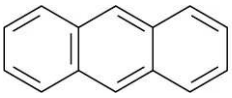
Structure of Aromatic Compounds

PROBLEM 2-23 Propose structures for aromatic hydrocarbons that meet the following descriptions:

- (a) C_9H_{12}; gives only one $C_9H_{11}Br$ product on substitution of a hydrogen on the aromatic ring with bromine
- (b) $C_{10}H_{14}$; gives only one $C_{10}H_{13}Cl$ product on substitution of a hydrogen on the aromatic ring with chlorine
- (c) C_8H_{10}; gives three C_8H_9Br products on substitution of a hydrogen on the aromatic ring with bromine
- (d) $C_{10}H_{14}$; gives two $C_{10}H_{13}Cl$ products on substitution of a hydrogen on the aromatic ring with chlorine

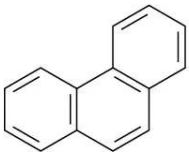
PROBLEM 2-24 Look at the three resonance structures of naphthalene shown in Section 2.7, and account for the fact that not all carbon–carbon bonds have the same length. The C1–C2 bond is 136 pm long, whereas the C2–C3 bond is 139 pm long.

PROBLEM 2-25 Anthracene has four resonance structures, one of which is shown. Draw the other three.



Anthracene

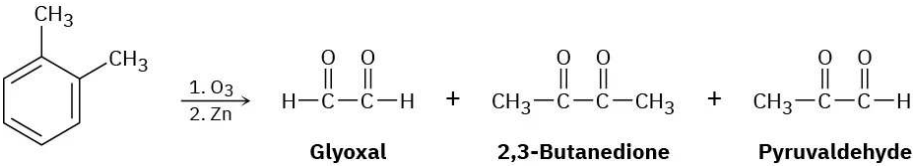
PROBLEM 2-26 Phenanthrene has five resonance structures, one of which is shown. Draw the other four.



Phenanthrene

PROBLEM 2-27 Look at the five resonance structures for phenanthrene (Problem 26), and predict which of its carbon–carbon bonds is shortest.

PROBLEM 2-28 In 1932, A. A. Levine and A. G. Cole studied the ozonolysis of *o*-xylene and isolated three products: glyoxal, 2,3-butanedione, and pyruvaldehyde:



Glyoxal **2,3-Butanedione** **Pyruvaldehyde**

In what ratio would you expect the three products to be formed if *o*-xylene is a resonance hybrid of two structures? The actual ratio found was 3 parts glyoxal, 1 part 2,3-butanedione, and 2 parts pyruvaldehyde. What conclusions can you draw about the structure of *o*-xylene?

Aromaticity and Hückel's Rule

PROBLEM 2-29 3-Chlorocyclopropene, on treatment with $AgBF_4$, gives a precipitate of AgCl and a stable solution of a product that shows a single ^1H NMR absorption at 11.04 δ. What is a likely structure for the product, and what is its relation to Hückel's rule?



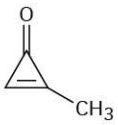
3-Chlorocyclopropene

PROBLEM 2-30 Draw an energy diagram for the three molecular orbitals of the cyclopropenyl system (C_3H_3). How are these three molecular orbitals occupied in the cyclopropenyl anion, cation, and radical? Which of the three substances is aromatic according to Hückel's rule?

PROBLEM 2-31 Cyclopropanone is highly reactive because of its large amount of angle strain. Methylcyclopropenone, although even more strained than cyclopropanone, is nevertheless quite stable and can even be distilled. Explain, taking the polarity of the carbonyl group into account.

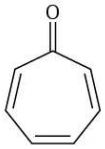


Cyclopropanone

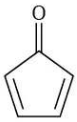


Methylcyclopropenone

PROBLEM 2-32 Cycloheptatrienone is stable, but cyclopentadienone is so reactive that it can't be isolated. Explain, taking the polarity of the carbonyl group into account.



Cycloheptatrienone

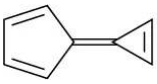


Cyclopentadienone

PROBLEM 2-33 Which would you expect to be most stable, cyclononatetraenyl radical, cation, or anion? (Cyclononatetraene has a ring of nine carbons and four double bonds.)

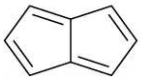
PROBLEM 2-34 How might you convert 1,3,5,7-cyclononatetraene to an aromatic substance?

PROBLEM 2-35 Calicene, like azulene (Problem 17), has an unusually large dipole moment for a hydrocarbon. Explain, using resonance structures.

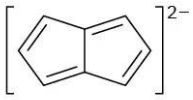


Calicene

PROBLEM 2-36 Pentalene is a most elusive molecule that has been isolated only at liquid-nitrogen temperature. The pentalene dianion, however, is well known and quite stable. Explain.



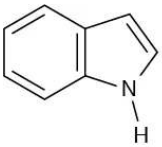
Pentalene



Pentalene dianion

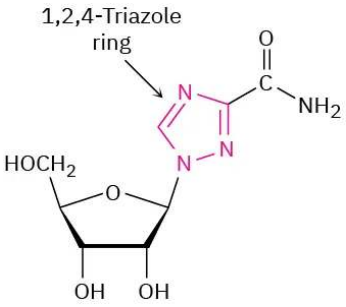
PROBLEM 2-37 Indole is an aromatic heterocycle that has a benzene ring fused to a pyrrole ring. Draw an orbital picture of indole.

- (a) How many π electrons does indole have?
- (b) What is the electronic relationship of indole to naphthalene?



Indole

PROBLEM 2-38 Ribavirin, an antiviral agent used against hepatitis C and viral pneumonia, contains a 1,2,4-triazole ring. Why is the ring aromatic?



Ribavirin

Spectroscopy

PROBLEM 2-39 Compound A, C_8H_{10}, yields three substitution products, C_8H_9Br, on reaction with Br_2. Propose two possible structures for A. The ^1H NMR spectrum of A shows a complex four-proton multiplet at 7.0 δ and a six-proton singlet at 2.30 δ. What is the structure of A?

PROBLEM 2-40 What is the structure of a hydrocarbon that has $M^+ = 120$ in its mass spectrum and has the following ^1H NMR spectrum?

7.25 δ (5 H, broad singlet); 2.90 δ (1 H, septet, J = 7 Hz); 1.22 δ (6 H, doublet, J = 7 Hz)

PROBLEM 2-41 Propose structures for compounds that fit the following descriptions:

(a) $C_{10}H_{14}$

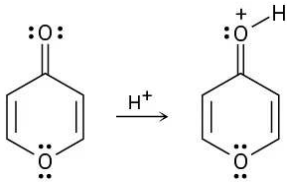
- ^1H NMR: 7.18 δ (4 H, broad singlet); 2.70 δ (4 H, quartet, J = 7 Hz); 1.20 δ (6 H, triplet, J = 7 Hz)
- IR absorption at 745 cm^{-1}

(b) $C_{10}H_{14}$

- ^1H NMR: 7.0 δ (4 H, broad singlet); 2.85 δ (1 H, septet, J = 8 Hz); 2.28 δ (3 H, singlet); 1.20 δ (6 H, doublet, J = 8 Hz)
- IR absorption at 825 cm^{-1}

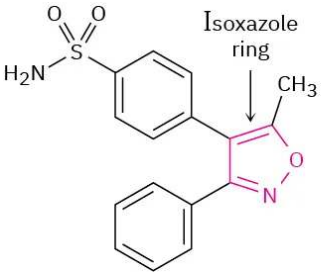
General Problems

PROBLEM 2-42 On reaction with acid, 4-pyrone is protonated on the carbonyl-group oxygen to give a stable cationic product. Using resonance structures and the Hückel $4n + 2$ rule, explain why the protonated product is so stable.



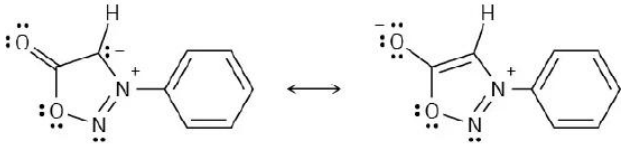
4-Pyrone

PROBLEM 2-43 Bextra, a COX-2 inhibitor once used in the treatment of arthritis, contains an isoxazole ring. Why is the ring aromatic?



Bextra

PROBLEM 2-44 *N*-Phenylsydnone, so-named because it was first studied at the University of Sydney, Australia, behaves like a typical aromatic molecule. Explain, using the Hückel $4n + 2$ rule.



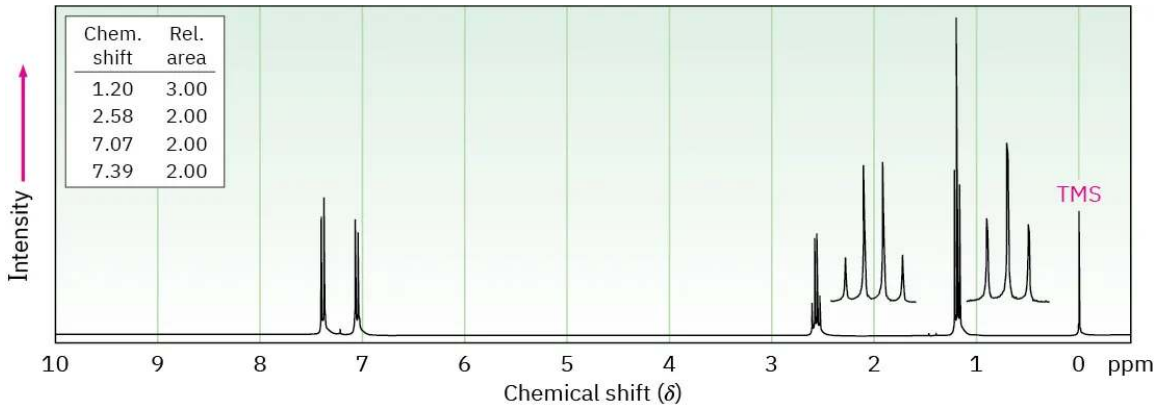
***N*-Phenylsydnone**

PROBLEM 2-45 Show the relative energy levels of the seven π molecular orbitals of the cycloheptatrienyl system. Tell which of the seven orbitals are filled in the cation, radical, and anion, and account for the aromaticity of the cycloheptatrienyl cation.

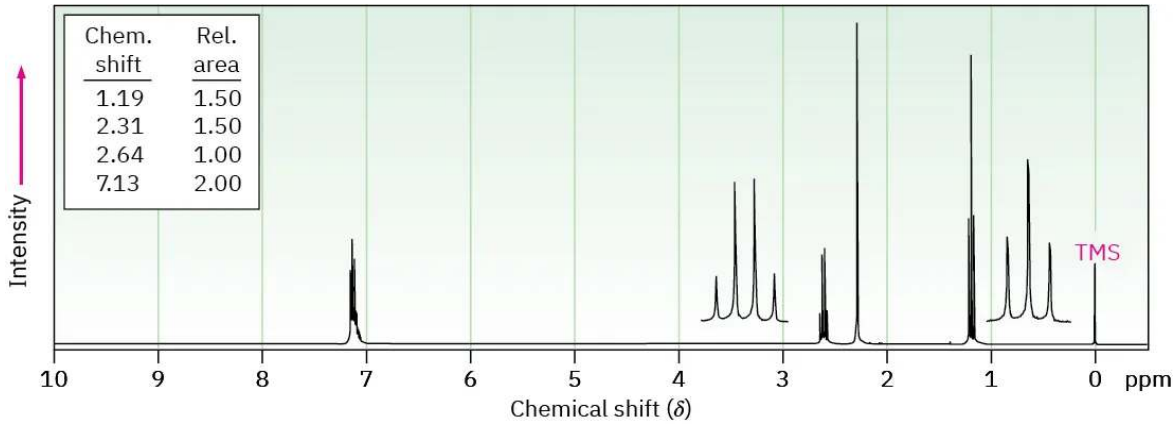
PROBLEM 2-46 1-Phenyl-2-butene has an ultraviolet absorption at λ_{max} = 208 nm (ε = 8000). On treatment with a small amount of strong acid, isomerization occurs and a new substance with λ_{max} = 250 nm (ε = 15,800) is formed. Propose a structure for this isomer, and suggest a mechanism for its formation.

PROBLEM 2-47 Propose structures for aromatic compounds that have the following ^{1}H NMR spectra:

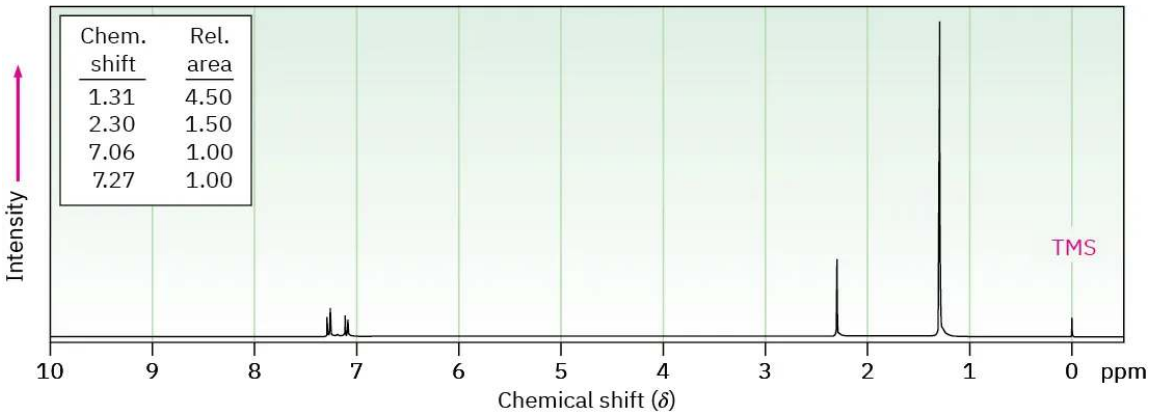
(a) C_8H_9Br - IR absorption at 820 cm^{-1}



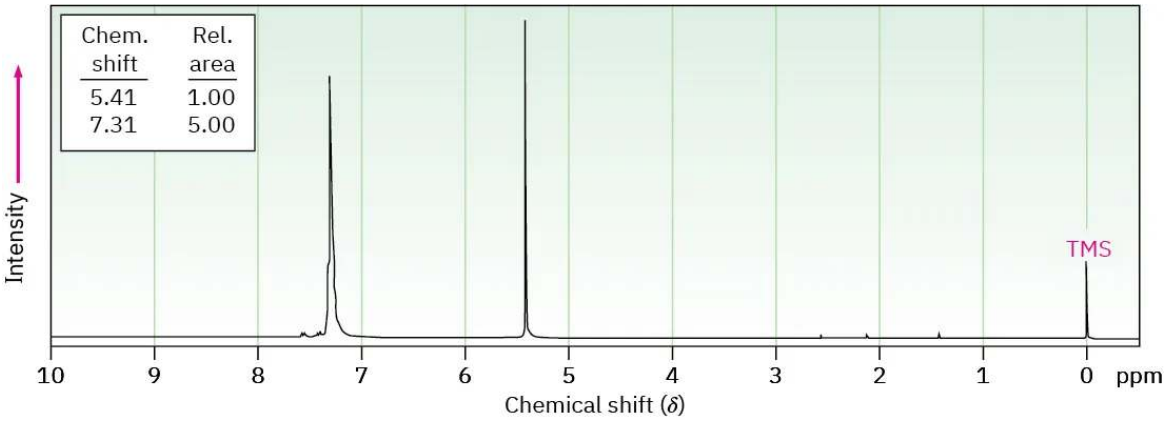
(b) C_9H_{12} - IR absorption at 750 cm^{-1}



(c) $C_{11}H_{16}$ - IR absorption at 820 cm^{-1}

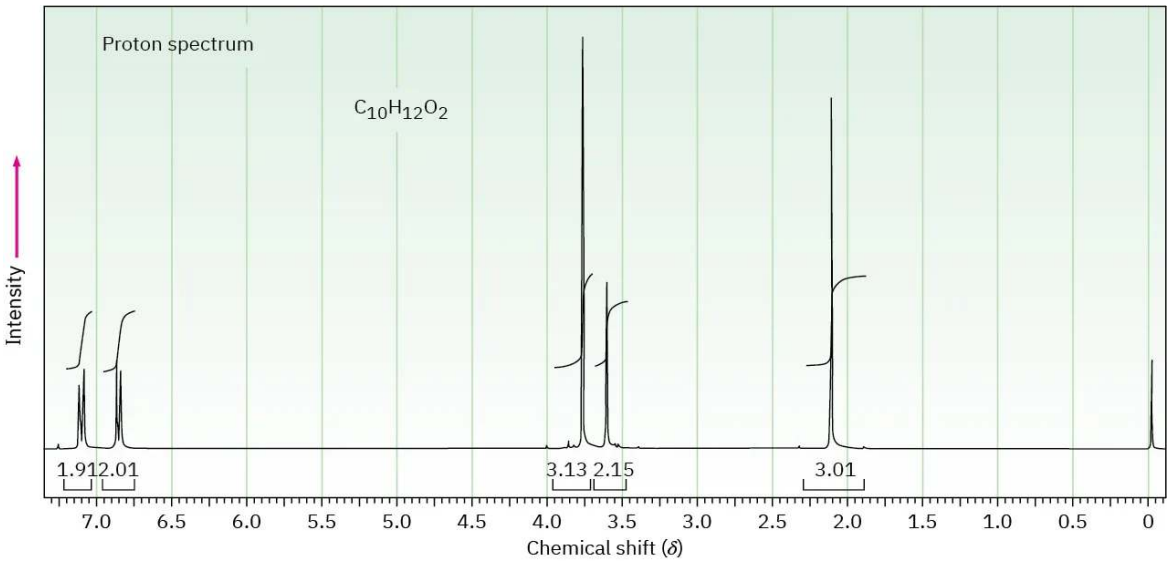


PROBLEM 2-48 Propose a structure for a molecule $C_{14}H_{12}$ that has the following ^1H NMR spectrum and has IR absorptions at 700, 740, and 890 cm^{-1}:



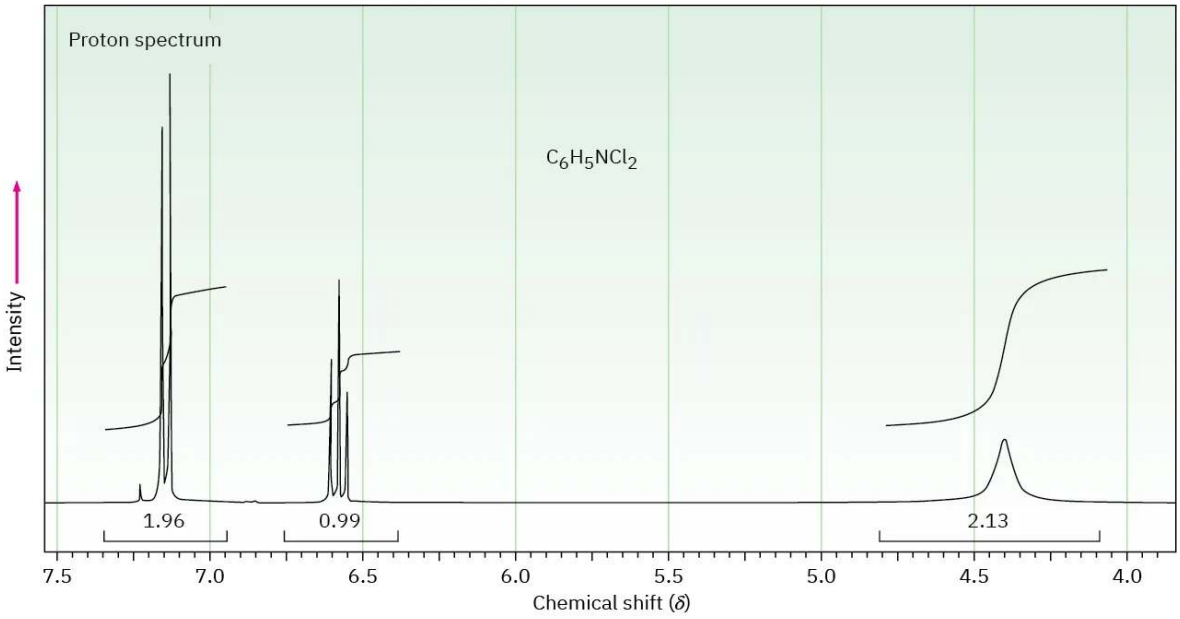
PROBLEM 2-49 The proton NMR spectrum for a compound with formula $C_{10}H_{12}O_2$ is shown. The infrared spectrum has a strong band at 1711 cm^{-1}. The normal carbon-13 NMR spectral results are tabulated along with the DEPT-135 and DEPT-90 information. Draw the structure of this compound.

Normal Carbon	DEPT-135	DEPT-90
29 ppm	Positive	No peak
50 ppm	Negative	No peak
55 ppm	Positive	No peak
114 ppm	Positive	Positive
126 ppm	No peak	No peak
130 ppm	Positive	Positive
159 ppm	No peak	No peak
207 ppm	No peak	No peak



PROBLEM 2-50 The proton NMR spectrum of a compound with formula $C_6H_5NCl_2$ is shown. The normal carbon-13 and DEPT experimental results are tabulated. The infrared spectrum shows peaks at 3432 and 3313 cm^{-1} and a series of medium-sized peaks between 1618 and 1466 cm^{-1}. Draw the structure of this compound.

Normal Carbon	DEPT-135	DEPT-90
118.0 ppm	Positive	Positive
119.5 ppm	No peak	No peak
128.0 ppm	Positive	Positive
140.0 ppm	No peak	No peak



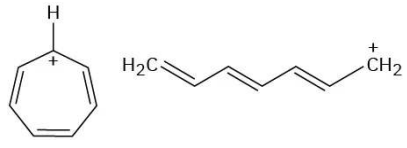
PROBLEM 2-51 Aromatic substitution reactions occur by the addition of an electrophile such as Br^+ to an aromatic ring to yield an allylic carbocation intermediate, followed by loss of H^+. Show the structure of the intermediate formed by the reaction of benzene with Br^+.

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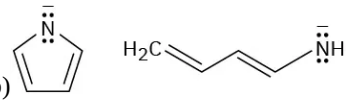
PROBLEM 2-52 The substitution reaction of toluene with Br_2 can, in principle, lead to the formation of three isomeric bromotoluene products. In practice, however, only *o*- and *p*-bromotoluene are formed in substantial amounts. The meta isomer is not formed. Draw the structures of the three possible carbocation intermediates (Problem 51), and explain why ortho and para products predominate over meta products.

PROBLEM 2-53 Look at the following aromatic anions and their linear counterparts, and draw all of the resonance forms for each. What patterns emerge?

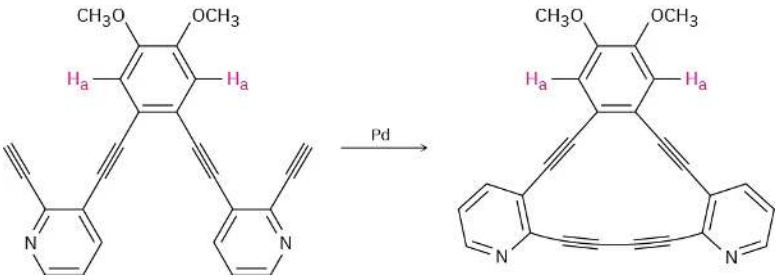
(a)



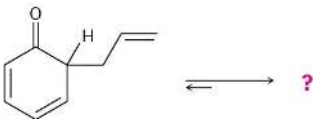
(b)



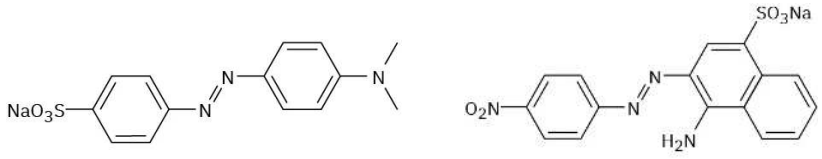
PROBLEM 2-54 After the following reaction, the chemical shift of H_a moves downfield from 6.98 ppm to 7.30 ppm. Explain.



PROBLEM 2-55 The following compound is the product initially formed in a Claisen rearrangement, which we'll see in Section 4.5. This product is not isolated, but tautomerizes to its enol form. Give the structure of the enol and provide an explanation as to why the enol tautomer is favored.



PROBLEM 2-56 Compounds called azo dyes are the major source of artificial color in textiles and food. Part of the reason for their intense coloring is the conjugation from an electron-donating group through the diazo bridge (−N=N−) to an electron-withdrawing group on the other side. For the following azo dyes, draw a resonance form that shows how the electron-donating group is related to the electron-withdrawing group on the other side of the diazo bridge. Used curved arrows to show how the electrons are reorganized.



(a) **Methyl Orange** (b) **C.I. Acid Red 74**

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2.S: Benzene and Aromaticity (Summary)

Concepts & Vocabulary

Introduction

- Aromatic compounds contain ring structures with a special type of resonance delocalization.
- Aromatic compounds can be drawn with alternating single and double bonds, each atom in the ring must have a p-orbital available.

2.1 Naming Aromatic Compounds

- Disubstituted benzene derivatives are often named using ortho (1,2), meta (1,3) and para (1,4).
- There are common benzene derivative names that are used by IUPAC such as toluene, phenol, benzoic acid and benzaldehyde.
- A benzene group that is named as a substituent is called phenyl.
- A benzene with a CH_2 as a substituent group is called benzyl.

2.2 Acidity of Phenol

- Phenols are aromatic counterparts of alcohols but are more acidic (pKa ≈ 10) because their corresponding phenoxide anions are resonance-stabilized by delocalization of the negative charge into the aromatic ring.
- Substitution of the aromatic ring by an electron-withdrawing group increases phenol acidity, and substitution by an electron-donating group decreases acidity.

2.3 Basicity of Aryl Amines

- When a nitrogen atom is incorporated into a ring, the basicity depends on where the lone pair resides.
- In a ring where the lone pair on the nitrogen atom resides in a hybrid orbital, then that lone pair is basic with the more basic equating with more s character in the hybrid orbital.
- In a ring where the lone pair on the nitrogen atom resides in a p orbital, then that lone pair is delocalized and less basic.

2.4 Structure and Stability of Benzene

- Benzene does not undergo the same reactions that alkenes do, due to its aromatic stability.
- Aromatic molecules must have all ring atoms in the same plane to allow delocalization of the pi electrons.
- Heats of hydrogenation can be used to show the special stability of benzene compared to what would be expected for a theoretical cyclohexatriene molecule.

2.5 Aromaticity and the Hückel 4n + 2 Rule

- The four criteria for aromaticity are that the molecule must:
  - be cyclic
  - be planar
  - be fully conjugated
  - have 4n+2 π Electrons
- Ionic molecules and heterocyclic molecules can also be aromatic if they meet the four criteria.

2.6 Aromatic Ions

- Carbanions and carbocations that meet the rules for aromaticity are also aromatic.

2.7 Aromatic Heterocycles: Pyridine and Pyrrole

- Heterocycles that meet the rules for aromaticty are also aromatic.
- If a lone pair of electrons on a ring atom can result in 4n+2 π Electrons, they will be in a p-orbital. If not, they will remain in hybrid orbitals.

2.8 Polycyclic Aromatic Compounds

- Benzene rings can be fused together to give larger aromatic compounds with mutliple rings called polycyclic aromatic compounds (or polycyclic aromatic hydrocarbons).

2.9 Oxidation of Aromatic Compounds

- Alkyl side-chains can be oxidized to benzoic acid (or a benzoic acid derivative if there are other groups present on the ring) by potassium permanganate ($KMnO_4$) as long as the benzylic carbon has at least one hydrogen attached.
- Radical halogenation will occur at the benzylic carbon, due to stabilization of radical intermediates.

2.10 Spectroscopy of Aromatic Compounds

- Aromatic compounds can be identified by common infrared absorptions in the 3000-3100 cm^{-1} and 1500-1600 cm^{-1}.
- In ^1H NMR, aromatic hydrogens appear in the 6.5-8 ppm region.

Skills to Master

- Skill 1 Using IUPAC rules to name substituted benzene molecules.
- Skill 2 Use heats of hydrogenation to explain aromatic stabilization.
- Skill 3 Explain acid-base properties of alcohols and phenols.
- Skill 4 Draw molecular orbital diagram for benzene (all 6 MO's).
- Skill 5 Use the criteria for aromaticity to determine if a molecule is aromatic or not.
- Skill 6 Determine whether lone pairs of electrons for ions and heterocycles will be in p orbitals or hybrid orbitals.
- Skill 7 Identify aromatic absorbances in infrared spectroscopy.
- Skill 8 Identify aromatic resonances in ^1H NMR spectroscopy.
- Skill 9 Explain the difference in basicity between pyridine, pyrrole, and other amines.
- Skill 10 Be able to draw the structure of furan, pyrrole, and imidazole.
- Skill 11 Use the Hückel $2n + 4$ rule to explain aromaticity.

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CHAPTER OVERVIEW

3: Chemistry of Benzene - Reactions of Aromatic Compounds

Learning Objectives

When you have completed Chapter 3, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. solve road-map problems that require an understanding of the chemistry discussed in this chapter and those that preceded it.
3. design multistep syntheses using the reactions discussed in this and the preceding chapters. In particular you should be prepared to show how an aromatic compound containing two or more substituents could be synthesized, taking care to introduce the substituents into the ring in the correct order.
4. define, and use in context, the key terms introduced.

In the preceding chapter, you studied the concept of aromaticity and spent considerable time on the theoretical aspects of the chemistry of aromatic compounds. In this chapter, you will begin to study the chemical reactions of aromatic compounds, focusing in particular on electrophilic aromatic substitution, and to a lesser extent on nucleophilic aromatic substitution. We will discuss, in detail, the mechanism of electrophilic substitution, paying particular attention to the factors that determine both the rate and position of substitution in those aromatic compounds which already have one or more substituents present in the aromatic ring. When we discuss nucleophilic aromatic substitution, you will see that it can be achieved by two different mechanisms, one of which involves the formation of an unusual looking intermediate, benzyne.

You will also see how alkyl and acyl groups can be introduced on to an aromatic ring; how, once introduced, alkyl groups can be converted to carboxyl groups; and how bromine can be introduced to the alkyl side chain of alkylbenzene. The latter reaction is particularly useful because the benzylic bromide so produced undergoes the reactions of a typical alkyl bromide, thus providing us with a synthetic route to a large variety of compounds.

3.0: Introduction
3.1: Electrophilic Aromatic Substitution Reactions - Bromination
3.2: Other Aromatic Substitutions
3.3: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction
3.4: Substituent Effects in the Reactivity of Aromatic Rings
3.5: The Direction of the Reaction
3.6: Trisubstituted Benzenes - Additivity of Effects
3.7: Nucleophilic Aromatic Substitution
3.8: Benzyne
3.9: Reduction of Aromatic Compounds
3.10: Synthesis of Polysubstituted Benzenes
3.11: Reactions of Arylamines
3.12: Additional Problems
3.S: Chemistry of Benzene - Electrophilic Aromatic Substitution (Summary)

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3.0: Introduction

Objective

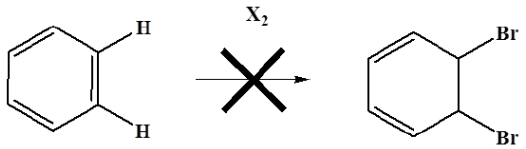
After completing this section, you should be able to identify electrophilic substitution as the single most important reaction of aromatic compounds.

In the preceding chapter, we looked at aromaticity—the stability associated with benzene and related compounds that contain a cyclic conjugated system of $4n + 2\ \pi$ electrons. In this chapter, we'll look at some of the unique reactions that aromatic molecules undergo.



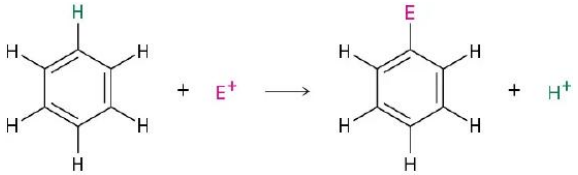
Figure 3.0.1: In the 19th and early-20th centuries, benzene was used as an aftershave lotion because of its pleasant smell and as a solvent to decaffeinate coffee beans. Neither is a good idea. (credit: modification of work "Ye Old Way" by Geo. H. Walker & Co./Library of Congress)

The six pi electrons obey Huckel's rule so benzene is especially stable. This means that the aromatic ring wants to be retained during reactions. Because of this, benzene does not undergo addition like other unsaturated hydrocarbons.



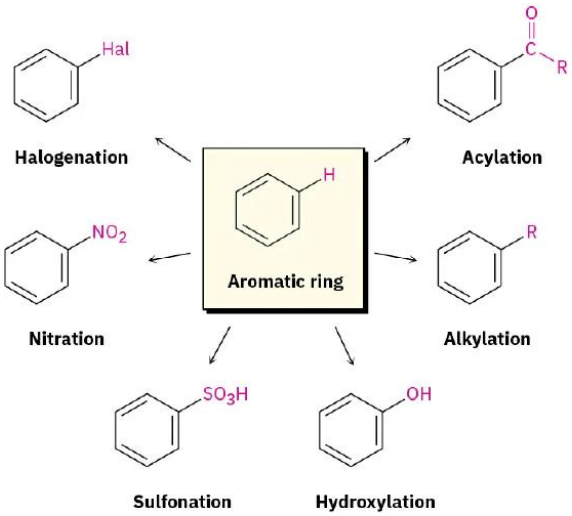
Non-Aromatic

The most common reaction of aromatic compounds is electrophilic aromatic substitution, in which an electrophile (E^+) reacts with an aromatic ring and substitutes for one of the hydrogens. The reaction is characteristic of all aromatic rings, not just benzene and substituted benzene, because aromaticity is maintained. In fact, the ability of a compound to undergo electrophilic substitution is a good test of aromaticity.



Other Examples of Electrophilic Aromatic Substitution

Many different substituents can be introduced onto an aromatic ring through electrophilic substitution. To list the five most useful reactions, an aromatic ring can be substituted by a halogen (–Cl, –Br, –I), a nitro group ($–NO_2$), a sulfonic acid group ($–SO_3H$), a hydroxyl group (–OH), an alkyl group (–R), or an acyl group (–COR). Starting from only a few simple materials, it's possible to prepare many thousands of substituted aromatic compounds.



Since the reagents and conditions employed in these reactions are electrophilic, these reactions are commonly referred to as **Electrophilic Aromatic Substitution**. The catalysts and co-reagents serve to generate the strong electrophilic species needed to effect the initial step of the substitution. The specific electrophile believed to function in each type of reaction is listed in the right hand column.

Reaction Type	Typical Equation				Electrophile $E^{(+)}$
Halogenation:	C_6H_6	+ Cl_2 & heat $FeCl_3$ catalyst	⟶	C_6H_5Cl + HCl Chlorobenzene	$Cl^{(+)}$ or $Br^{(+)}$
Nitration:	C_6H_6	+ HNO_3 & heat H_2SO_4 catalyst	⟶	$C_6H_5NO_2$ + H_2O Nitrobenzene	$NO_2^{(+)}$
Sulfonation:	C_6H_6	+ H_2SO_4 + SO_3 & heat	⟶	$C_6H_5SO_3H$ + H_2O Benzenesulfonic acid	$SO_3H^{(+)}$
Alkylation: Friedel-Crafts	C_6H_6	+ R-Cl & heat $AlCl_3$ catalyst	⟶	C_6H_5-R + HCl An Arene	$R^{(+)}$
Acylation: Friedel-Crafts	C_6H_6	+ RCOCl & heat $AlCl_3$ catalyst	⟶	C_6H_5COR + HCl An Aryl Ketone	$RCO^{(+)}$

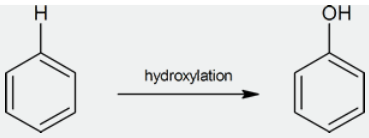
Key Terms

Make certain that you can define, and use in context, the key terms below.

- acylation
- alkylation
- electrophilic substitution
- halogenation
- hydroxylation
- nitration
- sulfonation

Study Notes

In this chapter, you will study all of the reactions shown in the Reaction Type table. In addition to these five reaction types, we also add a sixth common electrophilic substitution known as hydroxylation.



You must recognize the similarities between these reactions to minimize the material you must memorize.

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3.1: Electrophilic Aromatic Substitution Reactions - Bromination

Objectives

After completing this section, you should be able to

1. write the detailed mechanism for the reaction of bromine with benzene in the presence of a suitable catalyst.
2. draw the resonance contributors for the carbocation which is formed during the reaction of bromine with benzene.
3. compare the reaction which takes place between bromine and benzene and the reaction which takes place between bromine and an alkene.
4. draw an energy diagram for the reaction of bromine with benzene.
5. identify the reagents required to bring about aromatic bromination.
6. write an equation to represent aromatic bromination.

Before seeing how electrophilic aromatic substitutions occur, let's briefly recall what we learned about alkenes: Structure and Reactivity about electrophilic alkene additions. When a reagent such as Br_2 adds to an alkene, the π electrons of the double bond approach the electrophilic Br and form in a second step, the bromonium reacts with Br^- ion to yield the addition product. (First Reaction in Figure 1).

An electrophilic aromatic substitution reaction begins in a similar way, but there are a number of differences. One difference is that aromatic rings are less reactive toward electrophiles than alkenes. For example, Br_2 in CH_2Cl_2 solution reacts instantly with most alkenes but does not react with benzene at room temperature (Second Reaction in Figure 1). For the bromination of benzene to take place, a catalyst such as $FeBr_3$ is needed, which results in the substitution of hydrogen. (Third Reaction in Figure 1)

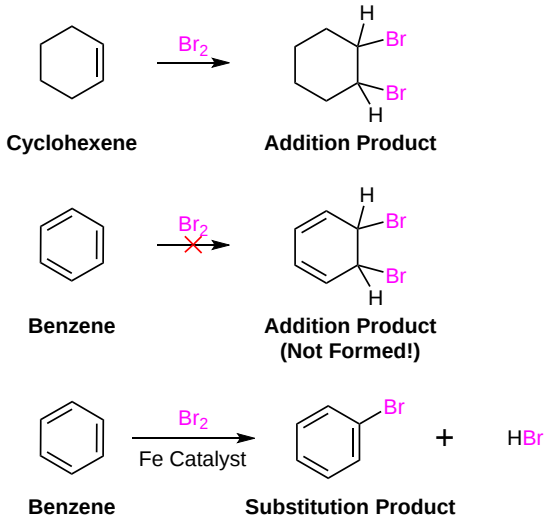
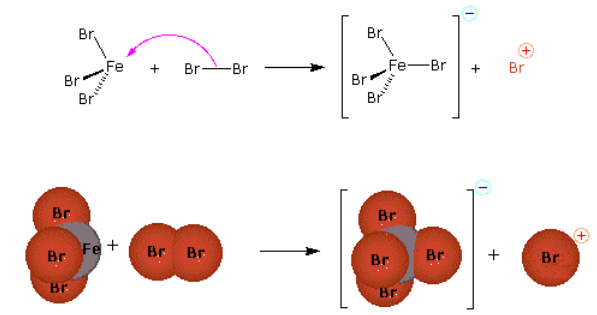


Figure 3.1.1: A comparison of the reactions of an electrophile (E^+) with an alkene and with benzene with and without a catalyst.

A Mechanism for Electrophilic Substitution Reactions of Benzene

The catalyst makes the Br_2 molecule more electrophilic by polarizing it to give a $FeBr_4{}^-Br^+$ species that reacts as if it were Br^+.



Ferric bromide and other Lewis acids enhance the electrophilic strength of bromine by forming a complex anion, in this case $FeBr_4^{\ominus}$. At the same time, this complexation creates the strongly electrophilic bromine cation, which reacts with nucleophiles.

Figure 3.1.2: Preliminary step: Formation of the strongly electrophilic bromine cation

A two-step mechanism has been proposed for these electrophilic substitution reactions. In the first, slow or rate-determining step, the polarized Br_2 molecule reacts with the nucleophilic benzene ring forming a sigma-bond to yield a nonaromatic carbocation intermediate that is doubly allylic and has three resonance forms. This intermediate is called **arenium intermediate**.

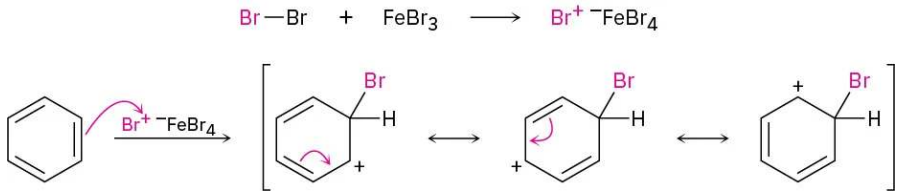


Figure 3.1.3: Formation of the **arenium intermediate.**

Although more stable than a typical alkyl carbocation because of resonance, the intermediate in electrophilic aromatic substitution is nevertheless much less stable than the starting benzene ring itself, with its 150 kJ/mol (36 kcal/mol) of aromatic stability. Thus, the reaction of an electrophile with a benzene ring is endergonic, has a substantial activation energy, and is rather slow. Figure 3.1.3 shows an energy diagram comparing the reaction of an electrophile with an alkene and with benzene. The benzene reaction is slower (higher $\Delta G^{\ddagger}$) because the starting material is more stable.

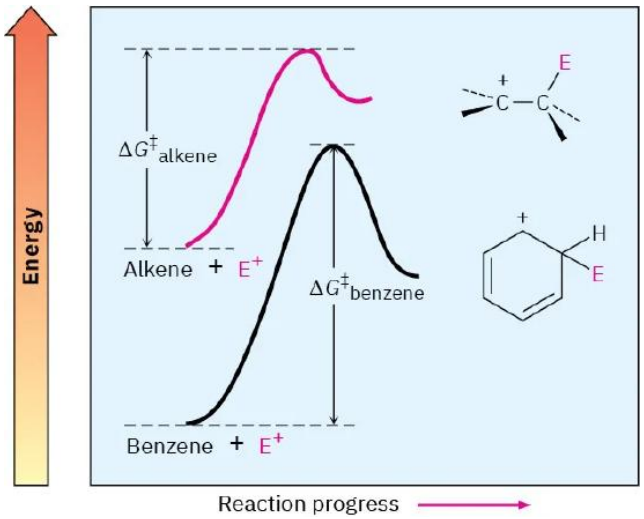


Figure 3.1.4: A comparison of the reactions of an electrophile (E^+) with an alkene and with benzene: $\Delta G\ddagger_{alkene} < \Delta G\ddagger_{benzene}$. The benzene reaction is slower than the alkene reaction because of the stability of the aromatic ring.

Another difference between alkene addition and aromatic substitution occurs after the carbocation intermediate has formed. Instead of adding Br^- to give the product of an addition reaction, the carbocation intermediate loses H^+ from the bromine-bearing carbon to

give a substitution product. Note that this loss of H^+ is similar to what occurs in the second step of an E1 reaction. The net effect of reaction of Br_2 with benzene is the substitution of H^+ by Br^+ by the overall mechanism shown in Figure 3.1.5.

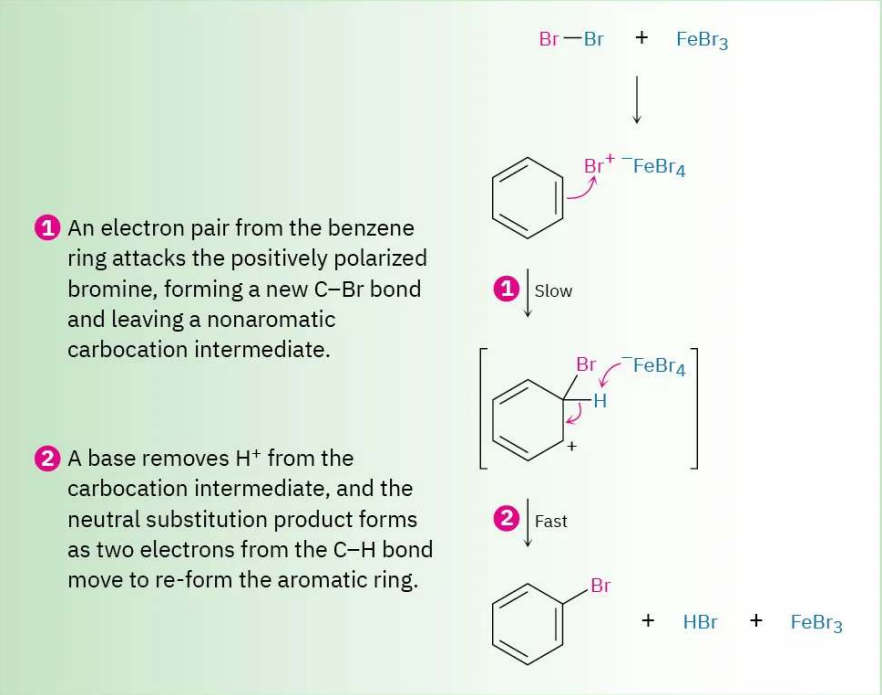


Figure 3.1.5: The mechanism for the electrophilic bromination of benzene. The reaction occurs in two steps and involves a resonance-stabilized carbocation intermediate.

Why does the reaction of Br_2 with benzene take a different course than its reaction with an alkene? The answer is straightforward. If addition occurred, the 150 kJ/mol stabilization energy of the aromatic ring would be lost and the overall reaction would be endergonic. When substitution occurs, though, the stability of the aromatic ring is retained and the reaction is exergonic. An energy diagram for the overall process is shown in Figure 3.1.6.

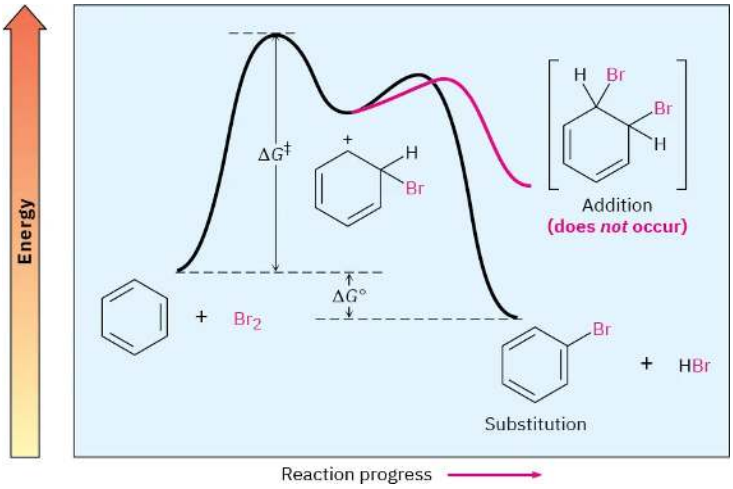
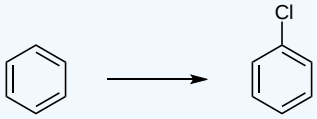


Figure 3.1.6: An energy diagram for the electrophilic bromination of benzene. Because the stability of the aromatic ring is retained, the overall process is exergonic.

Exercises

Exercise 3.1.1

What reagents would you need to get the given product?

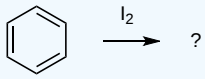


Answer

Cl_2 and $AlCl_3$ or Cl_2 and $FeCl_3$

Exercise 3.1.2

What product would result from the given reagents?

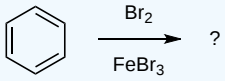


Answer

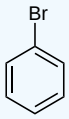
No Reaction

Exercise 3.1.3

What is the major product given the reagents below?



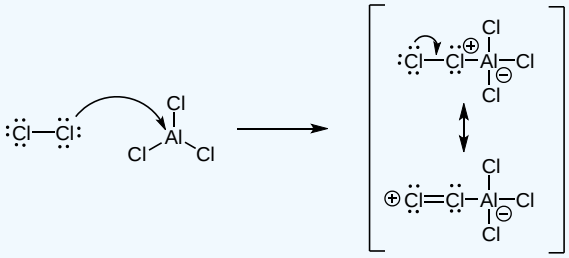
Answer



Exercise 3.1.4

Draw the formation of Cl^+ from $AlCl_3$ and Cl_2.

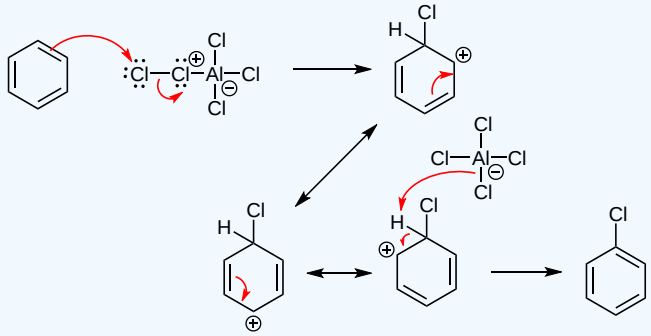
Answer



Exercise 3.1.5

Draw the mechanism of the reaction between Cl^+ and a benzene.

Answer



Study Notes

The mechanism presented in Figure 5 for electrophilic aromatic substitution should be considered in context with other mechanisms involving carbocation intermediates. These include S_N1 and E1 reactions of alkyl halides, and Brønsted acid addition reactions of alkenes.

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution or addition product.
2. The cation may transfer a proton to a base, giving a double bond product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

S_N1 and E1 reactions are respective examples of the first two modes of reaction. The second step of alkene addition reactions proceeds by the first mode, and any of these three reactions may exhibit molecular rearrangement if an initial unstable carbocation is formed. The carbocation intermediate in electrophilic aromatic substitution (the arenium ion) is stabilized by charge delocalization (resonance) so it is not subject to rearrangement. In principle it could react by either mode 1 or 2, but the energetic advantage of reforming an aromatic ring leads to exclusive reaction by mode 2 (*ie.* proton loss).

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3.2: Other Aromatic Substitutions

Objectives

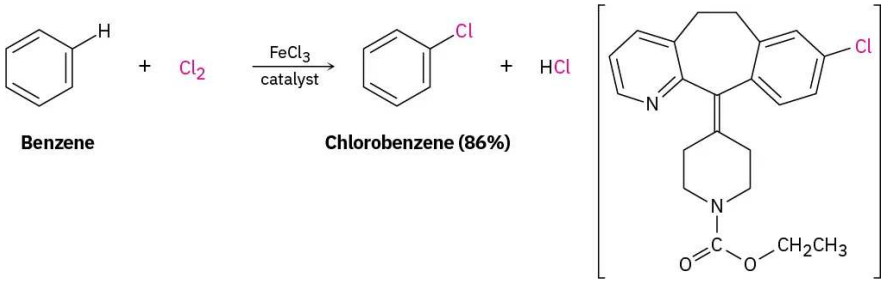
After completing this section, you should be able to

1. write a balanced equation for the halogenation (F, Cl, Br, I) of benzene in the presence of a suitable catalyst or promoter.
2. draw the resonance contributors for the carbocation which is formed during the reaction of chlorine or bromine with benzene.
3. write the equation for the nitration and sulfonation of benzene.
4. write the detailed mechanism for the nitration and sulfonation of benzene.
5. write the equation for the reduction of an aromatic nitro compound to an amine.
6. identify aromatic sulfonation as being a reversible process, and describe the conditions under which the forward and reverse reactions are favoured.
7. write the equation for the desulfonation of an aromatic sulfonic acid.
8. identify aromatic sulfonic acids as being key intermediates in the manufacture of sulfa drugs.

There are many other kinds of electrophilic aromatic substitutions besides bromination, and all occur by the same general mechanism. Let's look at some of these other reactions briefly.

Aromatic Halogenation

Aromatic rings react with Cl_2 in the presence of $FeCl_3$ catalyst to yield chlorobenzenes, just as they react with Br_2 and $FeBr_3$. This kind of reaction is used in the synthesis of numerous pharmaceutical agents, including the antiallergy medication loratadine, marketed as Claritin.



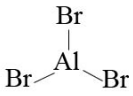
Benzene **Chlorobenzene (86%)** **Loratadine**

Lewis Acidic Catalysts

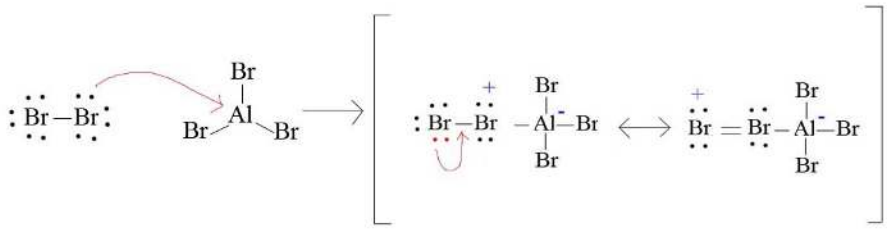
Halogens need the help and aid of Lewis Acidic Catalysts to activate and become very strong electrophiles as they polarize the Br-Br bond. An Activated halogen, X^+, where X= Br or Cl, reacts with benzene as it is a much better electrophile than X_2 alone.

Examples of Lewis Acidic Catalysts are Ferric halides (FeX_3) and Aluminum Halides (AlX_3) where X= Br or Cl. We had covered the activation of the halogens using Ferric halides (FeX_3); now, let's observe the activation using Aluminum Halides (AlX3).

In the example of bromine, in order to make bromine electrophillic enough to react with benzene, we use the aid of an aluminum halide such as aluminum bromide.



With aluminum bromide as a Lewis acid, Br_2 reacts with $AlBr_3$ to form a complex structure for Br^+. The presence of this complex for Br^+ is a much better electrophile than Br_2 alone.



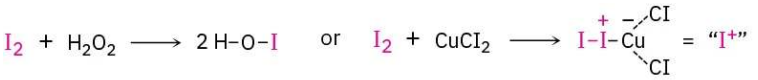
As the bromine has now become more electrophillic after activation of a catalyst, an electrophillic attack by the benzene occurs at the terminal bromine of Br-Br-$AlBr_3$. The mechanism continues as presented in the previous section. Since the by-product aluminum tetrabromide is a strong nucleophile, it pulls of a proton from the Hydrogen on the same carbon as bromine. In the end, the catalyst regenartes as it is not consumed during the reaction.

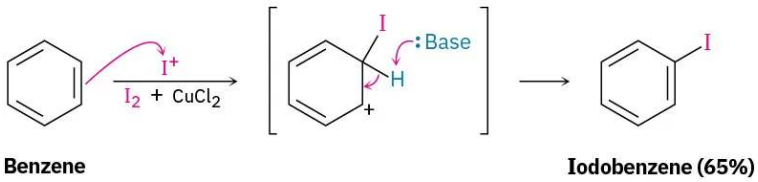
Dissociation Energies of Halogens and its Effect on Halogenation of Benzenes

The electrophillic bromination of benzenes is an exothermic reaction. Considering the exothermic rates of aromatic halogenation decreasing down the periodic table in the Halogen family. Fluoridation is the most exothermic, and Iodination is the least. Being so exothermic, a reaction of flourine with benzene is explosive! For iodine, electrophillic iodination is generally endothermic, hence a reaction is often not possible. Similar to bromide, chlorination would require the aid of an activating presence such as Alumnium Chloride or Ferric Chloride. The mechanism of this reaction is the same as with Bromination of benzene.

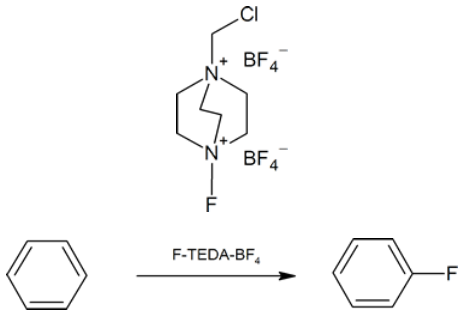
Iodine and Fluorine need specific reagents

Iodine and fluorine cannot be introduced into an aromatic ring by the method used for bromine and chlorine. On its own, iodine is unreactive with aromatic rings. Still, one method for aromatic iodination is treatment in the presence of a copper salt such as copper(II)chloride, where I_2 is oxidized to a more powerful electrophilic species that reacts as if it were I^+.





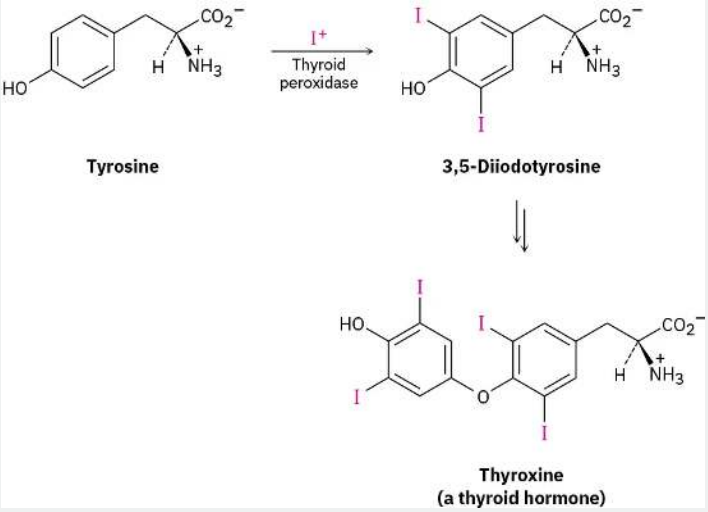
In contrast, fluorine is too reactive, so it cannot be used directly for aromatic monofluorination. However, fluorinating agents like 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (also known as F-TEDA-BF_4) sold commercially as Sectfluor® offer convenient sources of "F^+" for this type of reaction.



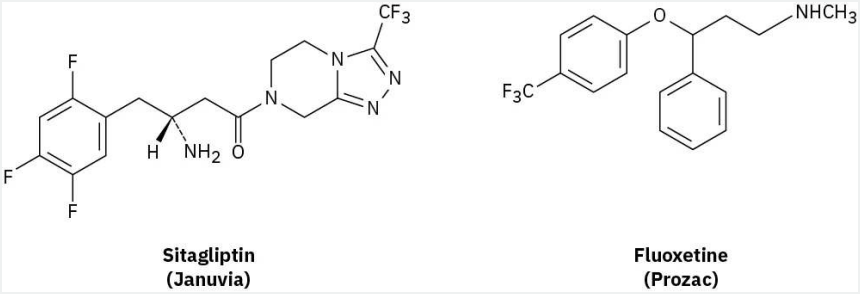
https://chem.libretexts.org/@go/page/500370

Biological impact

Electrophilic aromatic halogenations also occur in the biosynthesis of many naturally occurring molecules, particularly those produced by marine organisms. In humans, the best-known example occurs in the thyroid gland during the biosynthesis of thyroxine, a hormone involved in regulating growth and metabolism. The amino acid tyrosine is first iodinated by thyroid peroxidase, and two of the iodinated tyrosine molecules then couple. The electrophilic iodinating agent is an I^+ species, perhaps hypoiodous acid (HIO), that is formed from iodide ion by oxidation with H_2O_2.

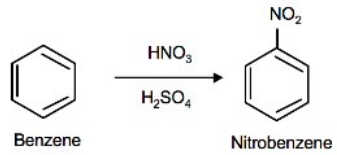


More than 20% of all pharmaceutical agents sold contain fluorine, including 30% of the top 100 drugs sold. Sitagliptin (Januvia), used to treat type 2 diabetes, fluoxetine (Prozac), an antidepressant, and atorvastatin (Lipitor), a statin used to lower cholesterol, are examples.



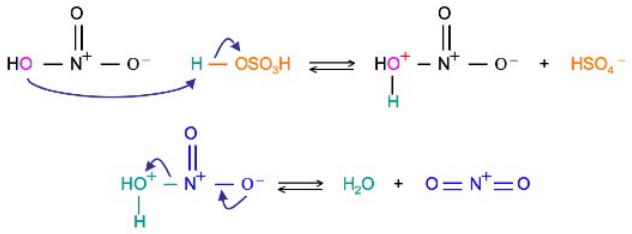
Aromatic Nitration

Aromatic rings are nitrated by reaction with a mixture of concentrated nitric and sulfuric acids.



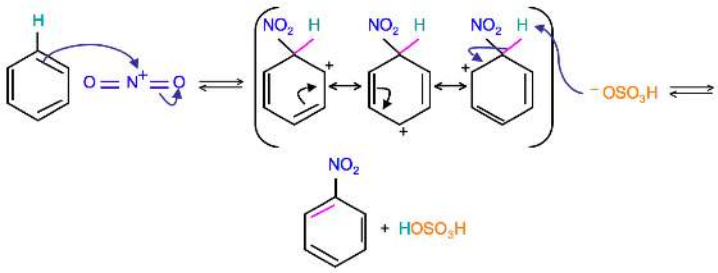
Sulfuric Acid Activation of Nitric Acid

The first step in the nitration of benzene is to activate HNO_3 with sulfuric acid to produce a stronger electrophile, the nitronium ion. The formation of the nitronium ion is through the protonation of nitric acid by sulfuric acid, which causes the loss of a water molecule and formation of a nitronium ion.



Because the nitronium ion is a good electrophile, it is attacked by benzene to produce Nitrobenzene.

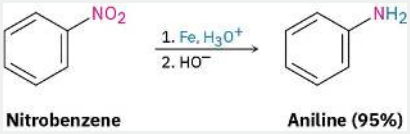
Mechanism



(Resonance forms of the intermediate can be seen in the generalized electrophilic aromatic substitution)

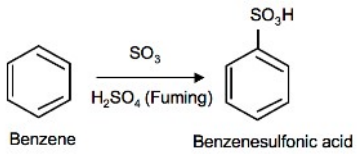
Synthetic Value

Electrophilic nitration of an aromatic ring does not occur in nature but is particularly important in the laboratory because the nitro-substituted product can be reduced by reagents such as iron, tin, or $SnCl_2$ to yield the corresponding *arylamine*, $ArNH_2$. Attachment of an amino group ($–NH_2$) to an aromatic ring by the two-step nitration/reduction sequence is a key part of the industrial synthesis of many dyes and pharmaceutical agents. We'll discuss more reactions of aromatic nitrogen compounds in Chapter 10.



Aromatic Sulfonation

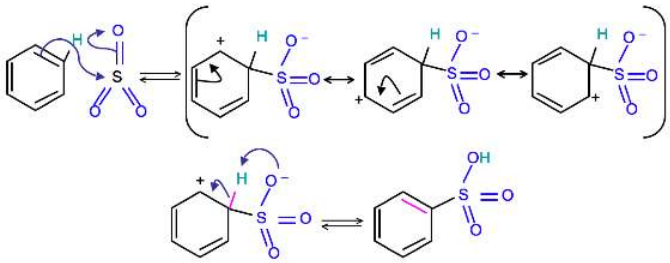
Aromatic rings can be sulfonated by reaction with so-called fuming sulfuric acid, a mixture of H_2SO_4 and SO_3. The reactive electrophile is either HSO_3^+ or neutral SO_3, depending on reaction conditions, and substitution occurs by the same two-step mechanism seen previously for bromination and nitration (Figure 3.2.2). Note, however, that the sulfonation reaction is readily reversible. It can occur either forward or backward, depending on the reaction conditions. Sulfonation is favored in strong acid, but desulfonation (benzenesulfonic acid to produce benzene) is favored in hot, dilute aqueous acid.



Mechanism

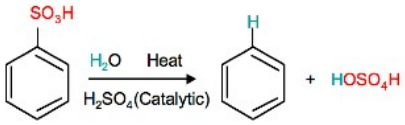
To produce benzenesulfonic acid from benzene, fuming sulfuric acid and sulfur trioxide are added. Fuming sulfuric acid is a concentrated solution of dissolved sulfur trioxide in sulfuric acid. The sulfur in sulfur trioxide is electrophilic because the oxygens

pull electrons away from it because oxygen is very electronegative. The benzene attacks the sulfur (and subsequent proton transfers occur) to produce benzenesulfonic acid.



Reverse Sulfonation

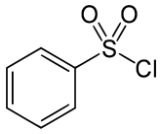
Sulfonation of benzene is a reversible reaction. Sulfur trioxide readily reacts with water to produce sulfuric acid and heat. Therefore, by adding heat to benzenesulfonic acid in diluted aqueous sulfuric acid the reaction is reversed.



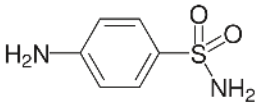
Because sulfonation is a reversible reaction, it can also be used in further substitution reactions in the form of a directing blocking group because it can be easily removed. The sulfonic group blocks the carbon from being attacked by other substituents and after the reaction is completed it can be removed by reverse sulfonation.

Synthetic Value

Aromatic sulfonation does not occur naturally but is widely used in the preparation of detergents, dyes, and pharmaceutical agents. For example, the sulfa drugs, such as sulfanilamide, were among the first clinically useful antibiotics. Although largely replaced today by more effective agents, sulfa drugs are still used in the treatment of meningitis and urinary tract infections. Another example is Bezenesulfonyl Chloride, which is a precursor to sulfonamides, which are used in chemotherapy. These drugs are prepared commercially by a process that involves aromatic sulfonation as its key step.



Bezenesulfonyl Chloride



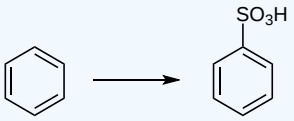
Sulfanilamide

Feeling Curious? https://en.wikipedia.org/wiki/Sulfanilamide

Exercises

Exercise 3.2.1

1. What is/are the required reagent(s)for the following reaction:

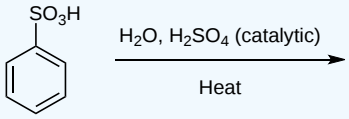


Answer

SO_3 and H_2SO_4 (fuming)

Exercise 3.2.2

What is the product of the following reaction:



Answer



Exercise 3.2.3

Why is it important that the nitration of benzene by nitric acid occurs in sulfuric acid?

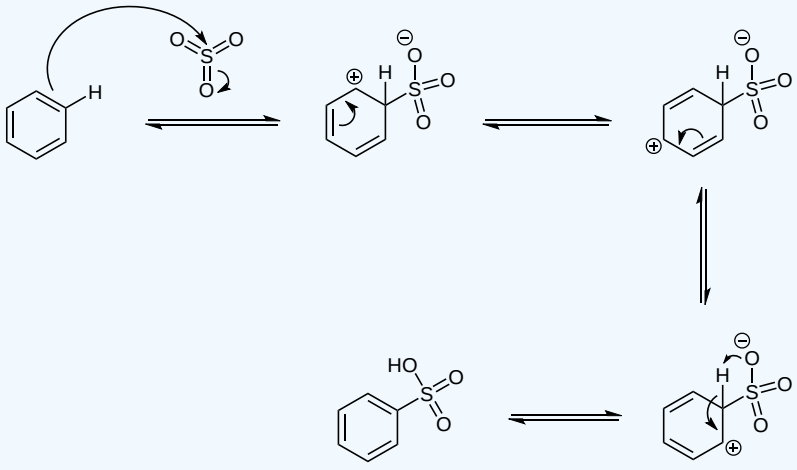
Answer

Sulfuric acid is needed in order for a good electrophile to form. Sulfuric acid protonates nitric acid to form the nitronium ion (water molecule is lost). The nitronium ion is a very good electrophile and is open to attack by benzene. Without sulfuric acid the reaction would not occur.

Exercise 3.2.4

Write a detailed mechanism for the sulfonation of benzene, including all resonance forms.

Answer

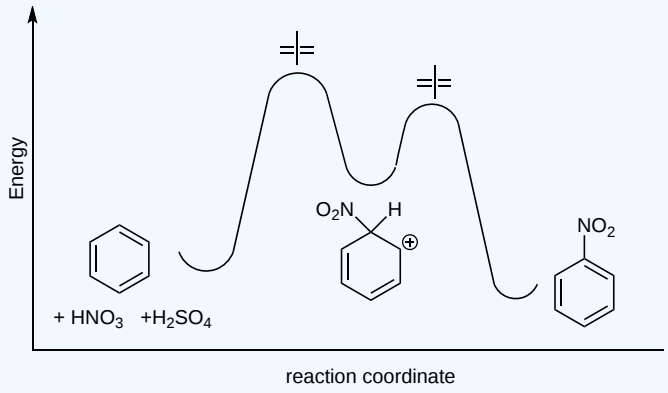


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Exercise 3.2.5

Draw an energy diagram for the nitration of benzene. Draw the intermediates, starting materials, and products. Label the transition states.

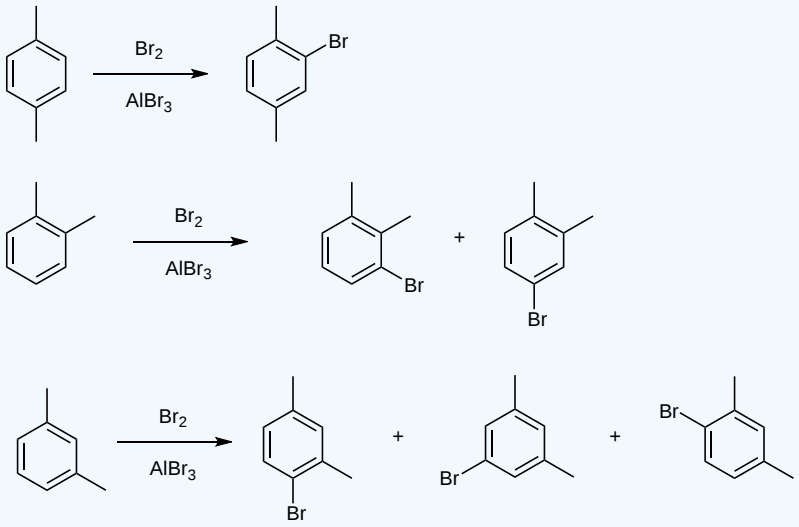
Answer



Exercise 3.2.6

In each case, how many products would be possible for the bromination of *p*-xylene, *o*-xylene, and *m*-xylene?

Answer

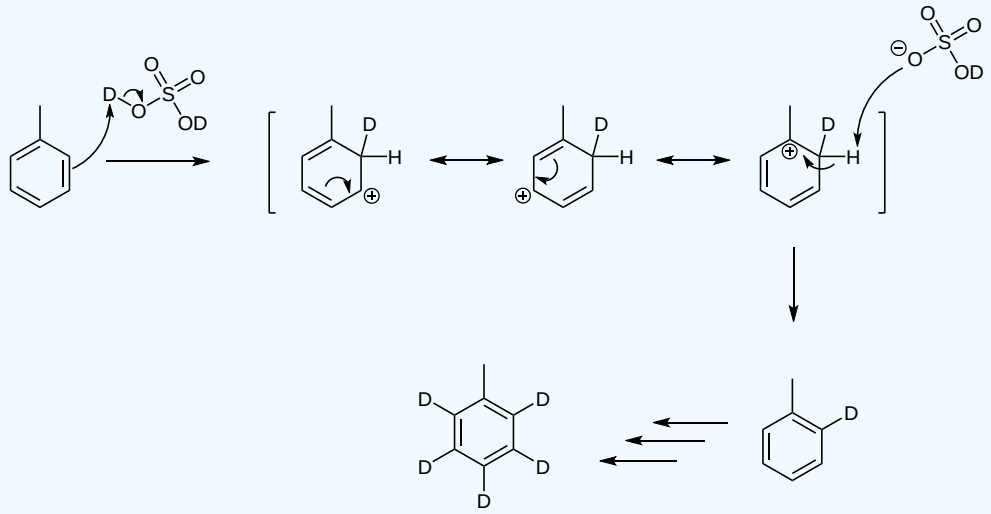


Exercise 3.2.7

If toluene is treated with D_2SO_4 all the hydrogen's are replaced with deuterium. Explain.

Answer

The deuterium is added to the ring. When the ring "re-aromatizes" the base scavenges the hydrogen before the deuterium and therefore is left on the ring. Continues for the rest of the hydrogen on the ring.



Key Terms

Make certain that you can define, and use in context, the key term below.

- nitronium ion, (NO^{+2})

References

1. Laali, Kenneth K., and Volkar J. Gettwert. “Electrophilic Nitration of Aromatics in Ionic Liquid Solvents.” The Journal of Organic Chemistry 66 (Dec. 2000): 35-40. American Chemical Society.
2. Malhotra, Ripudaman, Subhash C. Narang, and George A. Olah. Nitration: Methods and Mechanisms. New York: VCH Publishers, Inc., 1989.
3. Sauls, Thomas W., Walter H. Rueggeberg, and Samuel L. Norwood. “On the Mechanism of Sulfonation of the Aromatic Nucleus and Sulfone Formation.” The Journal of Organic Chemistry 66 (1955): 455-465. American Chemical Society.
4. Vollhardt, Peter. Organic Chemistry : Structure and Function. 5th ed. Boston: W. H. Freeman & Company, 2007.

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3.3: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

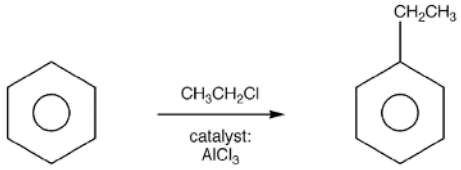
Objectives

After completing this section, you should be able to

- write the equation and the detailed mechanism for a typical Friedel-Crafts alkylation, then identify the similarities between this reaction and the previous presented electrophilic aromatic substitution reactions.
- identify the product formed from the Friedel-Crafts alkylation of a given aromatic compound.
- identify the aromatic compound needed to prepare a given arene by a Friedel-Crafts alkylation.
- identify the alkyl halide and catalyst needed to form a specified arene from a given aromatic compound.
- show how alkyl halides and acyl-halides can be used as alkylating agents in Friedel-Crafts alkylation reactions.
- discuss the limitations of the Friedel-Crafts alkylation reaction, paying particular attention to the structure of the alkyl halide, the structure of the aromatic substrate, and the problem of polyalkylation.
- write an equation and the detailed mechanism for a typical Friedel-Crafts acylation.
- identify the product formed by the Friedel-Crafts acylation of a given aromatic compound.
- identify the aromatic compound, and the reagent and catalyst needed to prepare a given ketone through a Friedel-Crafts acylation reaction.

Friedel-Crafts Alkylation

Among the most useful electrophilic aromatic substitution reactions in the laboratory is alkylation—the introduction of an alkyl group onto the benzene ring. Called the Friedel–Crafts reaction after its founders in 1877, Charles Friedel and James Crafts, the reaction is carried out by treating an aromatic compound with an alkyl chloride, RCl, in the presence of $AlCl_3$ to generate a carbocation electrophile, R^+.



Aluminum chloride catalyzes the reaction by helping the alkyl halide to generate a carbocation in much the same way that $FeBr_3$ catalyzes aromatic brominations by polarizing Br_2.

The reactivity of haloalkanes increases as we move up the periodic table and increase polarity. This means that an RF haloalkane is most reactive followed by RCl then RBr and finally RI. This means that the Lewis acids used as catalysts in Friedel-Crafts Alkylation reactions tend to have similar halogen combinations, such as BF_3, $SbCl_5$, $AlCl_3$, $SbCl_5$, and $AlBr_3$, all of which are commonly used in these reactions.

Mechanism

Step 1: An electron pair from the aromatic ring attacks the carbonation, forming a new C-C bond. The arenium ion intermediate results with stabilization from multiple resonance forms.

Steps 2: The loss of H^+ completes the reaction giving the neutral alkylated substitution product (Figure 3.3.1).

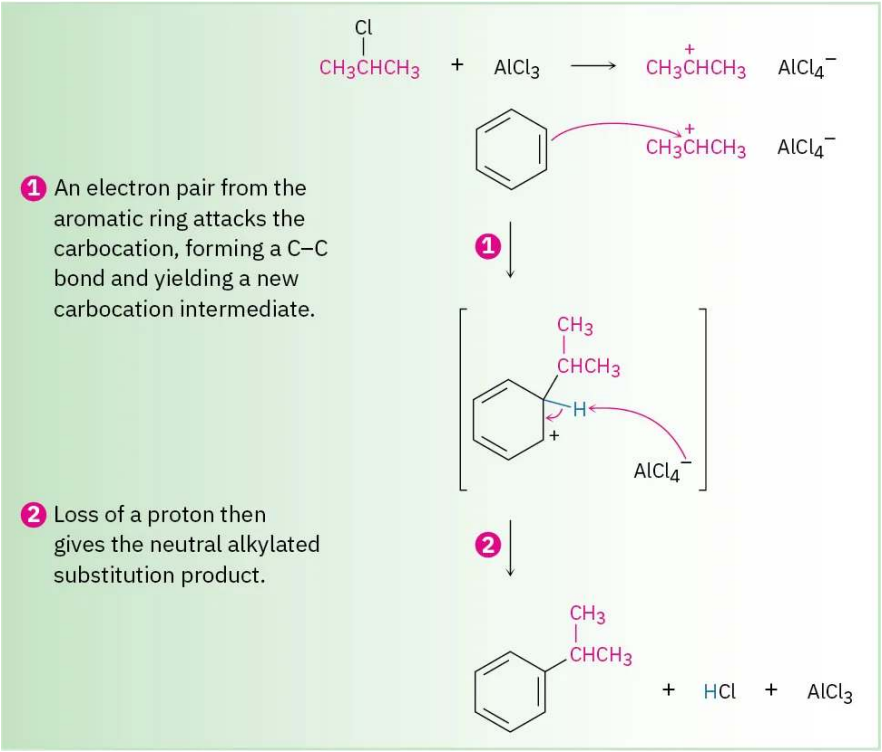


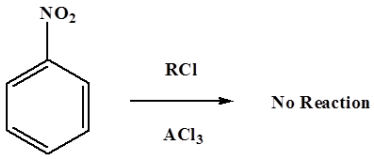
Figure 3.3.1: Mechanism for the Friedel–Crafts alkylation reaction of benzene with 2-chloropropane to yield isopropylbenzene (cumene). The electrophile is a carbocation, generated by $AlCl_3$-assisted dissociation of an alkyl halide.

Some limitations of Friedel-Crafts Alkylation

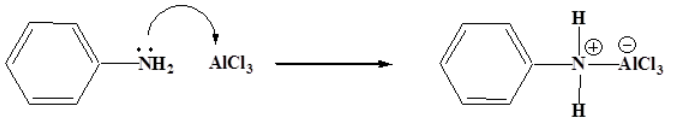
Despite its utility, the Friedel–Crafts alkylation has several limitations. For one thing, only alkyl halides can be used. Aromatic (aryl) halides and vinylic halides don't react because aryl and vinylic carbocations are too high in energy to form under Friedel–Crafts conditions.



Another limitation is that Friedel–Crafts reactions don't succeed on aromatic rings that are substituted by a strongly electron-withdrawing group, which will deactivate the ring, such as carbonyl (C=O) or nitro group (NO_2).



Adding to the list of substituents that will not allow the reaction to proceed are basic amino groups that can be protonated. The lone pair electrons on the amines react with the Lewis acid $AlCl_3$. This places a positive charge next to the benzene ring, which is so strongly activating that the Friedel-Crafts reaction cannot occur.



The positive charge strongly deactivates the benzene ring

We'll see in the next section that the presence of a substituent group already on a ring can have a dramatic effect on that ring's reactivity to further electrophilic substitution. Rings that contain any of the substituents listed in Figure 3.3.2 do not undergo Friedel–Crafts alkylation.

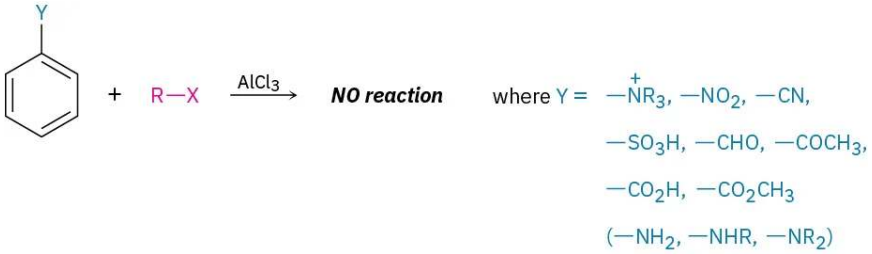
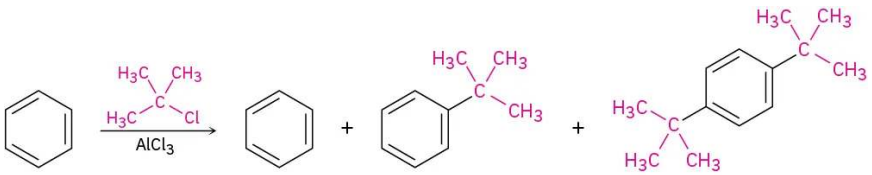


Figure 3.3.2: Limitations on the aromatic substrate in Friedel–Crafts reactions. No reaction occurs if the substrate has either an electron-withdrawing substituent or a basic amino group.

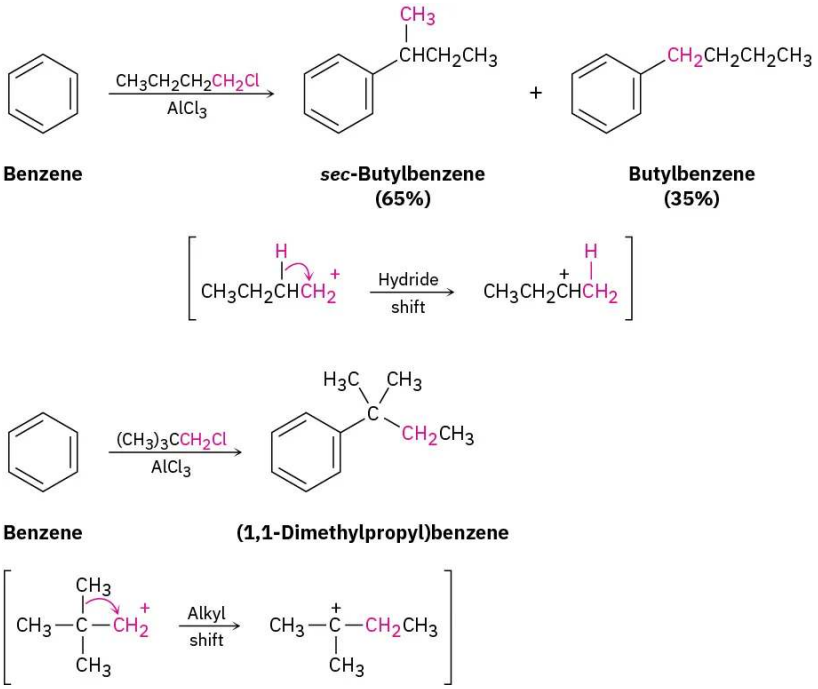
A third limitation to the Friedel–Crafts alkylation is that it's often difficult to stop the reaction after a single substitution. Once the first alkyl group is on the ring, a second substitution reaction is facilitated for reasons we'll discuss in the next section. Thus, we often observe *polyalkylation*. Reaction of benzene with 1 mol equivalent of 2-chloro-2-methylpropane, for example, yields *p*-di-*tert*-butylbenzene as the major product, along with small amounts of *tert*-butylbenzene and unreacted benzene. A high yield of mono-alkylation product is obtained only when a large excess of benzene is used.



Minor product **Major product**

A final limitation to the Friedel–Crafts reaction is that a skeletal rearrangement of the alkyl carbocation electrophile sometimes occurs during reaction, particularly when a primary alkyl halide is used. For instance, treating benzene with 1-chlorobutane at 0 °C gives an approximately 2 : 1 ratio of rearranged (*sec*-butyl) to unrearranged (butyl) products.

The carbocation rearrangements that accompany Friedel–Crafts reactions are like those that accompany electrophilic additions to alkenes and occur either by hydride shift or alkyl shift. For example, the relatively unstable primary butyl carbocation produced by reaction of 1-chlorobutane with $AlCl_3$ rearranges to the more stable secondary butyl carbocation by the shift of a hydrogen atom and its electron pair (a hydride ion, $H:^-$) from C2 to C1. Similarly, alkylation of benzene with 1-chloro-2,2-dimethylpropane yields (1,1-dimethylpropyl)benzene. The initially formed primary carbocation rearranges to a tertiary carbocation by shift of a methyl group and its electron pair from C2 to C1.

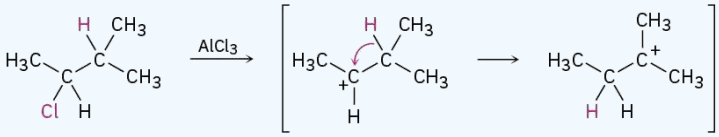


Worked Example 3.3.1: Predicting the Product of a Carbocation Rearrangement

The Friedel–Crafts reaction of benzene with 2-chloro-3-methylbutane in the presence of $AlCl_3$ occurs with a carbocation rearrangement. What is the structure of the product?

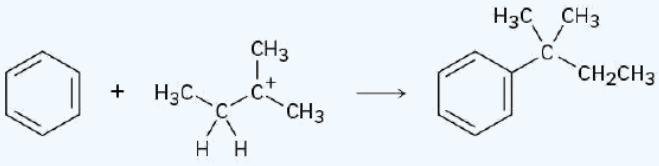
Strategy

A Friedel–Crafts reaction involves initial formation of a carbocation, which can rearrange by either a hydride shift or an alkyl shift to give a more stable carbocation. Draw the initial carbocation, assess its stability, and see if the shift of a hydride ion or an alkyl group from a neighboring carbon will result in increased stability. In the present instance, the initial carbocation is a secondary one that can rearrange to a more stable tertiary one by a hydride shift.



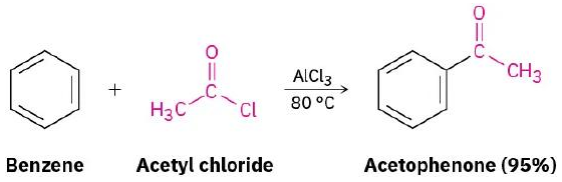
Use this more stable tertiary carbocation to complete the Friedel–Crafts reaction.

Solution



Friedel-Crafts Acylation

Just as an aromatic ring can be alkylated by reaction with an alkyl chloride, it can be acylated by reaction with a carboxylic acid chloride, RCOCl, in the presence of $AlCl_3$. That is, an acyl group (–COR; pronounced **a**-sil) is substituted onto the aromatic ring. For example, reaction of benzene with acetyl chloride yields the ketone acetophenone.



Mechanism

The mechanism of Friedel–Crafts acylation is similar to that of Friedel–Crafts alkylation, and the same limitations on the aromatic substrate noted previously in Figure 3.3.2 for alkylation also apply to acylation. The reactive electrophile is a resonance-stabilized acyl cation, generated by reaction between the acyl chloride and $AlCl_3$ (Figure 3.3.3). As the resonance structures in the figure indicate, an acyl cation is stabilized by interaction of the vacant orbital on carbon with lone-pair electrons on the neighboring oxygen. Because of this stabilization, no carbocation rearrangement occurs during acylation.

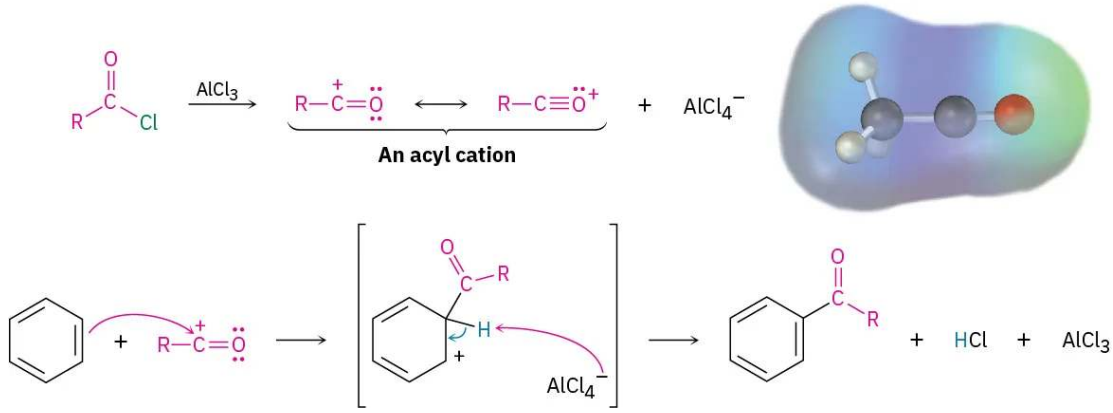


Figure 3.3.3: Mechanism of the Friedel–Crafts acylation reaction. As rhe electrophile is a resonance-stabilized acyl cation, no rearrangement occurs. The electrostatic potential map indicates that **carbon is the most positive atom.**

Unlike the multiple substitutions that often occur in Friedel–Crafts alkylations, acylations never occur more than once on a ring because the product acylbenzene is less reactive than the starting material.

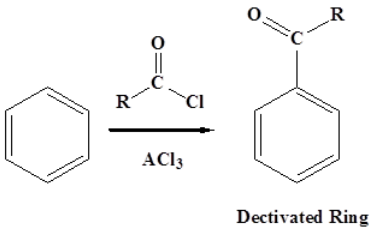
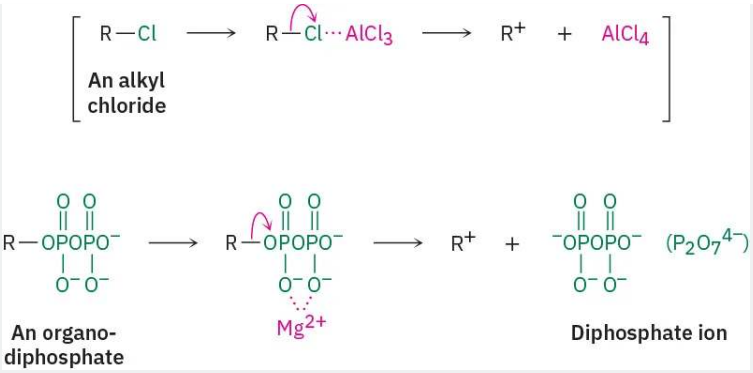


Figure 3.3.4: *Polyacylation* does not occur during Friedel-Crafts Acylation because an acyl group is deactivating, thus preventing further acylations.

Biological Impact

Aromatic alkylations occur in numerous biological pathways, although there is of course no $AlCl_3$ present in living systems to catalyze the reaction. Instead, the carbocation electrophile is typically formed by dissociation of an organodiphosphate. The dissociation is usually assisted by complexation to a divalent metal cation such as Mg^{2+}, just as the dissociation of an alkyl chloride is assisted by $AlCl_3$.



An example of a biological Friedel–Crafts reaction occurs during the biosynthesis of phylloquinone, or vitamin K_1, the human blood-clotting factor. Phylloquinone is formed by reaction of 1,4-dihydroxynaphthoic acid with phytyl diphosphate. Phytyl diphosphate first dissociates to a resonance-stabilized allylic carbocation, which then substitutes onto the aromatic ring in the typical way. Several further transformations lead to phylloquinone (Figure 3.3.4).

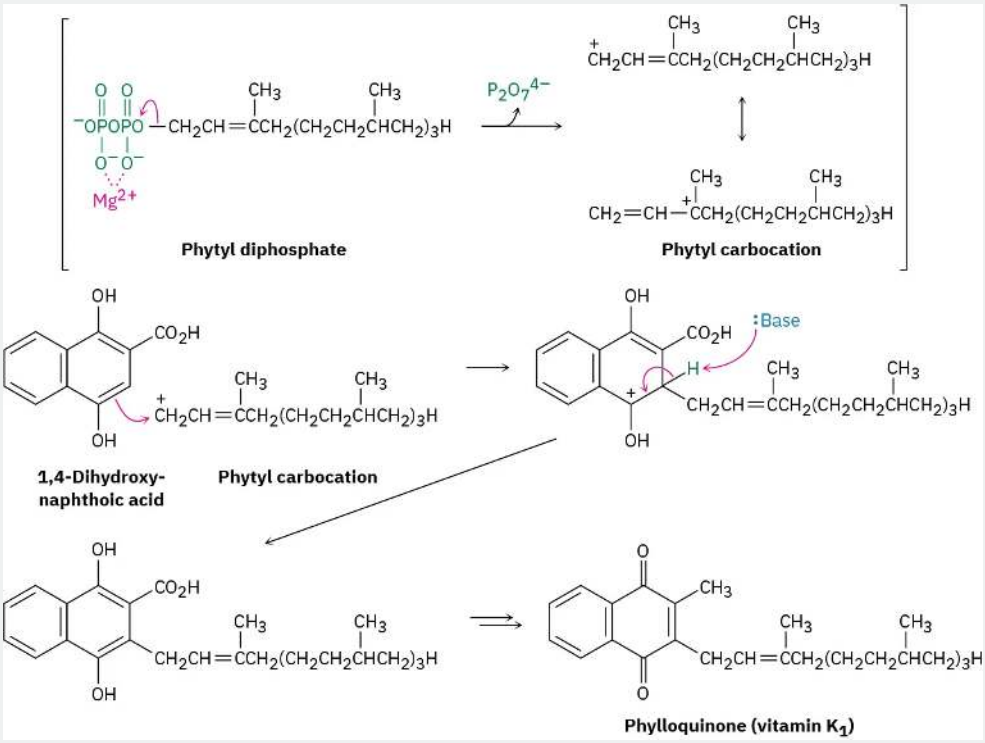
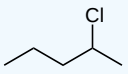
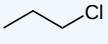


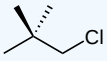
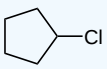
Figure 3.3.4: Biosynthesis of phylloquinone (vitamin K_1) from 1,4-dihydroxynaphthoic acid. The key step that joins the 20-carbon phytyl side chain to the aromatic ring is a Friedel–Crafts-like electrophilic substitution reaction with a diphosphate ion as the leaving group.

Exercises

? Exercise 3.3.1

Which of the following will NOT undergo a rearrangement in a Friedel-Crafts reaction?

A) CH_3Cl B)  C) 

D)  E) 

Answer

A, B, and E will not undergo a rearrangement.

Exercise 3.3.2

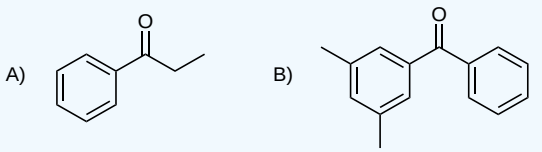
What is the major monosubstitution product from the Friedel–Crafts reaction of benzene with 1-chloro-2-methylpropane in the presence of $AlCl_3$?

Answer

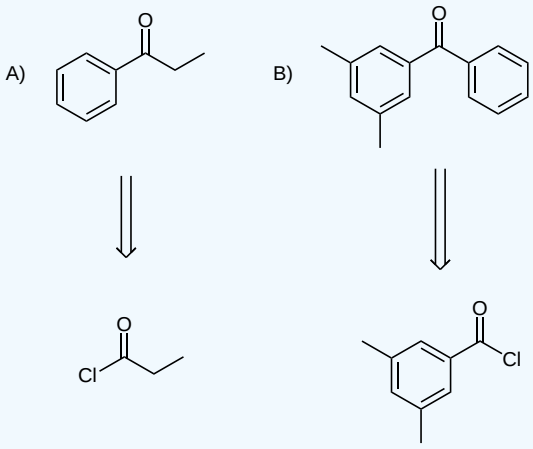
tert-Butylbenzene

Exercise 3.3.3

Suggest an acyl chloride that was used to make the following compounds:



Answer



Key Terms

Make certain that you can define, and use in context, the key terms below.

- acyl group
- Friedel-Crafts acylation reaction
- Friedel-Crafts alkylation reaction
- polyalkylation

Study Notes

A Friedel-Crafts alkylation reaction is an electrophilic aromatic substitution reaction in which a carbocation is attacked by a pi bond from an aromatic ring with the net result that one of the aromatic protons is replaced by an alkyl group. If you prefer, you may regard these reactions as involving an attack by an aromatic ring on a carbocation. The latter approach is the one used in the textbook, but the former approach is probably more common.

When more than one alkyl group is introduced into an aromatic ring during the course of a Friedel-Crafts alkylation reaction, polyalkylation is said to have occurred.

The four limitations on the use of Friedel-Crafts alkylations are as follows:

1. vinyl and aryl halides cannot be used to form carbocations.
2. the aromatic substrate must not contain a strongly deactivating group, or groups, such as NH_2, NHR or NR_2, which form complexes with the Lewis acid catalyst and in so doing become strongly deactivating.
3. polyalkylation, which can be overcome by using a large excess of the aromatic substrate.
4. carbocation rearrangements may occur in any reaction that involves a carbocation.

The reaction of an aromatic substrate with an acid chloride (or acid anhydride) in the presence of an aluminum chloride catalyst is used to introduce an acyl group (C=O) into the aromatic ring through an electrophilic aromatic substitution mechanism. Such reactions are Friedel-Crafts acylation reactions.

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3.4: Substituent Effects in the Reactivity of Aromatic Rings

Objectives

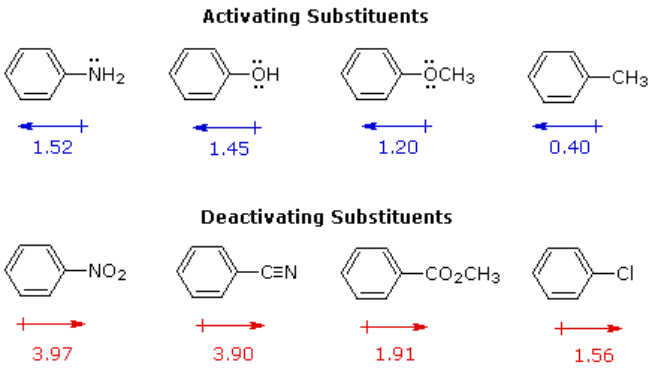
After completing this section, you should be able to

1. describe the two ways in which a substituent influences the electrophilic substitution of a monosubstituted aromatic compound.
2. classify each of the following substituents as being either activating or deactivating with respect to electrophilic aromatic substitution: $-NH_2$, $-OH$, $-NHR$, $-NR_2$, $-OR$, $-NHCOR$, alkyl (R), phenyl, R_3N^+, $-NO_2$, $-CN$, $-COR$, $-CO_2H$, $-CO_2R$, $-CHO$, halogens.
3. list a given series of substituents (selected from those given in Objective 2) in order of increasing or decreasing ability to activate or deactivate an aromatic ring with respect to electrophilic substitution.
4. explain, in general terms, the factors that determine whether a given substituent will activate or deactivate an aromatic ring with respect to electrophilic substitution.
5. list a given series of aromatic compounds in order of increasing or decreasing reactivity with respect to electrophilic substitution.
6. explain the inductive effects displayed by substituents such as nitro, carboxyl, alkyl and the halogens during electrophilic aromatic substitution reactions.
7. explain the resonance effects displayed by substituents such as nitro, carbonyl-containing, hydroxy, alkoxy and amino groups during electrophilic aromatic substitution reactions.

Reactivity of the Aromatic Ring

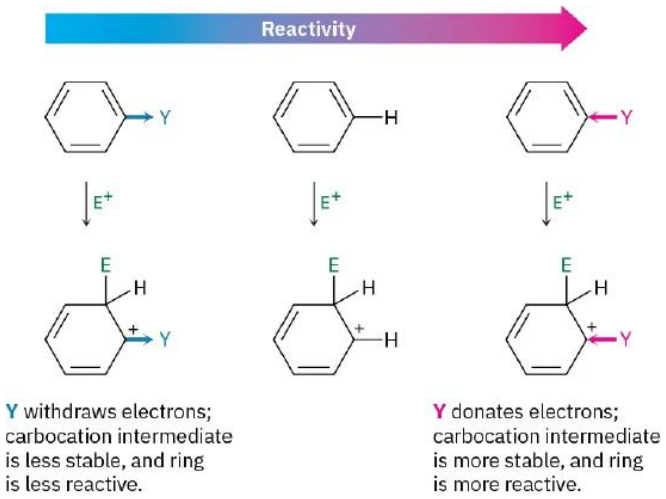
Substituted rings are divided into two groups based on the type of substituent that the ring carries:

- **Activated rings**: the substituents on the ring are groups that donate electrons.
- **Deactivated rings**: the substituents on the ring are groups that withdraw electrons.



Activating and Deactivating Effects

What makes a group either an activating or a deactivating one? The common characteristic of all activating groups is that they donate electrons to the ring, thereby making the ring more electron-rich, stabilizing the carbocation intermediate, and lowering the activation energy for its formation. Conversely, the common characteristic of all deactivating groups is that they withdraw electrons from the ring, thereby making the ring more electron-poor, destabilizing the carbocation intermediate, and raising the activation energy for its formation.



Compare the electrostatic potential maps of benzaldehyde (deactivated), chlorobenzene (weakly deactivated), and phenol (activated) with that of benzene. As shown in Figure 3.4.2, the ring is more positive (yellow-green) when an electron-withdrawing group such as –CHO or –Cl is present and more negative (red) when an electron-donating group such as –OH is present.

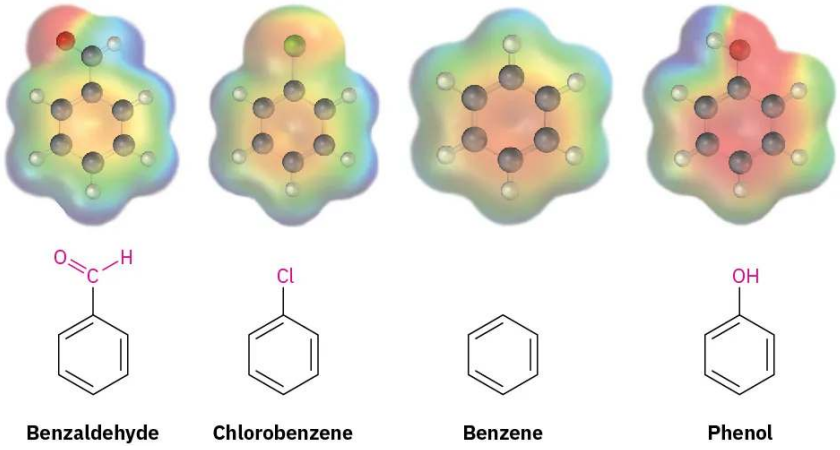
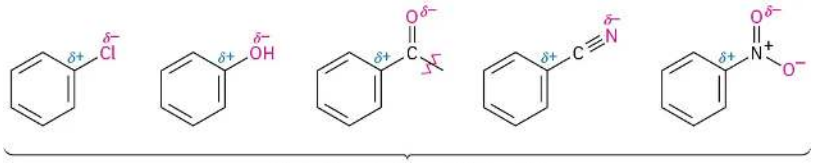


Figure 3.4.2: Electrostatic potential maps of benzene and several substituted benzenes show that an electron-withdrawing group (–CHO or –Cl) makes the ring more **electron-poor**, while an electron-donating group (–OH) makes the ring more **electron-rich**.

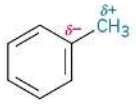
The withdrawal or donation of electrons by a substituent group is controlled by an interplay of *inductive effects* and *resonance effects*. The influence a substituent exerts on the reactivity of a benzene ring may be explained by the interaction of two effects:

Inductive Effect

An inductive effect is the withdrawal or donation of electrons through a σ bond due to electronegativity. Halogens, hydroxyl groups, carbonyl groups, cyano groups, and nitro groups inductively withdraw electrons through the σ bond linking the substituent to a benzene ring. This effect is most pronounced in halobenzenes and phenols, in which the electronegative atom is directly attached to the ring, but is also significant in carbonyl compounds, nitriles, and nitro compounds, in which the electronegative atom is farther removed. Alkyl groups, on the other hand, inductively donate electrons. This is the same hyperconjugative donating effect that causes alkyl substituents to stabilize alkenes and carbocations.



Inductive electron withdrawal

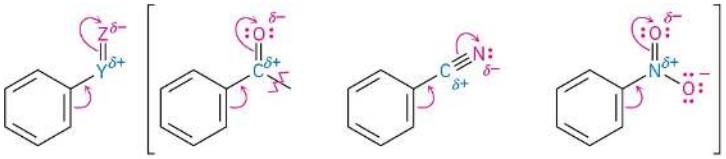


Inductive electron donation

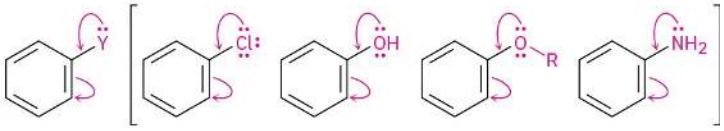
Resonance Effect

A resonance effect is the withdrawal or donation of electrons through a π bond due to the overlap of a *p* orbital on the substituent with a *p* orbital on the aromatic ring. Carbonyl, cyano, and nitro substituents, for example, withdraw electrons from the aromatic ring by resonance. The π electrons flow from the ring to the substituent, leaving a positive charge in the ring. Note that substituents with an electron-withdrawing resonance effect have the general structure –Y=Z, where the Z atom is more electronegative than Y.

Conversely, halogen, hydroxyl, alkoxyl (–OR), and amino substituents donate electrons to the aromatic ring by resonance. Lone-pair electrons flow from the substituents to the ring, placing a negative charge on the ring. Substituents with an electron-donating resonance effect have the general structure –Ÿ, where the Y atom has a lone pair of electrons available for donation to the ring.



Resonance electron-withdrawing groups



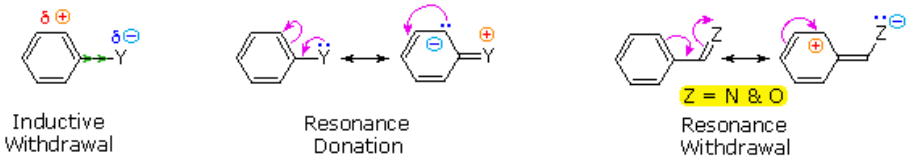
Resonance electron-donating groups

This conjugative interaction facilitates electron pair donation or withdrawal, to or from the benzene ring, in a manner different from the inductive shift. If the atom bonded to the ring has one or more non-bonding valence shell electron pairs, as do nitrogen, oxygen and the halogens, electrons may flow into the aromatic ring by p-π conjugation (resonance), as in the middle diagram. Finally, polar double and triple bonds conjugated with the benzene ring may withdraw electrons, as in the right-hand diagram. Note that in the resonance examples all the contributors are not shown. In both cases the charge distribution in the benzene ring is greatest at sites ortho and para to the substituent.

Inductive and Resonance may not Agree

One further point: inductive effects and resonance effects don't necessarily act in the same direction. Halogen, hydroxyl, alkoxyl, and amino substituents, for instance, have electron-withdrawing inductive effects because of the electronegativity of the –X, –O, or –N atom bonded to the aromatic ring but have electron-donating resonance effects because of the lone-pair electrons on those –X, –O, or –N atoms. When the two effects act in opposite directions, the stronger effect dominates. Thus, hydroxyl, alkoxyl, and amino substituents are activators because their stronger electron-donating resonance effect outweighs their weaker electron-withdrawing

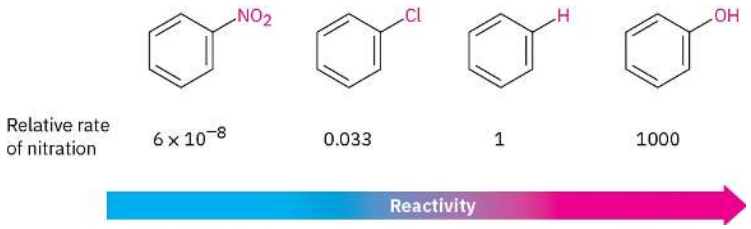
inductive effect. Halogens, however, are deactivators because their stronger electron-withdrawing inductive effect outweighs their weaker electron-donating resonance effect.



In the case of the nitrogen and oxygen activating groups displayed in the top row of the previous diagram, electron donation by resonance dominates the inductive effect and these compounds show exceptional reactivity in electrophilic substitution reactions. Although halogen atoms have non-bonding valence electron pairs that participate in p-π conjugation, their strong inductive effect predominates, and compounds such as chlorobenzene are less reactive than benzene. The three examples on the left of the bottom row (in the same diagram) are examples of electron withdrawal by conjugation to polar double or triple bonds, and in these cases the inductive effect further enhances the deactivation of the benzene ring. Alkyl substituents such as methyl increase the nucleophilicity of aromatic rings in the same fashion as they act on double bonds.

Net Effect

For instance, in aromatic nitration, an –OH substituent makes the ring 1000 times more reactive than benzene, while an $–NO_2$ substituent makes the ring more than 10 million times less reactive, getting the classification of strong activator and strong deactivator in that order. Chlorine makes the ring only 30 times less reactive than benzene, for such halogens are considered mild deactivators with increasing strength along the group.



Classification of Substituents

Examples of activating groups in the relative order from the most activating group to the least activating:

$$-NH_2, -NR_2 > -OH, -OR > -NHCOR > -CH_3 \text{ and other alkyl groups}$$

with R as alkyl groups (C_nH_{2n+1})

Examples of deactivating groups in the relative order from the most deactivating to the least deactivating:

$$-NO_2, -CF_3 > -COR, -CN, -CO_2R, -SO_3H > \text{Halogens}$$

with R as alkyl groups (C_nH_{2n+1})

The order of reactivity among Halogens from the most reactive (least deactivating substituent) to the least reactive (most deactivating substituent) halogen is:

$$F > Cl > Br > I$$

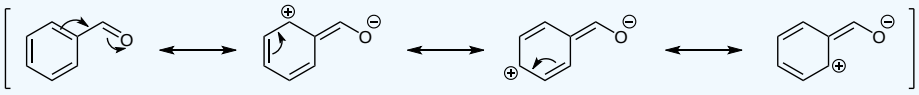
The order of reactivity of the benzene rings toward the electrophilic substitution when they are substituted with a halogen group follows the order of the size of the halogen attached. As the size of the halogen increases, the ring's reactivity decreases.

Exercises

Exercise 3.4.1

Draw the resonance structures for benzaldehyde to show the electron-withdrawing group.

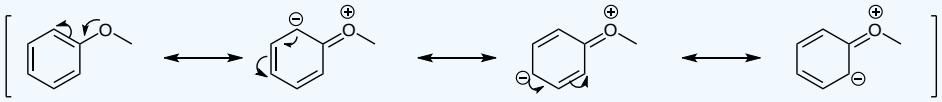
Answer



Exercise 3.4.2

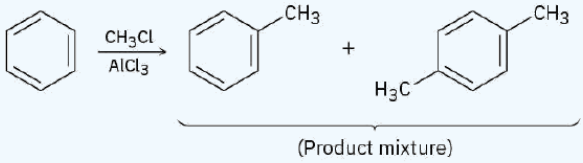
Draw the resonance structures for methoxybenzene to show the electron-donating group.

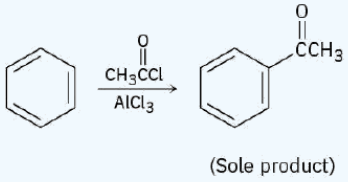
Answer



Exercise 3.4.3

Use Figure 3.4.1 to explain why Friedel–Crafts alkylations often give polysubstitution but Friedel–Crafts acylations do not.



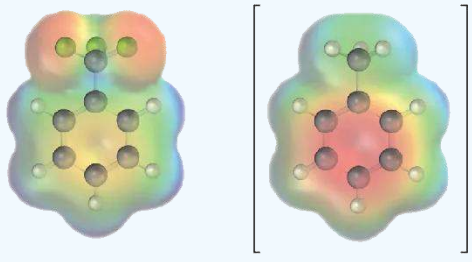


Answer

Alkylbenzenes are more reactive than benzene itself, but acylbenzenes are less reactive.

Exercise 3.4.4

An electrostatic potential map of (trifluoromethyl)benzene, $C_6H_5CF_3$, is shown. Would you expect (trifluoromethyl)benzene to be more reactive or less reactive than toluene toward electrophilic substitution? Explain.



(Trifluoromethyl)benzene Toluene

Answer

Toluene is more reactive; the trifluoromethyl group is electron-withdrawing.

Exercise 3.4.5

Classify these two groups as activating or deactivating groups:

1. alcohol
2. ester

Answer

1. Alcohol is an activating group.
2. Esters can be either. If the oxygen atom is next to the ring, esters are activated. However, if the carbonyl is next to the ring, the ester is a deactivating group.

Exercise 3.4.6

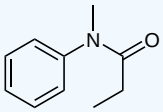
Does a chloride substituent activate or deactivate an aromatic ring?

Answer

Chloride deactivates an aromatic ring due to the inductive effect.

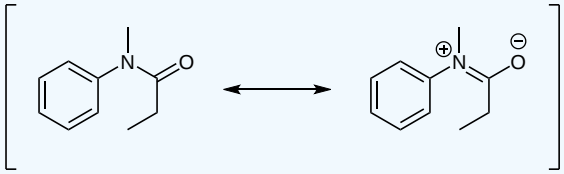
Exercise 3.4.7

Is the following compound less reactive towards electrophilic substitution than aniline? Explain.



Answer

As seen in resonance, the electron density is also localized off the ring, thereby deactivating it compared to aniline.



Key Terms

Make certain that you can define, and use in context, the key terms below.

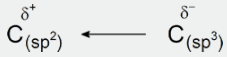
- inductive effect
- resonance effect

Study Notes

On reading Objective 2 students may exclaim “How am I ever going to memorize all of this!”—or words to that effect. The answer is that if you are trying to memorize such things, you are taking the wrong approach to organic chemistry. What you should be doing is trying to understand the factors that determine whether a given substituent will activate or deactivate a benzene ring with respect to electrophilic substitution.

You may wish to review earlier material on to the inductive effect. If so, refer to Sections 2.1, 7.9 (paying particular attention to the “Study Notes”) and 14.5.

Note that one argument sometimes used to explain the ability of alkyl groups to donate electrons inductively to an aromatic ring is that sp^2-hybridized carbon atoms are more electronegative than sp^3-hybridized carbon atoms. Thus, a sigma bond between sp^2- and sp^3-carbon is slightly polarized, as follows:



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3.5: The Direction of the Reaction

Objectives

After completing this section, you should be able to

1. draw the resonance contributors for the carbocation intermediate formed during the reaction of a given monosubstituted benzene derivative with any of the electrophiles discussed in this chapter.
2. classify substituents as either meta or ortho/para directing.
3. classify substituents as ortho/para directing activators, ortho/para directing deactivators, or meta directing deactivators.
4. predict the product or products formed from the reaction of a given monosubstituted benzene derivative with each of the electrophiles discussed in this chapter.
5. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic substitution of an alkyl benzene results in a mixture of mainly ortho- and para- substituted products.
6. explain why the electrophilic substitution of phenols, amines and their derivatives proceeds more rapidly than the electrophilic substitution of benzene itself.
7. explain, by drawing the resonance contributors for the intermediate carbocation, why meta substitution predominates in electrophilic aromatic substitution reactions carried out on benzene derivatives containing one of the substituents R_3N^+, NO_2, CO_2H, CN, CO_2R, COR or CHO.
8. explain why electrophilic aromatic substitution of benzene derivatives containing one of the substituents listed in Objective 7, above, proceeds more slowly than the electrophilic substitution of benzene itself.
9. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic aromatic substitution of halobenzenes produces a mixture of mainly ortho- and para-substituted products.
10. explain why the electrophilic aromatic substitution of halobenzenes proceeds more slowly than does the electrophilic substitution of benzene itself.

Substituents affect the *orientation* of the reaction.

The three possible disubstituted products—ortho, meta, and para—are usually not formed in equal amounts. Instead, the nature of the substituent initially present on the benzene ring determines the position of the second substitution. An –OH group directs substitution toward the ortho and para positions, for instance, while a carbonyl group such as –CHO directs substitution primarily toward the meta position. Table 1 lists experimental results for the nitration of some substituted benzenes.



Table 16.1 Orientation of Nitration in Substituted Benzenes

	Product (%)		
	Ortho	Meta	Para
Meta-directing deactivators			
$-\overset{+}{N}(CH_3)_3$	2	87	11
$-NO_2$	7	91	2
$-CO_2H$	22	76	2
–CN	17	81	2
$-CO_2CH_3$	28	66	6
$-COCH_3$	26	72	2
–CHO	19	72	9
Ortho- and para-directing deactivators			
–F	13	1	86
–Cl	35	1	64
–Br	43	1	56
–I	45	1	54
Ortho- and para-directing activators			
$-CH_3$	63	3	34
–OH	50	0	50
$-NHCOCH_3$	19	2	79

Substituents can be classified into three groups, as shown in Figure 3.5.1: *ortho- and para-directing activators*, *ortho- and para-directing deactivators*, and *meta-directing deactivators*. There are no meta-directing activators. Notice how the directing effect of a group correlates with its reactivity. All meta-directing groups are strongly deactivating, and most ortho- and para-directing groups are activating. The halogens are unique in being ortho- and para-directing but weakly deactivating.

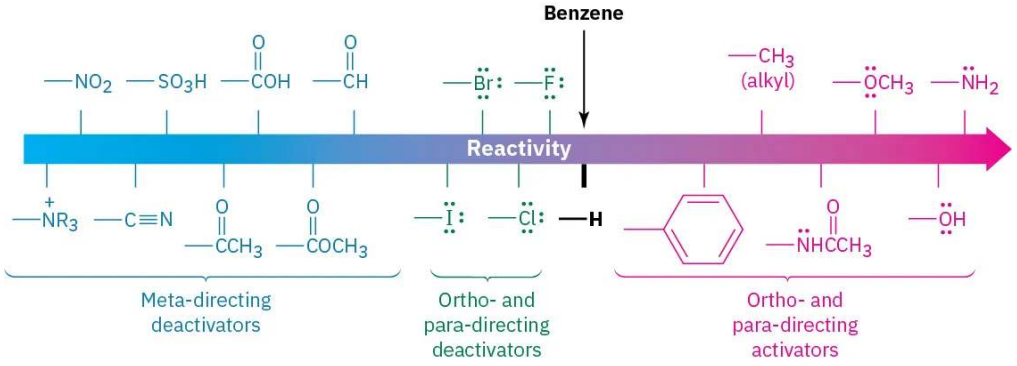


Figure 3.5.1: Classification of substituent effects in electrophilic aromatic substitution. All activating groups are ortho- and para-directing, and all deactivating groups other than halogen are meta-directing. Halogens are unique in being deactivating but ortho- and para-directing.

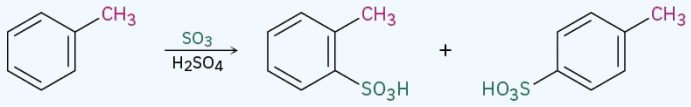
Worked Example 3.5.1: Predicting the Product of an Electrophilic Aromatic Substitution Reaction

Predict the major product of the sulfonation of toluene.

Strategy

Identify the substituent present on the ring, and decide whether it is ortho- and para-directing or meta-directing. According to Figure 3.5.1, an alkyl substituent is ortho- and para-directing, so sulfonation of toluene will primarily give a mixture of *o* -toluenesulfonic acid and *p* -toluenesulfonic acid.

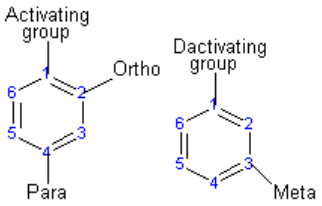
Solution



Toluene **o-Toluenesulfonic acid** **p-Toluenesulfonic acid**

The direction of the reaction

The activating group directs the reaction to the ortho or para position, meaning the electrophile substitutes for the hydrogen on carbon 2 or carbon 4. The deactivating group directs the reaction to the meta position, which means the electrophile substitutes for the hydrogen that is on carbon 3, with the exception of the halogens, which are deactivating groups but direct the ortho or para substitution.

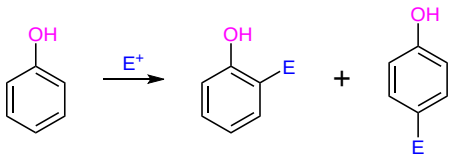


Substituents determine the reaction direction by resonance or inductive effect

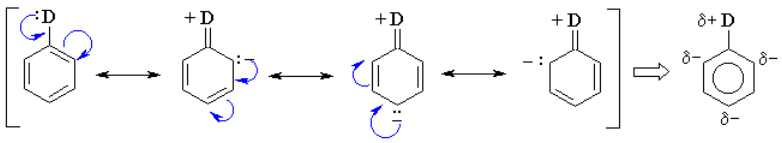
Resonance effect is the conjugation between the ring and the substituent, which means the delocalization of the π electrons between the ring and the substituent. Inductive effect is the withdrawal of the sigma (the single bond) electrons away from the ring toward the substituent, due to the higher electronegativity of the substituent compared to the carbon of the ring.

Activating groups (ortho or para directors)

The hydroxyl substituent of phenol is *ortho* and *para* directing and makes the aromatic ring strongly activated towards electrophilic aromatic substitution reaction.



When substituents such as -OH have an unshared pair of electrons, the resonance effect is stronger than the inductive effect, which makes these substituents stronger activators, since this resonance effect directs the electron toward the ring. In cases where the substrates are esters or amides, they are less activating because they form a resonance structure that pulls the electron density away from the ring.

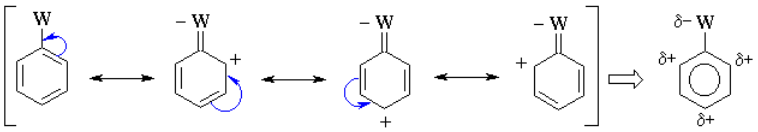


By looking at the mechanism above, we can see how electron-donating groups direct electrophilic substitution to the ortho and para positions. Since the extra electron density is localized on the ortho and para carbons, these carbons are more likely to react with the electrophile.

Inductive effects of alkyl groups activate the direction of the ortho or para substitution, which is when s electrons gets pushed toward the ring.

Deactivating group (meta directors)

The deactivating groups deactivate the ring via the inductive effect of electronegative atoms, which withdraw electron density from the ring.



The mechanism above shows that when electron density is withdrawn from the ring, it leaves the carbons at the ortho and para positions with partial positive charges, which is unfavorable for the electrophile; therefore, the electrophile attacks the carbon at the meta position.

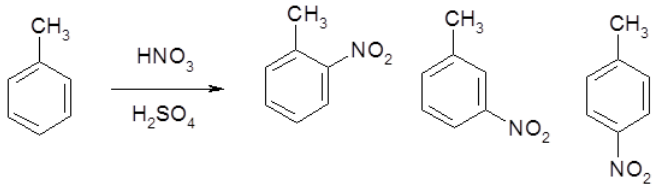
Halogens are an exception to the deactivating group that directs to the ortho or para substitution. The halogens deactivate the ring by inductive effect, not by resonance, even though they have an unpaired pair of electrons. The unpaired electron pair is donated to the ring, but the inductive effect pulls the ring's s electrons away due to the electronegativity of the halogens.

Substituents determine the reactivity of rings

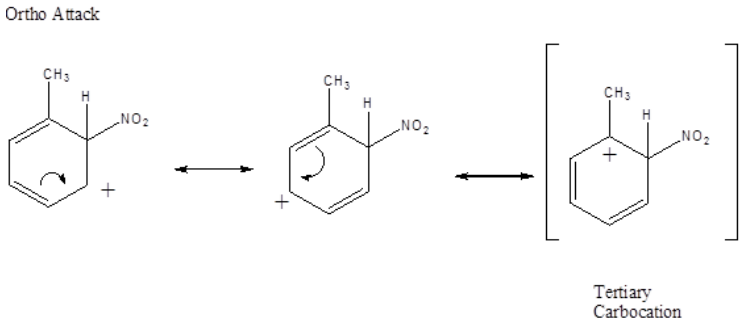
The reaction of a substituted ring with an activating group is faster than the same reaction with benzene. On the other hand, a substituted ring with a deactivated group reacts more slowly than benzene.

Activating groups speed up reaction with electrophiles due to increased electron density on the ring. This stabilizes the carbocation intermediate, thereby decreasing the reaction's activation energy. On the other hand, deactivating groups withdraw electron density from the carbocation formed in the intermediate step, thereby increasing the activation energy and slowing the reaction.

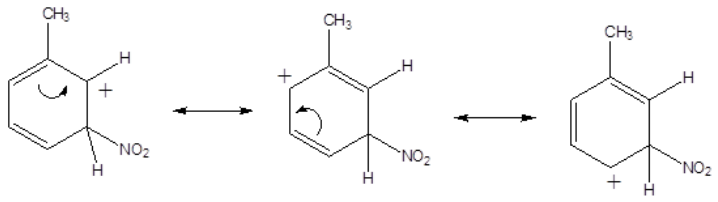
The CH_3 Group is an ortho, para director



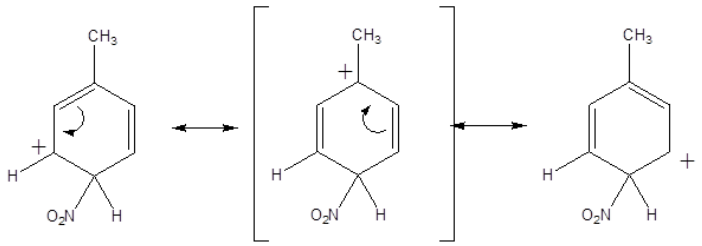
Alkyl groups are inductively donating, therefore are activators. This results in o/p attack to form a tertiary arenium carbocation, which speeds up the reaction.



Meta Attack

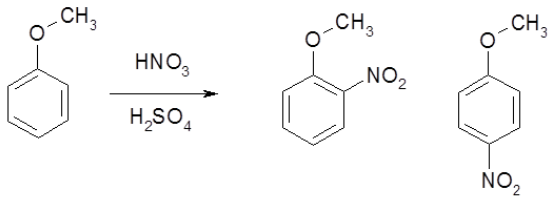


Para Attack



Tertiary Carbocation

The O-CH_3 Group is an ortho, para director

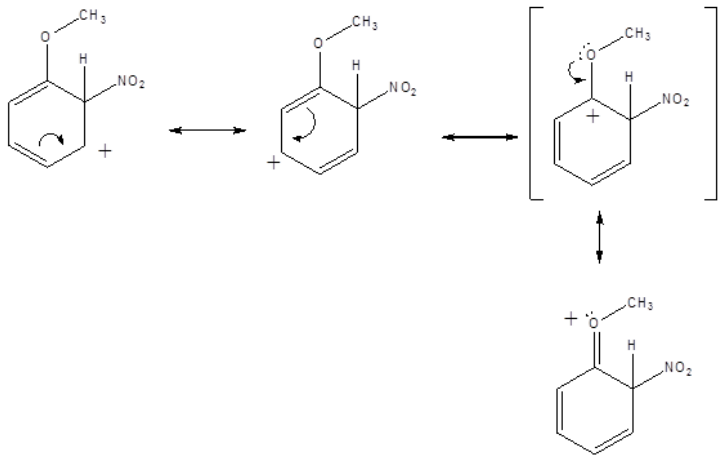


40% 60%

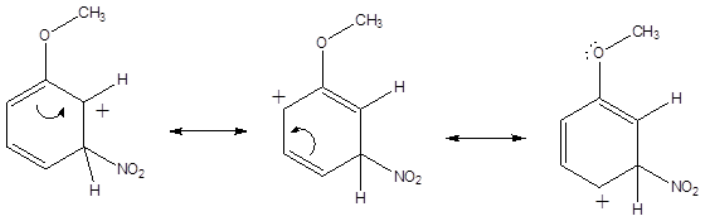
The methoxy group is an example of groups that are ortho, para directors by having an oxygen or nitrogen adjacent to the aromatic ring. This same activation is present with alcohols, amines, esters and amides (with the oxygen or nitrogen attached to the ring, not the carbonyl).

Groups with oxygen or nitrogen attached to the aromatic ring are ortho- and para-directing, since the O or N can withdraw electrons from the ring, making the ortho and para positions more reactive and stabilizing the arenium ion that forms. This causes ortho and para products to form faster than meta products. Generally, the para product is preferred because of steric effects.

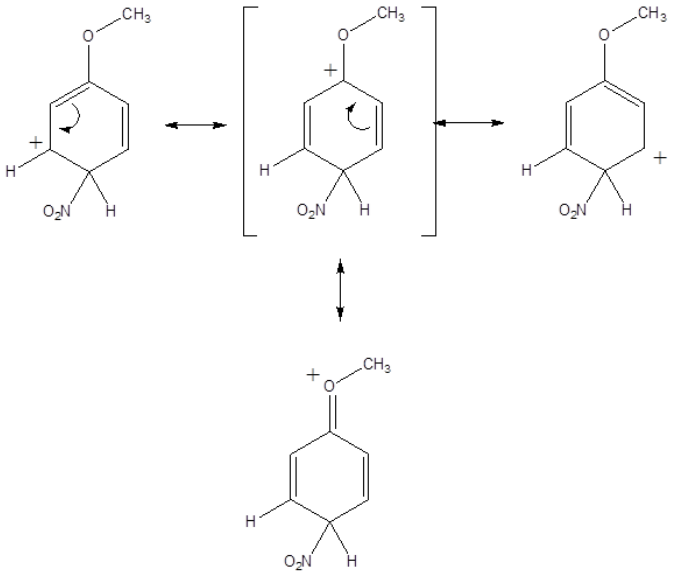
Ortho Attack



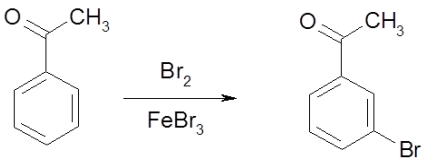
Meta Attack



Para Attack



Acyl groups are meta directors

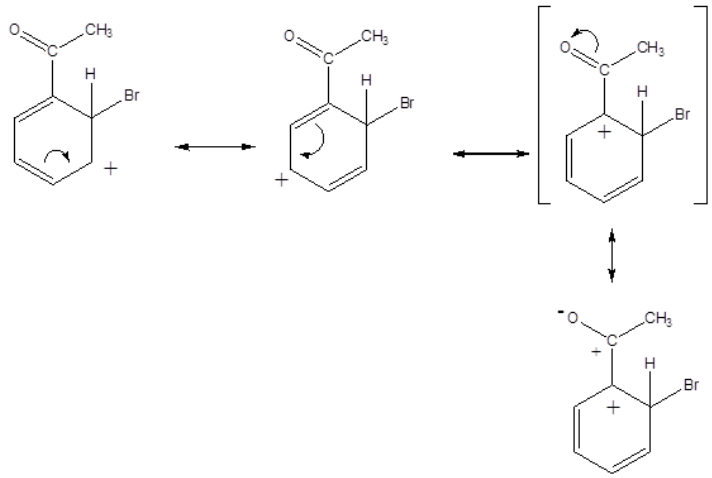


72%

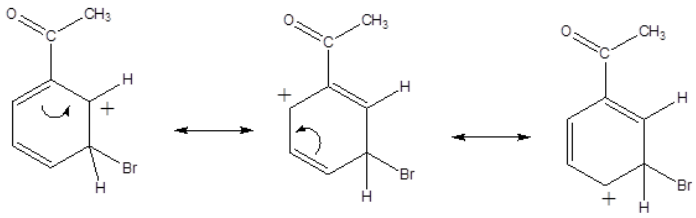
Ketones are an example of groups that deactivate an aromatic ring through resonance. Similar deactivation also occurs with ammonium ions, nitro groups, aldehydes, nitriles, sulfonic acids, and groups with a carbonyl attached to the ring (amides, esters, carboxylic acids, and anhydrides).

Acyl groups are resonance deactivators. Ortho and para attack produce a resonance structure which places the arenium cation next to an additional cation. This destabilizes the arenium cation and slows down the reaction over the ortho and para positions. By default, the meta product forms faster because it lacks this destabilizing resonance structure.

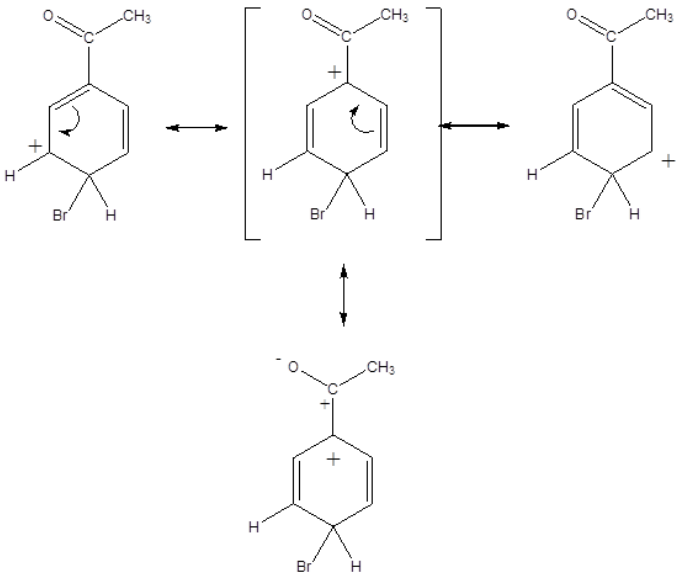
Ortho Attack



Meta Attack



Para Attack



Halogens

Halogens are an interesting hybrid case. They are ortho, para directors, but deactivators. Overall, they remove electron density from the ring, making it less reactive. However, due to their resonance donation to the ring, if it does react, it reacts primarily at ortho and para positions.

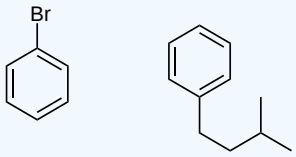
References

1. Schore, N.E. and P.C. Vollhardt. 2007. *Organic Chemistry, structure and function*, 5th ed. New York,NY: W.H. Freeman and Company.

2. Fryhle, C.B. and G. Solomons. 2008. *Organic Chemistry*, 9th ed.Danvers,MA: Wiley.

? Exercise 3.5.1

Predict the pattern of the electrophilic substitution on these rings:



Answer

The first substitution will be ortho and/or para substitution, since we have a halogen substituent. The second substitution is going to be ortho and/or para substitution, also, since we have an alkyl substituent.

? Exercise 3.5.2

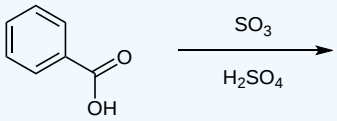
Which nitration product is going to form faster: nitration of aniline or nitration of nitrobenzene?

Answer

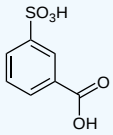
The nitration of aniline is going to be faster than the nitration of nitrobenzene, since the aniline is a ring with NH_2 substituent and nitrobenzene is a ring with NO_2 substituent. As described above NH_2 is an activating group which speeds up the reaction and NO_2 is a deactivating group that slows down the reaction.

? Exercise 3.5.3

Predict the product of the following sulfonation reaction:

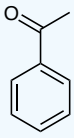


Answer

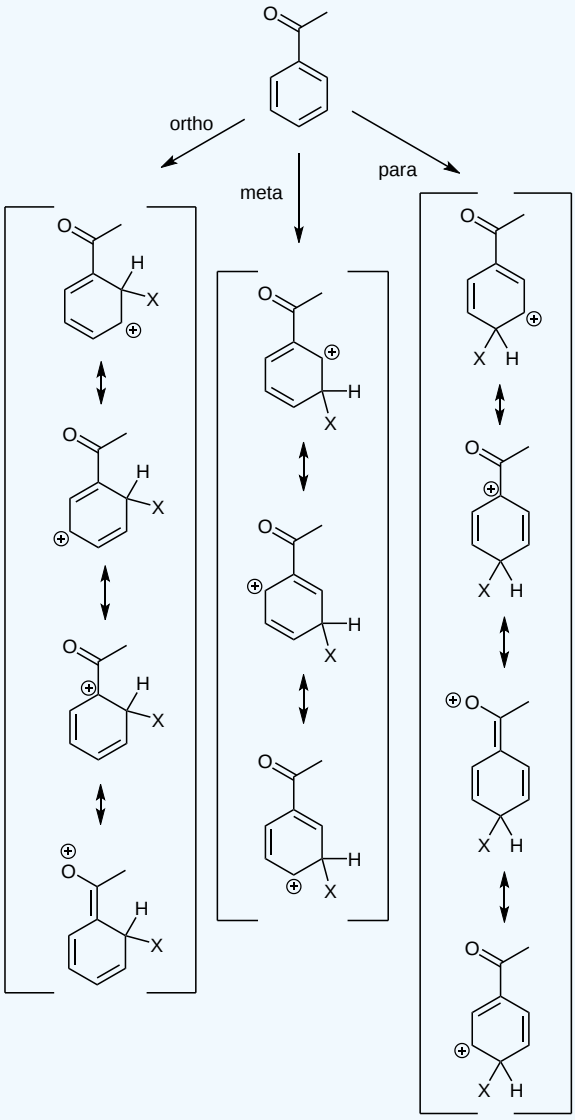


? Exercise 3.5.8

Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para attacks.



Answer



Key Terms

Make sure you can define and use the key terms below in context.

- steric effect
- steric hindrance

Study Notes

As you saw in Section 16.4, a substituent on a benzene ring can be an activator or a deactivator. At the same time, a substituent can also be a meta-directing or ortho/para-directing substituent. Of the four possible combinations, only three are known—there are no meta directing activators.

If you look at the data for the nitration of toluene, you will see that the yield of *o*-nitrotoluene is 63% and that of *p*-nitrotoluene is 34%. Statistically, we should expect to obtain twice as much ortho product as para product, because the former is produced by attack at either of two carbon atoms whereas the latter is produced by attack at only one carbon atom (see Figure below).

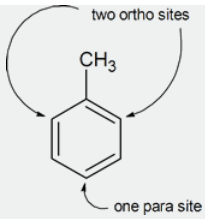


Figure 3.5.1: Proportions of *o*-nitrotoluene and *p*-nitrotoluene produced by the nitration of toluene

In this instance, the observed ortho/para ratio is almost 2:1, as we might expect. However, if we study the ortho/para ratio found in the nitration of a number of other arenes, we see that this is not always the case. Note that the data for the nitration of toluene given in the table below differ from those presented elsewhere. The variation may result from a difference in temperature, reaction conditions or reagent, and emphasizes the point that it is the trends which are important, not the numbers themselves.

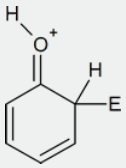
Substrate	% ortho	% para	ortho/para ratio
toluene	58	37	1.57:1
ethylbenzene	45	49	0.92:1
isopropylbenzene	30	62	0.48:1
tert-butylbenzene	16	73	0.22:1

[**Source:** These data were taken from the audiocassette *Some Organic Reaction Pathways*, by Peter Sykes. London: Educational Techniques Subject Group, The Chemical Society, 1975.]

Table 3.5.1**:** Nitration of arenes

The table above shows us that as the size of the alkyl substituent already present in the ring increases, attack at the ortho position becomes more difficult, and the percentage of ortho isomers in the mixture of products decreases. This is an example of a *steric effect*—an effect caused by the size of the substituent—and we would say that as the size of the alkyl group increases, attack at the ortho position becomes less favorable as a result of *steric hindrance*. Note that the size of the electrophile can also be a factor in determining the ortho/para ratio: the larger the electrophile, the less able it is to attack at the ortho position, particularly if the substituent already present in the ring is itself quite bulky.

When drawing the resonance contributors to the carbocation formed during an electrophilic aromatic substitution, bear in mind that those of the type



are particularly important because, in such structures, each atom has a complete octet of electrons.

Note that, as do the hydroxyl and amino groups, the halogens have an inductive electron-withdrawing effect and a resonance electron-releasing effect on a benzene ring. The difference in behavior during electrophilic substitutions arises because, with the hydroxyl and amino groups, the resonance effect is much greater than the inductive effect, whereas with the halogens, there is a much finer balance. In the case of the latter, the inductive effect reduces the overall reactivity, but the resonance effect means that this reduction is felt less at the ortho and para positions than at the meta position.

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3.6: Trisubstituted Benzenes - Additivity of Effects

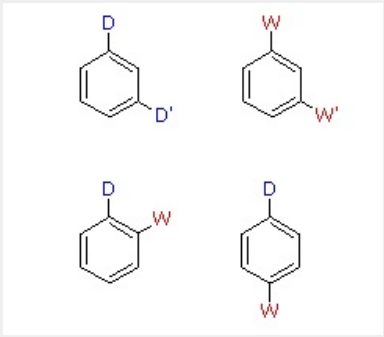
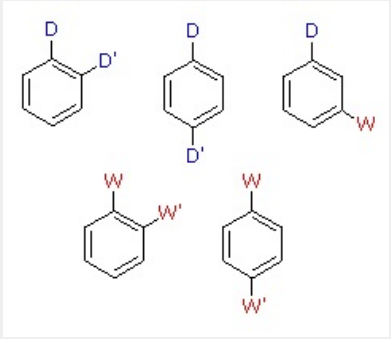
Objectives

After completing this section, you should be able to

1. predict the position or positions at which electrophilic substitution will occur when a third substituent is introduced into a disubstituted benzene ring.
2. explain the observed substitution pattern when a third substituent is introduced into a disubstituted benzene ring.

Orientational Interaction of Substituents

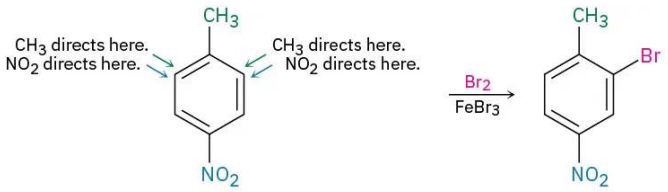
When a benzene ring has two substituent groups, each exerts an influence on subsequent substitution reactions. The activation or deactivation of the ring can be predicted more or less by the sum of the individual effects of these substituents. The site at which a new substituent is introduced depends on the orientation of the existing groups and their individual directing effects. We can identify two general behavior categories, as shown in the following table. Thus, the groups may be oriented in such a manner that their directing influences act in concert, reinforcing the outcome; or are opposed (antagonistic) to each other. Note that the orientations in each category change depending on whether the groups have similar or opposite individual directing effects.

Antagonistic or Non-Cooperative	**Reinforcing or Cooperative**
	

D = Electron Donating Group (ortho/para-directing)
W = Electron Withdrawing Group (meta-directing)

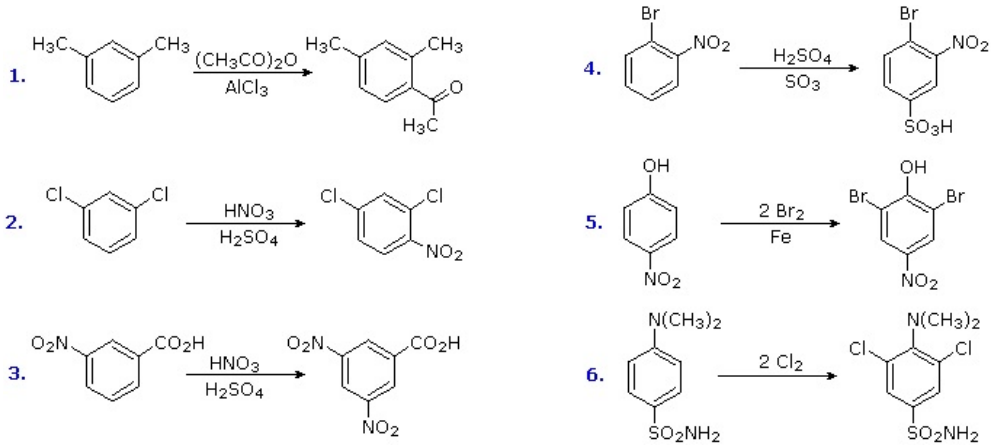
Reinforcing or Cooperative Substitutions

The products from substitution reactions of compounds with a reinforcing orientation of substituents are easier to predict than those with antagonistic substituents. In *p*-nitrotoluene, for example, both the methyl and the nitro group direct further substitution to the same position (ortho to the methyl = meta to the nitro). A single product is thus formed on electrophilic substitution.



***p*-Nitrotoluene** **2-Bromo-4-nitrotoluene**

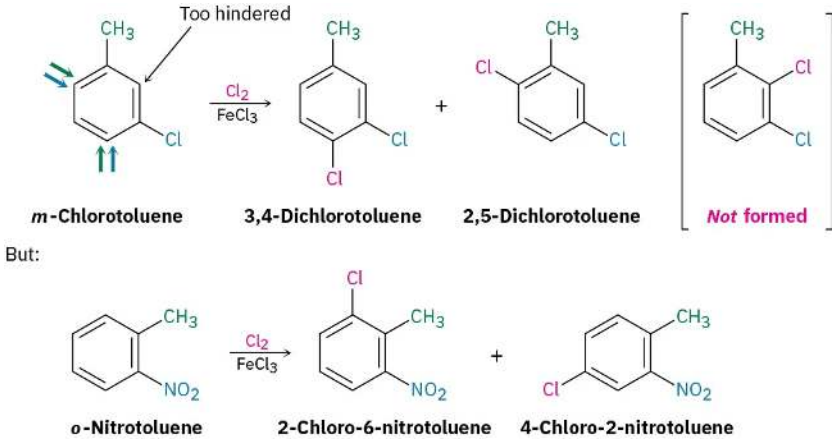
For example, the six equations shown below are all examples of reinforcing or cooperative directing effects operating in the expected manner. Symmetry, as in the first two cases, makes it easy to predict the site at which substitution is likely to occur. Note that if two different sites are favored, substitution will usually occur at the one that is least hindered by ortho groups.



The first three examples have two similar directing groups in a meta-relationship. In examples 4 through 6, oppositely directing groups have an ortho or para-relationship. The major products of electrophilic substitution, as shown, are the sum of the individual group effects. The strongly activating hydroxyl (–OH) and amino ($–NH_2$) substituents favor dihalogenation in examples 5 and 6.

Spatial Limitation

Further substitution rarely occurs between the two groups in a meta-disubstituted compound because this site is too hindered. Aromatic rings with three adjacent substituents must therefore be prepared by some other route, such as by substitution of an ortho-disubstituted compound.



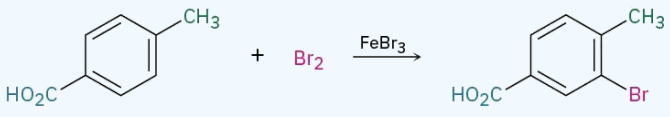
Worked Example 3.6.1: Predicting the Product of Substitution on a Disubstituted Benzene

What product would you expect from bromination of *p*-methylbenzoic acid?

Strategy

Identify the two substituents present on the ring, decide the directing effect of each and, if necessary, decide which substituent is the stronger activator. In the present case, the carboxyl group ($–CO_2H$) is a meta director and the methyl group is an ortho and para director. Both groups undergo direct bromination at the position adjacent to the methyl group, yielding 3-bromo-4-methylbenzoic acid.

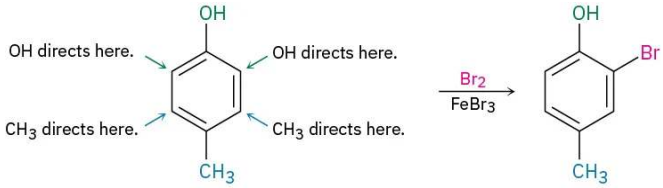
Solution



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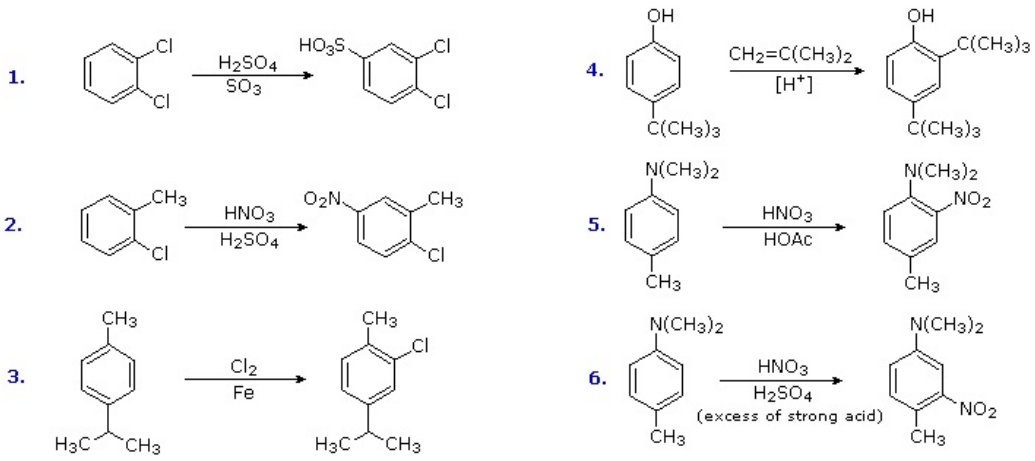
Antagonistic or Non-Cooperative Substitutions

Substitution reactions of compounds having an antagonistic orientation of substituents require a more careful analysis. If the directing effects of the two groups oppose each other, the more powerful activating group has the dominant influence, but mixtures of products are often formed. For example, bromination of *p*-methylphenol yields primarily 2-bromo-4-methylphenol because –OH is a more powerful activator than $–CH_3$.



***p*-Methylphenol** **2-Bromo-4-methylphenol**

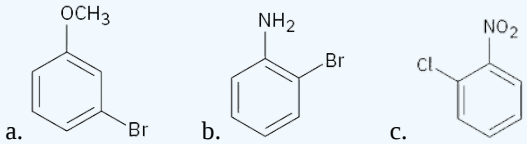
If the substituents are identical, as in example 1 below, the symmetry of the molecule will again simplify the decision. When one substituent has a pair of non-bonding electrons available for adjacent charge stabilization, it will normally exert the product determining influence, examples 2, 4 & 5, even though it may be overall deactivating (case 2). Case 3 reflects a combination of steric hindrance and the superior innate stabilizing ability of methyl groups relative to other alkyl substituents. Example 6 is interesting in that it demonstrates the conversion of an activating ortho/para-directing group into a deactivating meta-directing "onium" cation [$–NH(CH_3)_2^{(+)}$] in a strong acid environment.



Exercises

? Exercise 3.6.1

At what position would you expect electrophilic substitution to occur in each of the following substances:

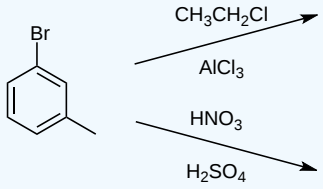


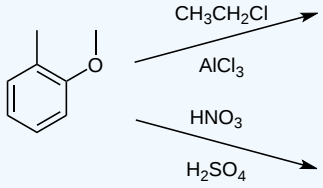
Answer

a. Ortho and para to $-OCH_3$
b. Ortho and para to $-NH_2$
c. Ortho and para to $-Cl$

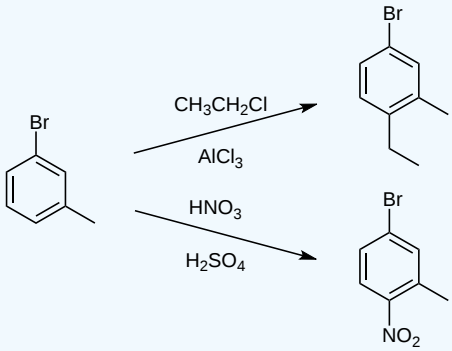
Exercise 3.6.2

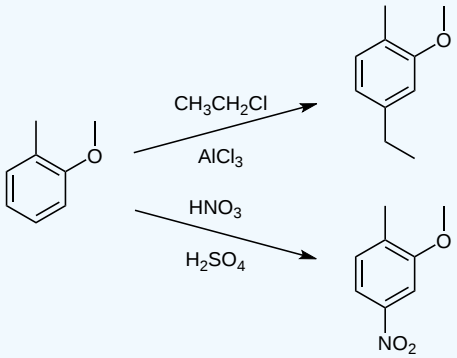
Predict the products of the following reactions:





Answer

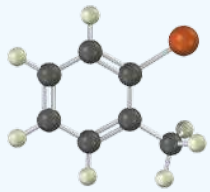




Exercise 3.6.3

Show the major product(s) from reaction of the following substances with (1) $CH_3CH_2C(O)Cl$, $AlCl_3$ and (2) SO_3, H_2SO_4:

https://chem.libretexts.org/@go/page/500374



Answer

The reactions occur ortho and para to the $-CH_3$ group.

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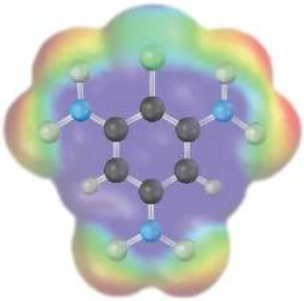
3.7: Nucleophilic Aromatic Substitution

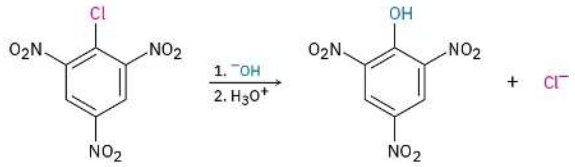
Objectives

After completing this section, you should be able to

1. identify the conditions necessary for an aryl halide to undergo nucleophilic aromatic substitution, and give an example of such a reaction.
2. write the detailed mechanism for a nucleophilic aromatic substitution reaction.
3. compare the mechanism of a nucleophilic aromatic substitution reaction and the S_N1 and S_N2 mechanisms discussed earlier.
4. identify the product formed when a given nucleophile reacts with a given aryl halide in a nucleophilic aromatic substitution reaction.

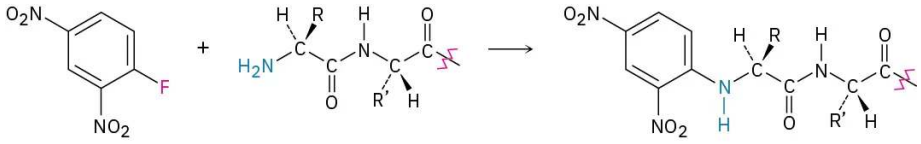
Although aromatic substitution reactions usually occur by an *electrophilic* mechanism, aryl halides that have electron-withdrawing substituents can also undergo a *nucleophilic* substitution reaction. For example, 2,4,6-trinitrochlorobenzene reacts with aqueous NaOH at room temperature to give 2,4,6-trinitrophenol. Here, the nucleophile OH^- substitutes for Cl^-.





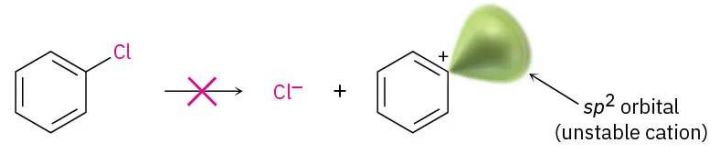
2,4,6-Trinitrochlorobenzene **2,4,6-Trinitrophenol (100%)**

Nucleophilic aromatic substitution is much less common than electrophilic substitution but nevertheless does have certain uses. One such use is the reaction of proteins with 2,4-dinitrofluorobenzene, known as *Sanger's reagent*, to attach a "label" to the terminal NH_2 group of the amino acid at one end of the protein chain.

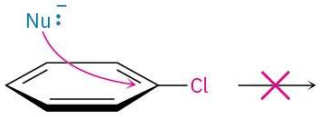


2,4-Dinitro-fluorobenzene **A protein** **A labeled protein**

Although the reaction appears superficially similar to the S_N1 and S_N2 nucleophilic substitutions of alkyl halides discussed in the chapter on Reactions of Alkyl Halides: Nucleophilic Substitutions and Eliminations, it must be different because aryl halides are inert to both S_N1 and S_N2 conditions. S_N1 reactions don't occur with aryl halides because dissociation of the halide is energetically unfavorable, due to the instability of the potential aryl cation product. S_N2 reactions don't occur with aryl halides because the halo-substituted carbon of the aromatic ring is sterically shielded from a backside approach. For a nucleophile to react with an aryl halide, it would have to approach directly through the aromatic ring and invert the stereochemistry of the aromatic ring carbon—a geometric impossibility.



Dissociation reaction does not occur because the aryl cation is unstable; therefore, no S_N1 reaction.



Backside displacement is sterically blocked; therefore, no S_N2 reaction.

Conditions for Nucleophilic Aromatic Substitution Reactions of Aryl Halides

The carbon-halogen bonds of aryl halides are like those of alkenyl halides in being much stronger than those of alkyl halides. The simple aryl halides generally are resistant to attack by nucleophiles in either S_N1 or S_N2 reactions. However, this low reactivity can be changed dramatically by changes in the reaction conditions and the structure of the aryl halide. In fact, nucleophilic displacement becomes quite rapid

a. when the aryl halide is activated by substitution with strongly electron-attracting groups such as NO_2, and
b. when very strongly basic nucleophilic reagents are used.

Addition-Elimination Mechanism

The nucleophilic substitutions on an aromatic ring proceed by the mechanism shown in Figure 3.7.1. The nucleophile first adds to the electron-deficient aryl halide, forming a resonance-stabilized, negatively charged intermediate called a *Meisenheimer complex* after its discoverer. Halide ion is then eliminated.

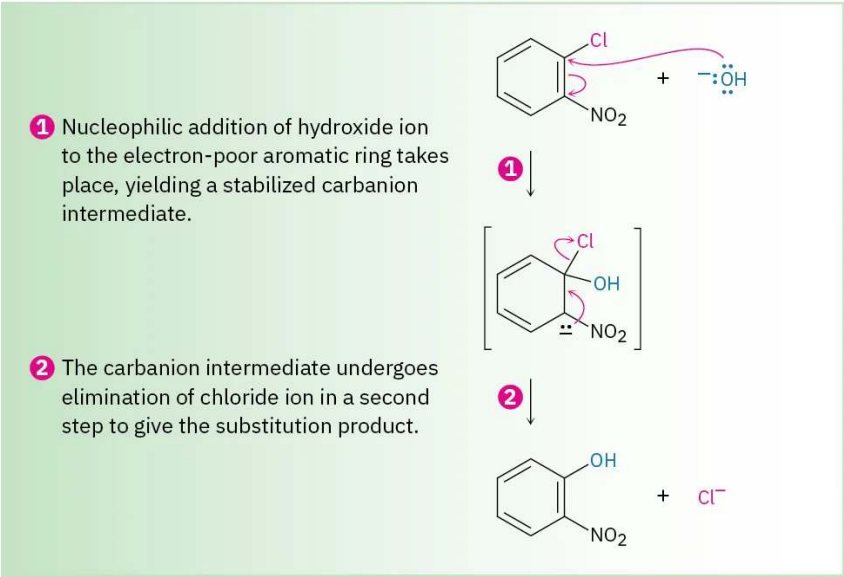


Figure 3.7.1: Mechanism of nucleophilic aromatic substitution. The reaction occurs in two steps and involves a resonance-stabilized carbanion intermediate.

Nucleophilic aromatic substitution occurs only if the aromatic ring has an electron-withdrawing substituent in a position ortho or para to the leaving group to stabilize the anion intermediate through resonance (Figure 3.7.2). A meta substituent offers no such resonance stabilization. Thus, *p*-chloronitrobenzene and *o*-chloronitrobenzene react with hydroxide ion at 130 °C to yield substitution products, but *m*-chloronitrobenzene is inert to OH^-.

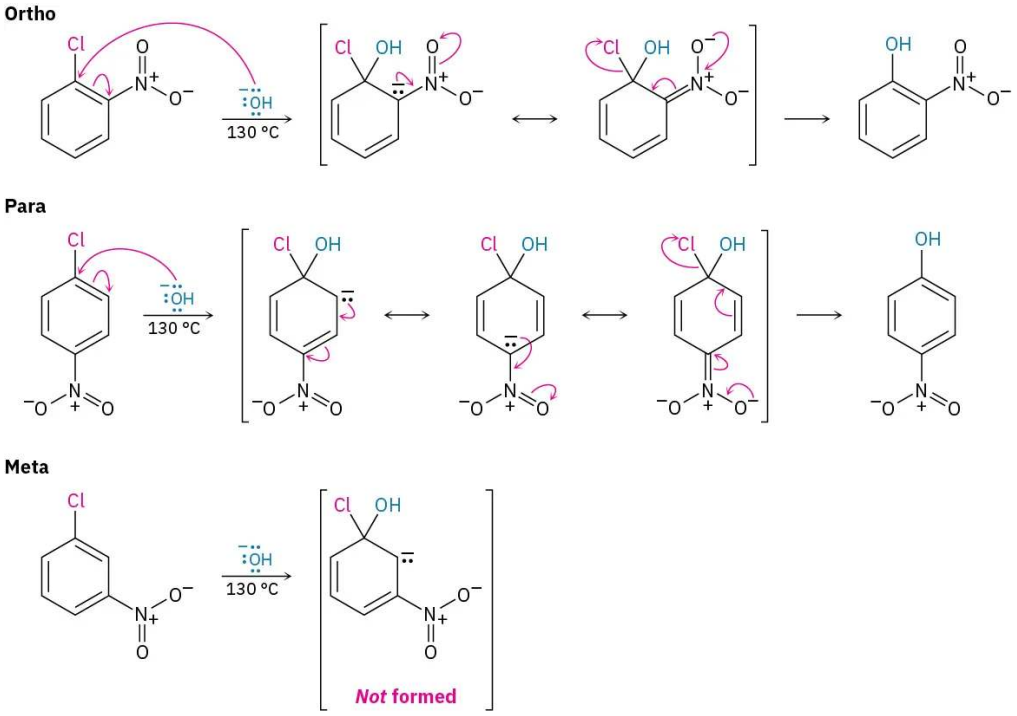
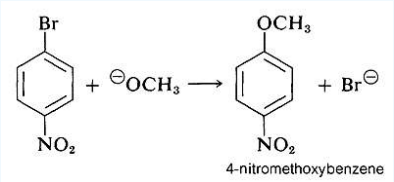


Figure 3.7.2: Nucleophilic aromatic substitution on nitrochlorobenzenes. Only in the ortho and para intermediates is the negative charge stabilized by a resonance interaction with the nitro group, so only the ortho and para isomers undergo reaction.

Worked Example 3.7.1: Predicting the Product of Substitution on a Disubstituted Benzene

Propose a mechanism for the following reaction:

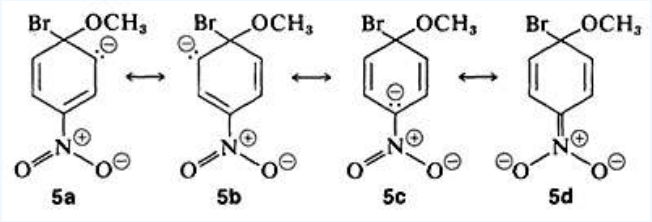


Strategy

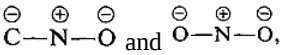
when strongly electron-attracting groups are located on the ring at the ortho-para positions, the intermediate anion is stabilized by delocalization of electrons from the ring carbons to more favorable locations on the substituent groups. In this example, consider the displacement of bromine by methoxid (OCH_3) in the reaction of 4-bromonitrobenzene and methoxide ion.

The anionic intermediate formed by addition of methoxide ion to the aryl halide can be described by the valence-bond structures 5a-5d. Of these structures 5d is especially important because in it the charge is transferred from the ring carbons to the oxygen of the nitro substituent.

Solution



Electron-attracting groups in Meta Position

Substituents in the meta positions have much less effect on the reactivity of an aryl halide because delocalization of electrons to the substituent is not possible. No formulas can be written analogous to 5c and 5d in which the negative charges are both on atoms next to positive nitrogen,  and ,

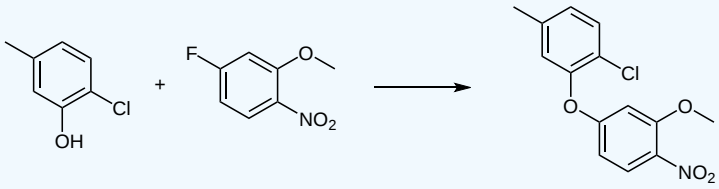


Note the differences between electrophilic and nucleophilic aromatic substitutions. Electrophilic substitutions are favored by electron-donating substituents, which stabilize a carbocation intermediate, while nucleophilic substitutions are favored by electron-withdrawing substituents, which stabilize a carbanion intermediate. Thus, the electron-withdrawing groups that deactivate rings for electrophilic substitution (nitro, carbonyl, cyano, and so forth) activate them for nucleophilic substitution. What's more, these functional groups are meta directors in electrophilic substitution but are ortho–para directors in nucleophilic substitution. And finally, electrophilic substitutions replace hydrogen on the ring, while nucleophilic substitutions replace a leaving group, usually halide ion.

Exercises

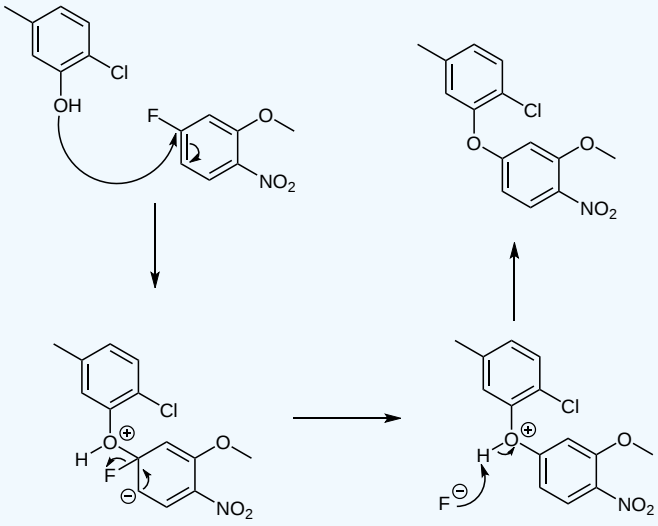
? Exercise 3.7.1

Propose a mechanism for the following reaction:



Answer

The reaction starts when the phenol is deprotonated by KOH to give an anion that carries out a nucleophilic acyl substitution reaction on the 5-fluoro-2-nitroanisole.



Key Terms

Make certain that you can define, and use in context, the key terms below.

- Meisenheimer complex
- nucleophilic aromatic substitution

Study Notes

A *nucleophilic aromatic substitution reaction* is a reaction in which one of the substituents in an aromatic ring is replaced by a nucleophile.

A *Meisenheimer complex* is a negatively charged intermediate formed by the attack of a nucleophile upon one of the aromatic-ring carbons during the course of a nucleophilic aromatic substitution reaction. A typical Meisenheimer complex is shown in the reaction scheme below. Notice how this particular complex can be formed from two different starting materials by using a different nucleophile in each case.

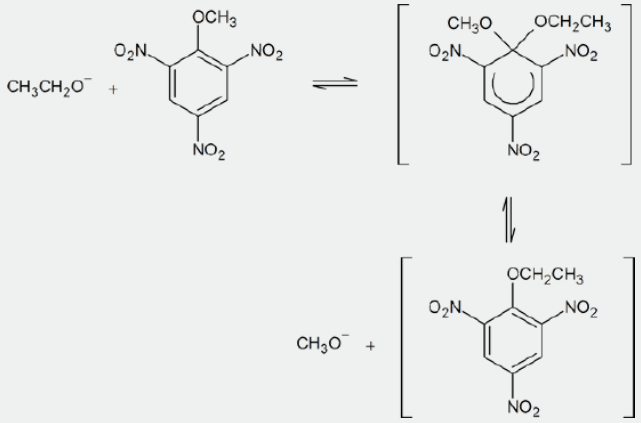


Figure 3.7.3: The formation of a typical Meisenheimer complex

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3.8: Benzyne

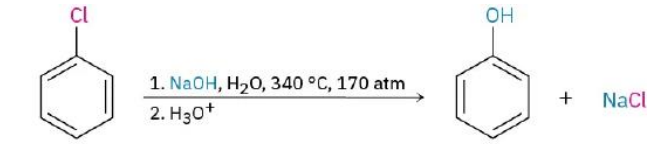
Objectives

After completing this section, you should be able to

1. identify the reagents and conditions required to produce phenol from chlorobenzene on an industrial scale.
2. write the mechanism for the conversion of an alkyl halide to a phenol through a benzyne intermediate.
3. discuss the experimental evidence which supports the existence of benzyne intermediates.
4. discuss the bonding in benzyne, and hence account for its high reactivity.

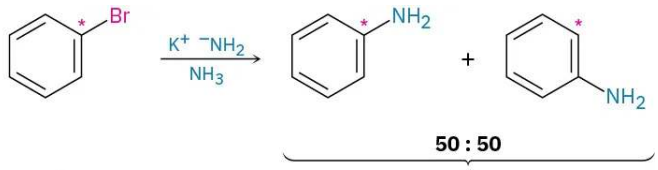
Halobenzenes without electron-withdrawing substituents don't react with nucleophiles under most conditions. At high temperature and pressure, however, even chlorobenzene can be forced to react. The elimination-addition mechanism of nucleophilic aromatic substitution involves the remarkable intermediate called benzyne or arynes.

Chemists at the Dow Chemical Company discovered in 1928 that phenol could be prepared on an industrial scale by treatment of chlorobenzene with dilute aqueous NaOH at 340°C under 170 atm pressure.



Chlorobenzene **Phenol**

A similar substitution reaction occurs with other strong bases. Treatment of bromobenzene with potassium amide (KNH_2) in liquid NH_3 solvent (-33°C), for instance, gives aniline. Curiously, though, when using bromobenzene labeled with radioactive ^{14}C at the C1 position, the substitution product has equal amounts of the label at both C1 and C2, implying the presence of a symmetrical reaction intermediate in which C1 and C2 are equivalent.

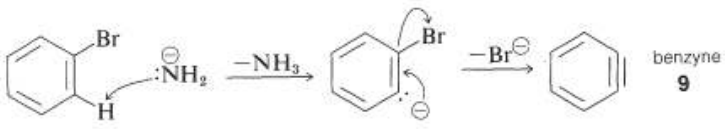


Bromobenzene **Aniline**

Elimination-Addition Mechanism of Nucleophilic Aromatic Substitution. Arynes

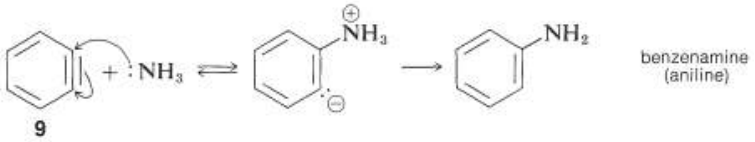
The mechanism of this type of reaction has been studied extensively, and much evidence has accumulated in support of a stepwise process, which proceeds first by base-catalyzed *elimination* of hydrogen halide (HX) from the aryl halide - as illustrated below for the amination of bromobenzene:

Step 1: Elimination



The product of the elimination reaction is a highly reactive intermediate 9 called **benzyne**, or **dehydrobenzene**, which differs from benzene in having two less hydrogen and an extra bond between two ortho carbons. Benzyne reacts rapidly with any available nucleophile, in this case the solvent, ammonia, to give an addition product:

Step 2: Addition



9

The electronic structure of benzyne, shown in Figure 3.8.1, is that of a highly distorted alkyne. Although a typical alkyne triple bond uses *sp*-hybridized carbon atoms, the benzyne triple bond uses sp^2-hybridized carbons. Furthermore, a typical alkyne triple bond has two mutually perpendicular π bonds formed by *p*–*p* overlap, but the benzyne triple bond has one π bond formed by *p*–*p* overlap and one π bond formed by sp^2–sp^2 overlap. The latter π bond is in the plane of the ring and is very weak.

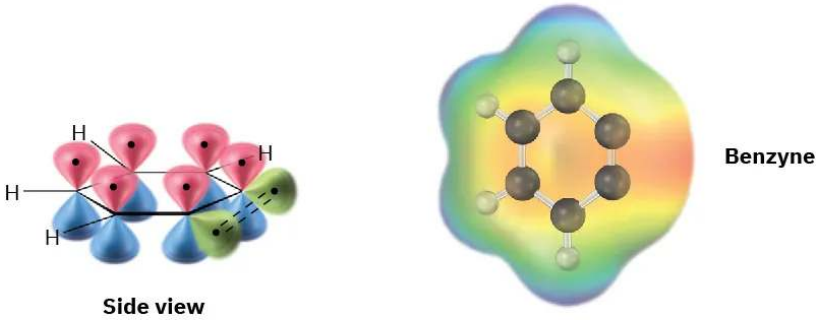
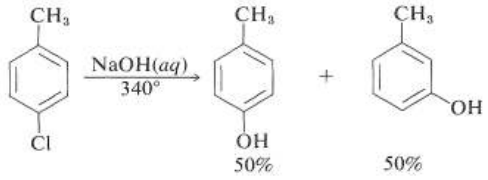


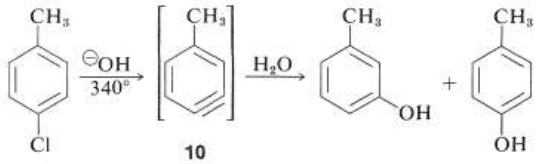
Figure 3.8.1: An orbital picture and electrostatic potential map of benzyne. The benzyne carbons are sp^2-hybridized, and the "third" bond results from weak overlap of two adjacent sp^2 orbitals.

Disubstituted Substrates

The rearrangements in these reactions result from the attack of the nucleophile at one or the other of the carbons of the extra bond in the intermediate. With benzyne the symmetry is such that no rearrangement would be detected. With substituted benzynes isomeric products may result. That is, *the entering group does not always occupy the same position on the ring as that vacated by the halogen substituent*. For example, the hydrolysis of 4-chloromethylbenzene at 340° gives an equimolar mixture of 3- and 4-methylbenzenols:

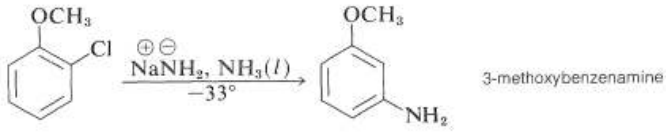


Thus 4-methylbenzyne, 10, from the reaction of hydroxide ion with 4-chloro-1-methylbenzene gives both 3- and 4-methylbenzenols:



10

Even more striking is the exclusive formation of 3-methoxybenzenamine in the amination of 2-chloromethoxybenzene. Notice that this result is a violation of the principle of least structural change:



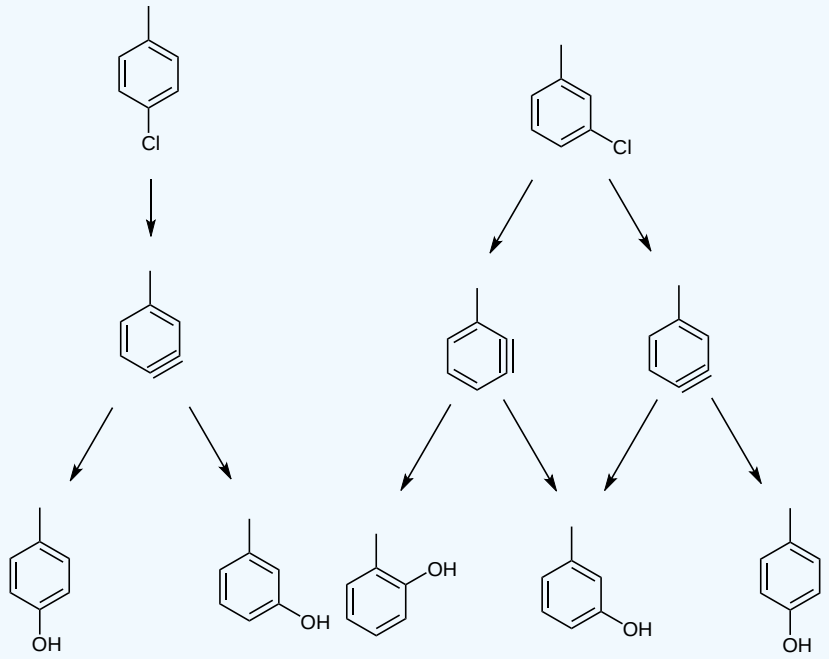
3-methoxybenzenamine

Exercise 3.8.1

When *p*-chlorotoluene is reacted with NaOH, two products are seen. While when *m*-chlorotoluene is reacted with NaOH, three products are seen. Explain this.

Answer

You need to look at the benzyne intermediates. The para substituted only allows for two products, while the para produces two different alkynes which give three different products.



Key Terms

Make certain that you can define, and use in context, the key terms below.

- benzyne
- elimination-addition mechanism

Study Notes

An elimination-addition mechanism involves removing elements from a small molecule to produce a highly reactive intermediate, which then undergoes an addition reaction.

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3.9: Reduction of Aromatic Compounds

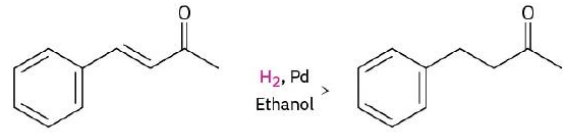
Objectives

After completing this section, you should be able to

- write an equation to represent the reduction of a substituted benzene to a substituted cyclohexane.
- identify the catalyst and reagents used to reduce aromatic rings.
- compare the ease of reduction of alkenes with the difficulty in reducing benzene rings, and show how this difference in reactivity can be used in organic synthesis.
- write an equation to illustrate the reduction of an aromatic ketone to an arene.
- explain why Friedel-Crafts acylation, followed by reduction, provides a better route to primary alkylbenzenes than does direct alkylation.
- show how a specified alkylbenzene may be prepared by a Friedel-Crafts acylation, followed by reduction. Specify all reagents, the structure of the intermediate ketone, and the necessary starting material.

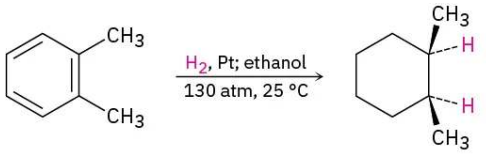
Catalytic Hydrogenation of Aromatic Rings

Just as aromatic rings are generally inert to oxidation, they're also inert to catalytic hydrogenation under conditions that reduce typical alkene double bonds. As a result, it's possible to reduce an alkene double bond selectively in the presence of an aromatic ring. For example, 4-phenyl-3-buten-2-one is reduced to 4-phenyl-2-butanone using a palladium catalyst at room temperature and atmospheric pressure. Neither the benzene ring nor the ketone carbonyl group is affected.

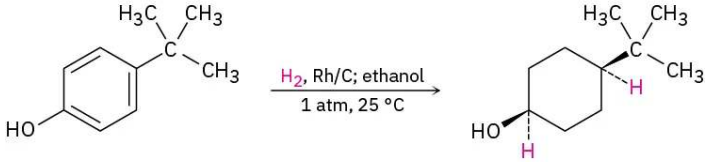


4-Phenyl-3-buten-2-one → **4-Phenyl-2-butanone (100%)**

To hydrogenate an aromatic ring, it's necessary either to use a platinum catalyst with hydrogen gas at a pressure of several hundred atmospheres or to use a more effective catalyst such as rhodium on carbon. Under these conditions, aromatic rings are converted into cyclohexanes. For example, *o*-xylene yields 1,2-dimethylcyclohexane, and 4-*tert*-butylphenol gives 4-*tert*-butylcyclohexanol.



***o*-Xylene** → ***cis*-1,2-Dimethyl-cyclohexane**

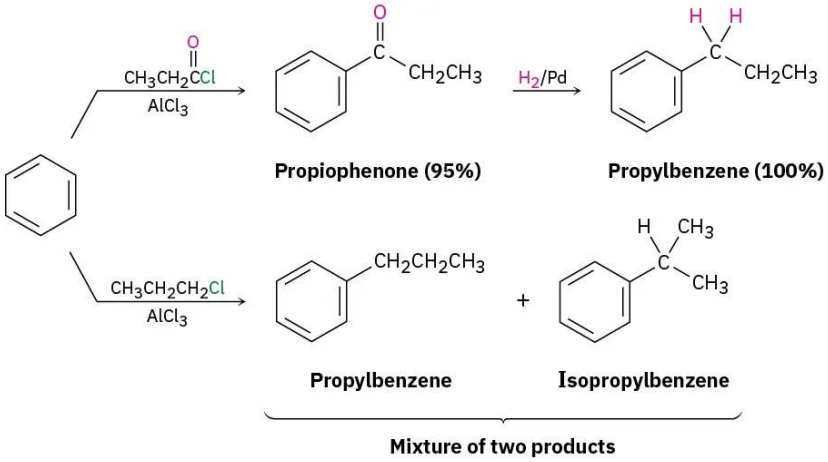


4-*tert*-Butylphenol → ***cis*-4-*tert*-Butyl-cyclohexanol**

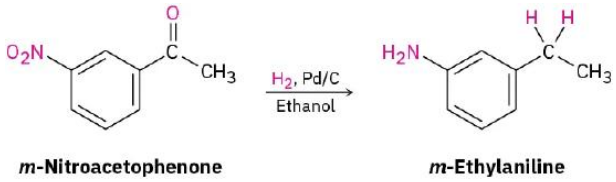
Reduction of Aryl Alkyl Ketones

In the same way that an aromatic ring activates a neighboring (benzylic) C–H toward oxidation, it also activates a benzylic carbonyl group toward reduction. Thus, an aryl alkyl ketone prepared by Friedel–Crafts acylation of an aromatic ring can be converted into an alkylbenzene by catalytic hydrogenation over a palladium catalyst. Propiophenone, for instance, is reduced to

propylbenzene by catalytic hydrogenation. Because the net effect of Friedel–Crafts acylation followed by reduction is the preparation of a primary alkylbenzene, this two-step sequence of reactions makes it possible to circumvent the carbocation rearrangement problems associated with direct Friedel–Crafts alkylation using a primary alkyl halide.

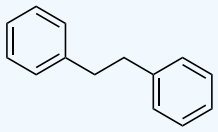


The conversion of a carbonyl group into a methylene group ($C{=}O \rightarrow CH_2$) by catalytic hydrogenation is limited to *aryl* alkyl ketones; dialkyl ketones are not reduced under these conditions. Furthermore, the catalytic reduction of aryl alkyl ketones is not compatible with the presence of a nitro substituent on the aromatic ring because a nitro group is reduced to an amino group under reaction conditions.

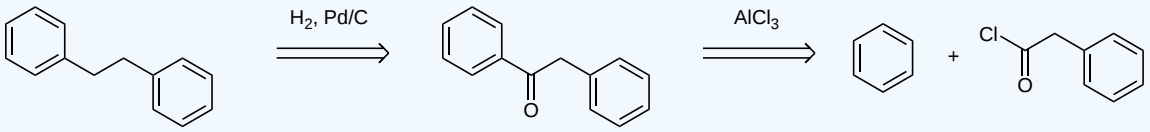


? Exercise 3.9.1

How would you make the following from benzene and an acid chloride?

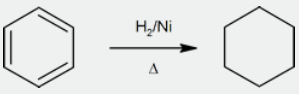


Answer

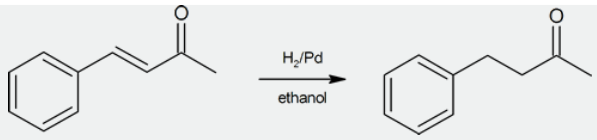


Study Notes

Catalytic hydrogenation of aromatic rings requires forcing conditions (high heat and hydrogen pressure).

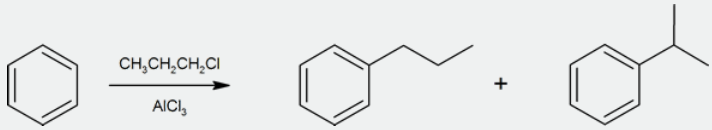


Under milder conditions, it is possible to reduce the double bond of an alkene without reducing the aromatic ring.

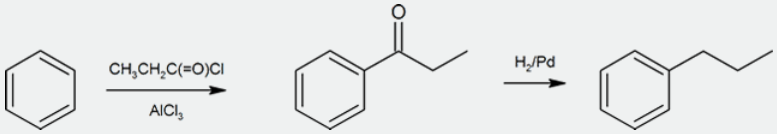


Notice in the above equation that H_2/Pd does not reduce the keto-carbonyl group. Remember, however, that H_2/Pd will reduce a keto-carbonyl group when it is directly attached to an aromatic ring (see equations 4 and 5 under Carbonyl Reductions).

This reduction of the (C=O) group next to an aromatic ring is an important synthetic tool. Recall the Friedel-Crafts alkylation from Section 16.3. When attaching larger alkyl groups to arenes, there is a possibility of rearrangement of the alkyl group structure.



To generate the target compound (in this case *n*-propylbenzene) in a more controlled fashion, one can simply use the equivalent Friedel-Crafts acylation and then reduce the keto-carbonyl group next to the ring as a final step.



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3.10: Synthesis of Polysubstituted Benzenes

Objectives

After completing this section, you should be able to

- Design a multistep synthesis which may involve reactions in the alkyl side chain of an alkylbenzene and the electrophilic substitution reactions discussed in this chapter. You should pay particular attention to
  - carrying out the reactions in the correct order.
  - using the most appropriate reagents and conditions.
  - the limitations of certain types of reactions.
- Analyze a proposed multistep synthesis involving aromatic substitution to determine its feasibility, point out any errors in the proposal and identify possible problem areas.

One of the surest ways to learn organic chemistry is to work on synthesis problems. The ability to plan a successful multistep synthesis of a complex molecule requires a working knowledge of the uses and limitations of a great many organic reactions. Not only must you know which reactions to use, you must also know when to use them because the order in which reactions are carried out is often critical to the success of the overall scheme.

The ability to plan a sequence of reactions in the right order is particularly important in the synthesis of substituted aromatic rings, where the introduction of a new substituent is strongly affected by the directing effects of other substituents. Planning syntheses of substituted aromatic compounds is, therefore, a good way to gain confidence in using the many reactions discussed in the past few chapters.

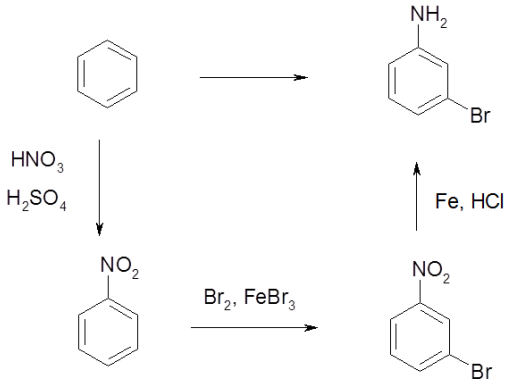
It's usually best to work a synthesis problem backward, or *retrosynthetically.* Look at the target molecule and ask yourself, "What is an immediate precursor of this compound?" Choose a likely answer and continue working backward, one step at a time, until you arrive at a simple starting material. Let's try some examples.

From benzene make *m*-bromoaniline

In this reaction, three reactions are required.

1. A nitration
2. A conversion from the nitro group to an amine
3. A bromination

Because the end product is meta a meta directing group must be utilized. Of the nitro, bromine, and amine group, only the nitro group is meta direction. This means that the first step need to be the nitration and not the bromination. Also, the conversion of the nitro group to an amine must occur last because the amine group is ortho/para direction.

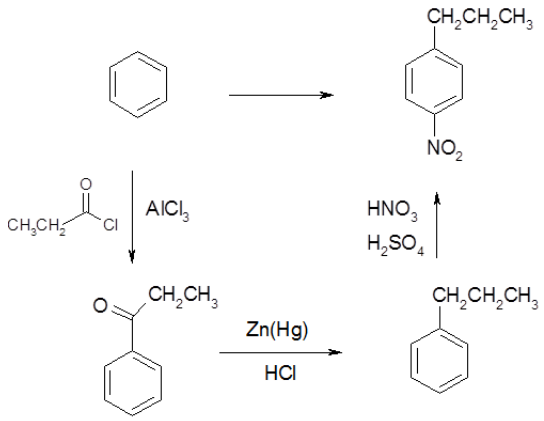


From benzene make *p*-nitropropylbenzene :

In this reaction three reactions are required.

1. A Friedel Crafts acylation
2. A conversion from the acyl group to an alkane
3. A nitration

Because the propyl group has more than two carbons, it must be added in two steps. A Friedel Crafts acylation followed by a Clemmensen Reduction. Remember that Friedel Crafts reactions are hindered if the benzene ring is strongly deactivated. This means that the acyl group must go on first. Because the end product is para a para directing group must be utilized. Of the nitro, acyl, and alkane group, only the alkane group is meta direction. This means that the acyl group must be converted to an alkane prior to the nitration step.

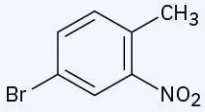


Worked Example 3.10.1: Synthesizing a Polysubstituted Benzene

How would you synthesize 4-bromo-2-nitrotoluene from benzene?

Strategy

Draw the target molecule, identify the substituents, and recall how each group can be introduced separately. Then plan retrosynthetically.

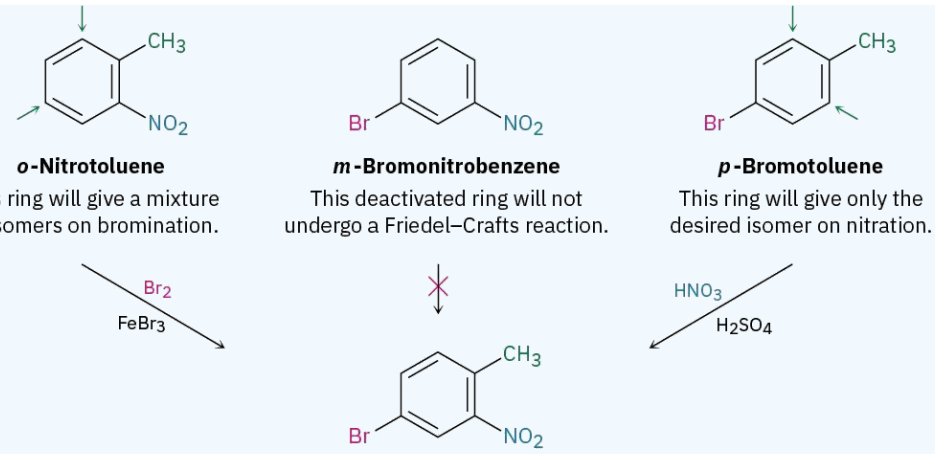


4-Bromo-2-nitrotoluene

The three substituents on the ring are a bromine, a methyl group, and a nitro group. A bromine can be introduced by bromination with $Br_2/FeBr_3$, a methyl group can be introduced by Friedel–Crafts alkylation with $CH_3Cl/AlCl_3$, and a nitro group can be introduced by nitration with HNO_3/H_2SO_4.

Solution

Ask yourself, “What is an immediate precursor of the target?” The final step will involve introduction of one of three groups—bromine, methyl, or nitro—so we have to consider three possibilities. Of the three, the bromination of *o*-nitrotoluene could be used because the activating methyl group would dominate the deactivating nitro group and direct bromination to the correct position. Unfortunately, a mixture of product isomers would be formed. A Friedel–Crafts reaction can’t be used as the final step because this reaction doesn’t work on a nitro-substituted (strongly deactivated) benzene. The best precursor of the desired product is probably *p*-bromotoluene, which can be nitrated ortho to the activating methyl group to give a single product.



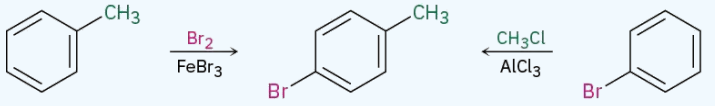
***o*-Nitrotoluene**
This ring will give a mixture of isomers on bromination.

***m*-Bromonitrobenzene**
This deactivated ring will not undergo a Friedel–Crafts reaction.

***p*-Bromotoluene**
This ring will give only the desired isomer on nitration.

4-Bromo-2-nitrotoluene

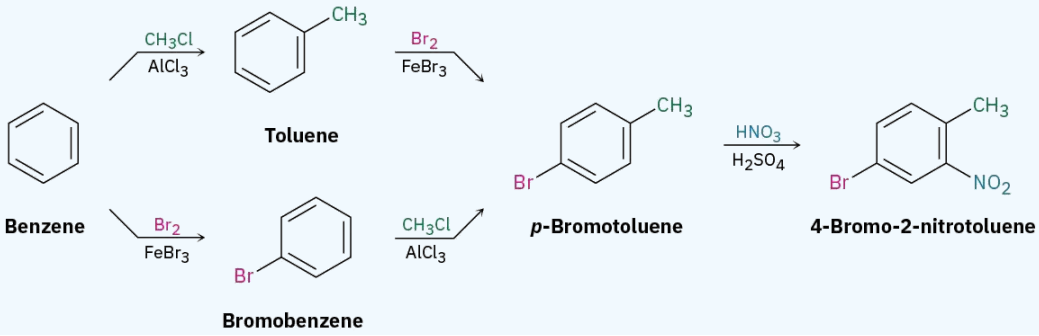
Next ask, "What is an immediate precursor of *p*-bromotoluene?" Perhaps toluene is an immediate precursor because the methyl group would direct bromination to the ortho and para positions. Alternatively, bromobenzene might be an immediate precursor because we could carry out a Friedel–Crafts methylation and obtain a mixture of ortho and para products. Both answers are satisfactory, although both would also lead unavoidably to a mixture of products that would have to be separated.



Toluene | ***p*-Bromotoluene (+ ortho isomer)** | **Bromobenzene**

"What is an immediate precursor of toluene?" Benzene, which could be methylated in a Friedel–Crafts reaction. Alternatively, "What is an immediate precursor of bromobenzene?" Benzene, which could be brominated.

The retrosynthetic analysis has provided two valid routes from benzene to 4-bromo-2-nitrotoluene.

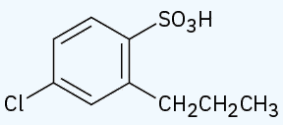


✔ Worked Example 3.10.2: Synthesizing a Polysubstituted Benzene

Synthesize 4-chloro-2-propylbenzenesulfonic acid from benzene.

Strategy

Draw the target molecule, identify its substituents, and recall how each of the three can be introduced. Then plan retrosynthetically.



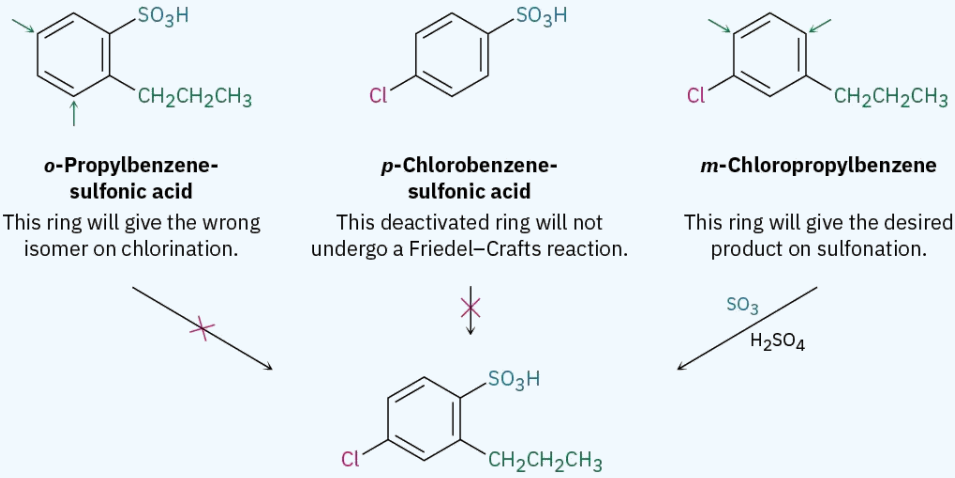
4-Chloro-2-propylbenzenesulfonic acid

The three substituents on the ring are a chlorine, a propyl group, and a sulfonic acid group. A chlorine can be introduced by chlorination with $Cl_2/FeCl_3$, a propyl group can be introduced by Friedel–Crafts acylation with $CH_3CH_2COCl/AlCl_3$ followed

by reduction with H_2/Pd, and a sulfonic acid group can be introduced by sulfonation with SO_3/H_2SO_4.

Solution

"What is an immediate precursor of the target?" The final step will involve introduction of one of three groups—chlorine, propyl, or sulfonic acid—so we have to consider three possibilities. Of the three, the chlorination of *o*-propylbenzenesulfonic acid can't be used because the reaction would occur at the wrong position. Similarly, a Friedel–Crafts reaction can't be used as the final step because this reaction doesn't work on sulfonic-acid-substituted (strongly deactivated) benzenes. Thus, the immediate precursor of the desired product is probably *m*-chloropropylbenzene, which can be sulfonated to give a mixture of product isomers that must then be separated.



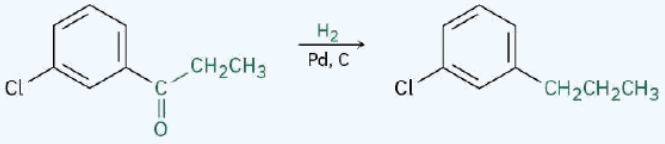
***o*-Propylbenzene-sulfonic acid**
This ring will give the wrong isomer on chlorination.

***p*-Chlorobenzene-sulfonic acid**
This deactivated ring will not undergo a Friedel–Crafts reaction.

***m*-Chloropropylbenzene**
This ring will give the desired product on sulfonation.

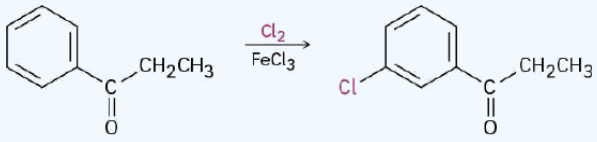
4-Chloro-2-propylbenzenesulfonic acid

"What is an immediate precursor of *m*-chloropropylbenzene?" Because the two substituents have a meta relationship, the first substituent placed on the ring must be a meta director so that the second substitution will take place at the proper position. Furthermore, because primary alkyl groups such as propyl can't be introduced directly by Friedel–Crafts alkylation, the precursor of *m*-chloropropylbenzene is probably *m*-chloropropiophenone, which could be catalytically reduced.



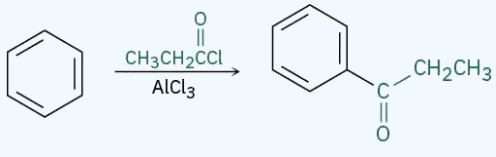
***m*-Chloropropiophenone** ***m*-Chloropropylbenzene**

"What is an immediate precursor of *m*-chloropropiophenone?" Propiophenone, which could be chlorinated in the meta position.



Propiophenone ***m*-Chloropropiophenone**

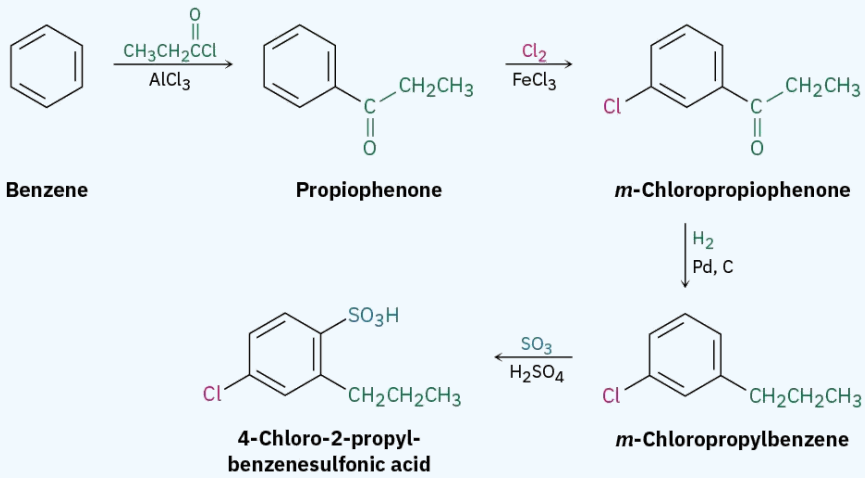
"What is an immediate precursor of propiophenone?" Benzene, which could undergo Friedel–Crafts acylation with propanoyl chloride and $AlCl_3$.



Benzene **Propiophenone**

https://chem.libretexts.org/@go/page/500379

The final synthesis is a four-step route from benzene:



Benzene **Propiophenone** ***m*-Chloropropiophenone**

***m*-Chloropropylbenzene** **4-Chloro-2-propyl-benzenesulfonic acid**

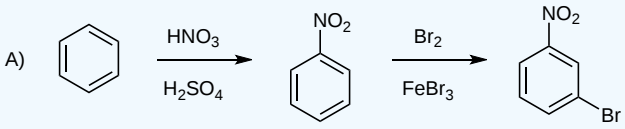
Exercise 3.10.1

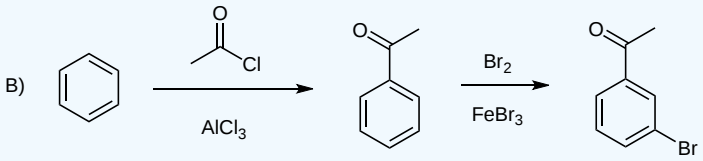
How would make the following compounds from benzene?

a. *m*-bromonitrobenzene
b. *m*-bromoethylbenzene
c. 4-Chloro-1-nitro-2-propylbenzene
d. 3-Bromo-2-methylbenzenesulfonic acid

Answer

Only one possible synthesis is shown for each compound. There are multiple possibilities.





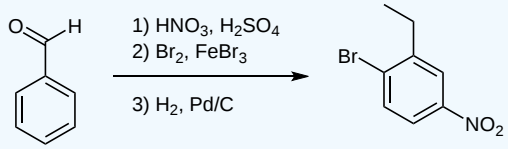
C) 1. CH_3CH_2COCl, $AlCl_3$; 2. Cl_2, $FeCl_3$; 3. H_2/Pd; 4. HNO_3, H_2SO_4

D) 1. CH_3Cl, $AlCl_3$; 2. Br_2, $FeBr_3$; 3. SO_3, H_2SO_4

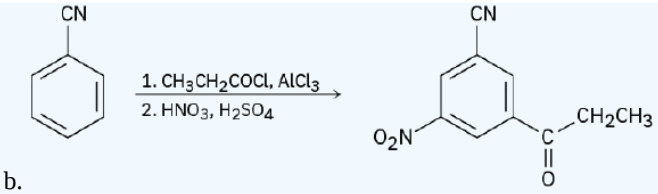
Exercise 3.10.2

In planning a synthesis, it's as important to know what not to do as to know what to do. As written, the following reaction schemes have flaws in them. What is wrong with each?

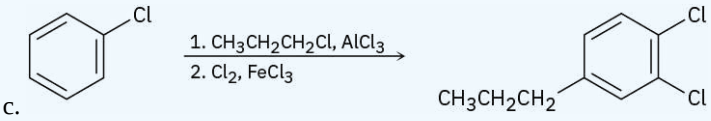
a.



b.



c.



Answer

a. The bromine should be in the meta position. Right now it is in the ortho position, from perhaps having the ethyl group present first and then the having it substituted there. BUT the ethyl group is last to form, and the aldehyde and nitro groups would both encourage a meta substitution.
b. Friedel–Crafts acylation does not occur on a deactivated ring.
c. Rearrangement occurs during Friedel–Crafts alkylation with primary halides; chlorination occurs ortho to the alkyl group.

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3.11: Reactions of Arylamines

Objectives

After completing this section, you should be able to

1. a. identify the product formed when a given arylamine is reacted with aqueous bromine.
   b. give an appropriate example to illustrate the high reactivity of arylamines in electrophilic aromatic substitution reactions.
   c. explain why arylamines cannot be used in Friedel-Crafts reactions.
2. a. show how the problems associated with carrying out electrophilic aromatic substitution reactions on arylamines can be circumvented by first converting the amine to an amide, and illustrate this process with an appropriate example.
   b. design a multi-step synthesis for a given compound in which it is necessary to protect the amino group by acetylation.
3. a. write a general equation to describe the formation of an arenediazonium salt.
   b. identify the product formed when a given arenediazonium salt is reacted with any of the following compounds: copper(I) chloride, copper(I) bromide, sodium iodide, copper(I) cyanide, hot aqueous acid, hypophosphorous acid.
   c. identify the arenediazonium salt, the inorganic reagents, or both, needed to produce a given compound by a diazonium replacement reaction.
4. a. illustrate, with appropriate examples, the importance to the synthetic chemist of the overall reaction sequence A nitration, B reduction, C diazotization, and D replacement.
   b. show how the removal of an amino (or nitro) group from an aromatic ring through the reaction of an arenediazonium salt with hypophosphorous acid (H_3PO_2) can sometimes be of use in organic synthesis.
5. a. write a general equation to represent a diazonium coupling reaction.
   b. write the detailed mechanism for the coupling reaction which takes place between arenediazonium salts and the electon-rich aromatic rings of phenols and arylamines.
   c. identify the product formed from the reaction of a given arenediazonium salt with a given arylamine or phenol.
   d. identify the arenediazonium salt and the arylamine or phenol needed to prepare a given azo compound.

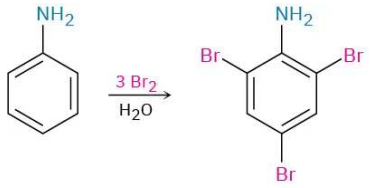
Key Terms

Make certain that you can define, and use in context, the key terms below.

- arenediazonium salt
- azo compound
- Sandmeyer reaction
- sulfa drug

Electrophilic Aromatic Substitutions

Arylamines are very reactive towards electrophilic aromomatic substitution. The strongest activating and ortho/para-directing substituents are the amino ($-NH_2$) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed. Monobromination of both phenol and aniline is difficult to control, with di- and tri-bromo products forming readily.

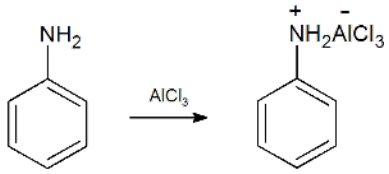


Aniline **2,4,6-Tribromoaniline (100%)**

Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives. The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents.

$$C_6H_5{-}NH_2 + I_2 + NaHCO_3 \longrightarrow p\text{-}I{-}C_6H_4{-}NH_2 + NaI + CO_2 + H_2O$$

Another drawback to the use of amino-substituted benzenes in electrophilic aromatic substitution reactions is that Friedel–Crafts reactions are not successful (Section 16.3). The amino group forms an acid–base complex with the $AlCl_3$ catalyst, which prevents further reaction.



Both drawbacks can be overcome, however, by carrying out electrophilic aromatic substitution reactions on the corresponding amide rather than on the free amine.

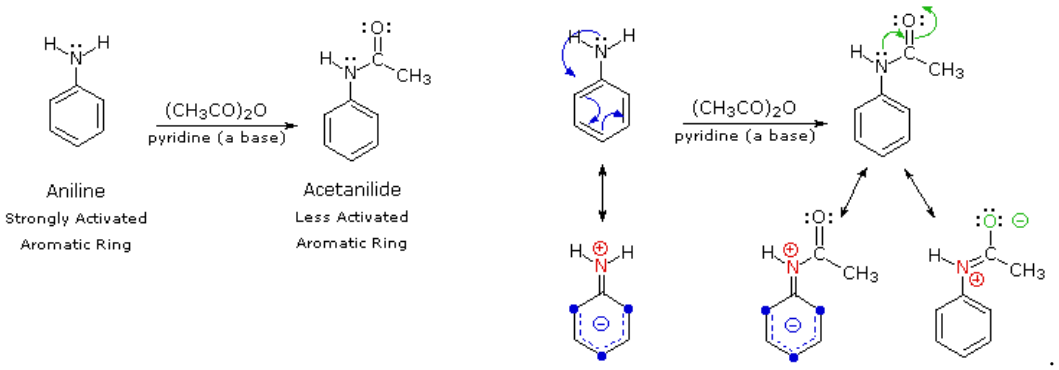
Modifying the Strength of the Activating Group

Treatment of an amine with acetic anhydride yields the corresponding acetyl amide, or acetamide. Although still activating and ortho-, para-directing, amido substituents (R–N–C=O R–N–C=O) are less strongly activating and less basic than amino groups because their nitrogen lone-pair electrons are delocalized by the neighboring carbonyl group.

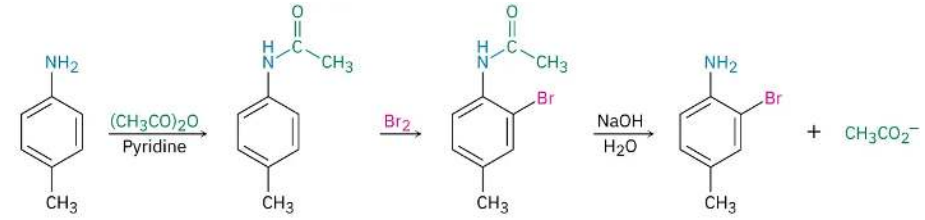
By acetylating the heteroatom substituent on aniline, its activating influence can be substantially attenuated. For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield. The modifying acetyl group can then be removed by acid-catalyzed hydrolysis (last step), to yield para-nitroaniline. Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.

$$C_6H_5{-}NH_2 + (CH_3CO)_2O \xrightarrow{\text{pyridine (a base)}} C_6H_5{-}NHCOCH_3 \xrightarrow{HNO_3\ ,\ 5\ ^oC} p\text{-}O_2N{-}C_6H_4{-}NHCOCH_3 \xrightarrow{H_3O^+\ \text{and heat}} p\text{-}O_2N{-}C_6H_4{-}NH \quad (3.11.1)$$

The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating and ortho/para-directing.

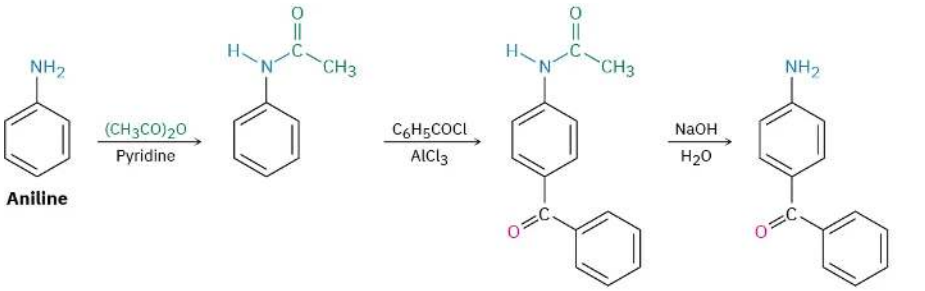


As a result, bromination of an *N*-arylamide occurs cleanly to give a monobromo product, and hydrolysis of the amide with aqueous base then gives the free amine. For example, *p*-toluidine (4-methylaniline) can be acetylated, brominated, and hydrolyzed to yield 2-bromo-4-methylaniline. None of the 2,6-dibrominated product is obtained.



***p*-Toluidine** **2-Bromo-4-methyl-aniline (79%)**

Friedel–Crafts alkylations and acylations of *N*-arylamides also proceed normally. For example, benzoylation of acetanilide (*N*-acetylaniline) under Friedel–Crafts conditions gives 4-aminobenzophenone in 80% yield after hydrolysis.



Aniline **4-Aminobenzophenone (80%)**

Moderating the reactivity of an amino-substituted benzene by forming an amide is a useful trick that allows many kinds of electrophilic aromatic substitutions to be carried out that would otherwise be impossible. One example is the preparation of the sulfa drugs, such as sulfanilamide.

? Exercise 3.11.1

Propose syntheses of the following compounds from benzene:

a. *N*,*N*-Dimethylaniline
b. *p*-Chloroaniline
c. *m*-Chloroaniline
d. 2,4-Dimethylaniline

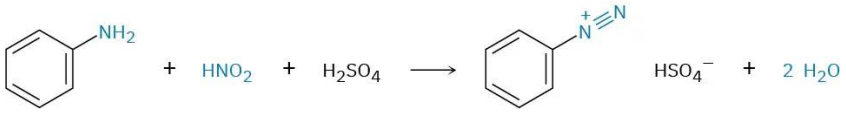
Answer

a. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. 2 CH_3Br
b. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. Cl_2; 5. H_2O, NaOH

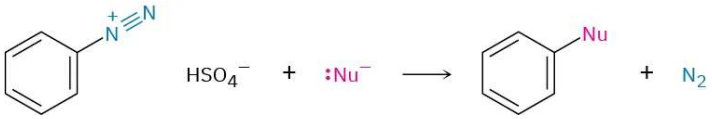
c. 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$
d. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 CH_3Cl, $AlCl_3$; 5. H_2O, NaOH

Diazonium Salts: The Sandmeyer Reaction

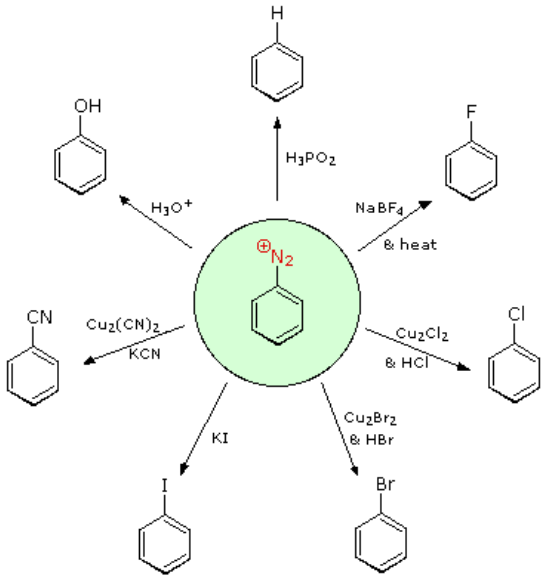
Primary arylamines react with nitrous acid, HNO_2, to yield stable arenediazonium salts, $Ar-\overset{+}{N}\equiv NX^-$ a process called a **diazotization reaction**. Alkylamines also react with nitrous acid, but the corresponding alkanediazonium products are so reactive they can't be isolated. Instead, they lose nitrogen instantly to yield carbocations. The analogous loss of N_2 from an arenediazonium ion to yield an aryl cation is disfavored by the instability of the cation. Aryl diazonium salts are important intermediates. They are prepared in cold (0 º to 10 ºC) aqueous solution.



Arenediazonium salts are useful because the diazonio group (−N≡N) can be replaced by a nucleophile in a substitution reaction with loss of nitrogen.



Some of the more commonly used substitution reactions are shown in the following diagram. Since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored. Substitution reactions catalyzed by cuprous salts are known as **Sandmeyer reactions**. Fluoride substitution occurs on treatment with $BF_4^{(-)}$, a reaction known as the **Schiemann reaction**. Stable diazonium tetrafluoroborate salts may be isolated, and on heating these lose nitrogen to give an arylfluoride product. The top reaction with hypophosphorus acid, H_3PO_2, is noteworthy because it achieves the reductive removal of an amino (or nitro) group. Unlike the nucleophilic substitution reactions, this reduction probably proceeds by a radical mechanism.



These aryl diazonium substitution reactions significantly expand the tactics available for the synthesis of polysubstituted benzene derivatives. Consider the following options:

I. The usual precursor to an aryl amine is the corresponding nitro compound. A nitro substituent deactivates an aromatic ring and directs electrophilic substitution to meta locations.

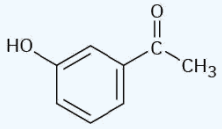
II. Reduction of a nitro group to an amine may be achieved in several ways. The resulting amine substituent strongly activates an aromatic ring and directs electrophilic substitution to ortho & para locations.

III. The activating character of an amine substituent may be attenuated by formation of an amide derivative (reversible), or even changed to deactivating and meta-directing by formation of a quaternary-ammonium salt (irreversible).

IV. Conversion of an aryl amine to a diazonium ion intermediate allows it to be replaced by a variety of different groups (including hydrogen), which may in turn be used in subsequent reactions.

Worked Example 3.11.1: Using Diazonium Replacement Reactions

How would you prepare m-hydroxyacetophenone from benzene, using a diazonium replacement reaction in your scheme?



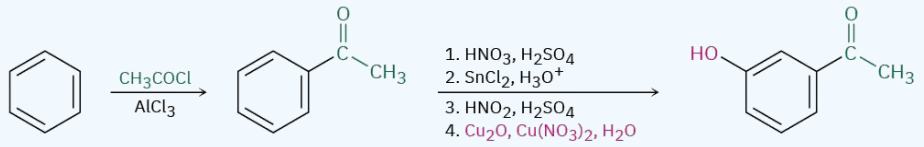
***m*-Hydroxyacetophenone**

Strategy

As always, organic syntheses are planned by working retrosynthetically from the final product, one step at a time. First, identify the functional groups in the product and recall how those groups can be synthesized. m-Hydroxyacetophenone has an –OH group and a $–COCH_3$ group in a meta relationship on a benzene ring. A hydroxyl group is generally introduced onto an aromatic ring by a four-step sequence of nitration, reduction, diazotization, and diazonio replacement. An acetyl group is introduced by a Friedel–Crafts acylation reaction.

Next, ask yourself what an immediate precursor of the target might be. Since an acetyl group is a meta director while a hydroxyl group is an ortho and para director, acetophenone might be a precursor of m-hydroxyacetophenone. Benzene, in turn, is a precursor of acetophenone.

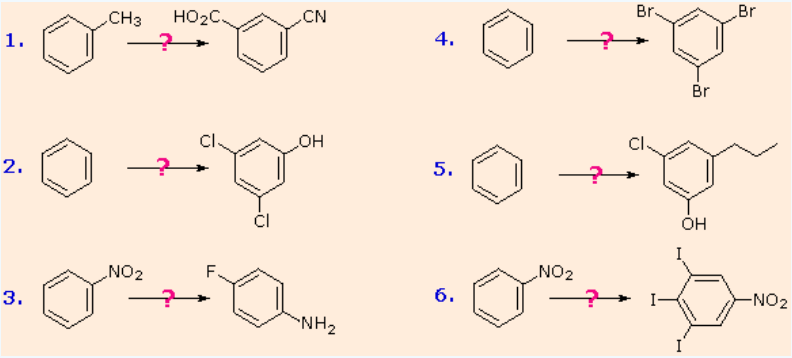
Solution



Benzene **Acetophenone** ***m*-Hydroxyacetophenone**

Worked Example 3.11.2

The following examples illustrate some combined applications of these options to specific cases. You should try to conceive a plausible reaction sequence for each. Once you have done so, you may check the suggested answers below.

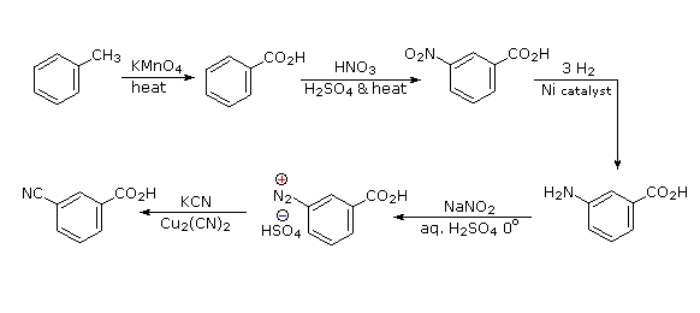


Solution

Answer 1:

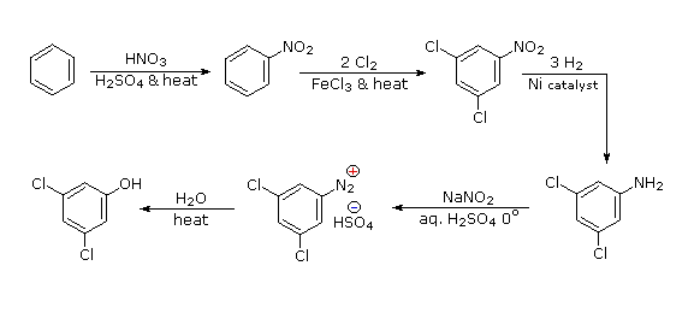
It should be clear that the methyl substituent will eventually be oxidized to a carboxylic acid function. The timing is important, since a methyl substituent is ortho/para-directing and the carboxyl substituent is meta-directing. The cyano

group will be introduced by a diazonium intermediate, so a nitration followed by reduction to an amine must precede this step.



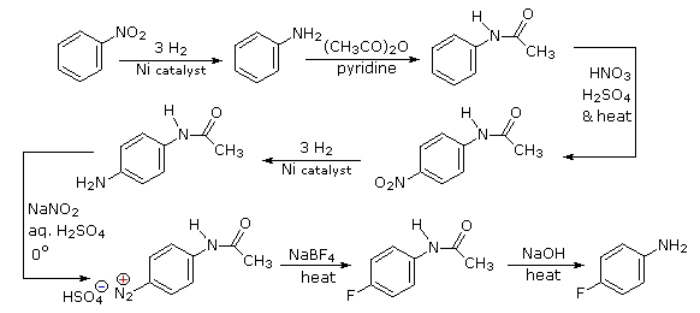
Answer 2:

The hydroxyl group is a strong activating substituent and would direct aromatic ring chlorination to locations ortho & para to itself, leading to the wrong product. As an alternative, the nitro group is not only meta-directing, it can be converted to a hydroxyl group by way of a diazonium intermediate. The resulting strategy is self evident.



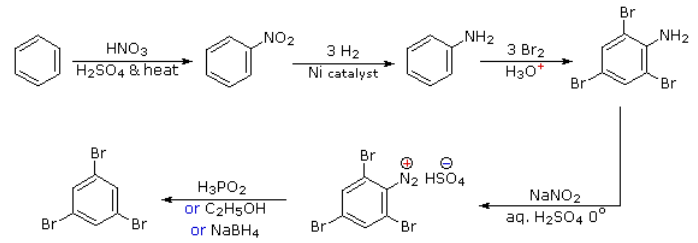
Answer 3:

Selective introduction of a fluorine is best achieved by treating a diazonium intermediate with boron tetrafluoride anion. To get the necessary intermediate we need to make p-nitroaniline. Since the nitro substituent on the starting material would direct a new substituent to a meta-location, we must first reduce it to an ortho/para-directing amino group. Amino groups are powerful activating substituents, so we deactivate it by acetylation before nitration. The acetyl substituent also protects the initial amine function from reaction with nitrous acid later on. It is removed in the last step.



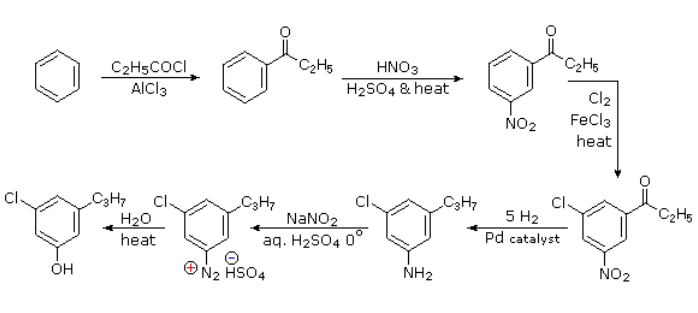
Answer 4:

Polybromination of benzene would lead to ortho/para substitution. In order to achieve the mutual meta-relationship of three bromines, it is necessary to introduce a powerful ortho/para-directing prior to bromination, and then remove it following the tribromination. An amino group is ideal for this purpose. Reductive removal of the diazonium group may be accomplished in several ways (three are shown).



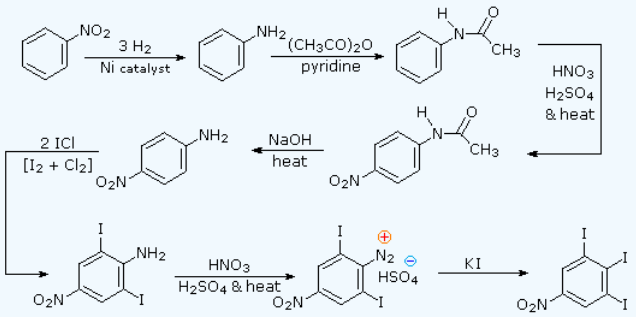
Answer 5:

The propyl substituent is best introduced by Friedel-Crafts acylation followed by reduction, and this cannot be carried out in the presence of a nitro substituent. Since an acyl substituent is a meta-director, it is logical to use this property to locate the nitro and chloro groups before reducing the carbonyl moiety. The same reduction method can be used to reduce both the nitro group (to an amine) and the carbonyl group to propyl. We have already seen the use of diazonium intermediates as precursors to phenols.



Answer 6:

Aromatic iodination can only be accomplished directly on highly activated benzene compounds, such as aniline, or indirectly by way of a diazonium intermediate. Once again, a deactivated amino group is the precursor of p-nitroaniline (prb.#3). This aniline derivative requires the more electrophilic iodine chloride (ICl) for ortho-iodination because of the presence of a deactivating nitro substituent. Finally, the third iodine is introduced by the diazonium ion procedure.



Exercise 3.11.3

How would you prepare the following compounds from benzene, using a diazonium replacement reaction in your scheme?

a. p-Bromobenzoic acid
b. m-Bromobenzoic acid
c. m-Bromochlorobenzene
d. p-Methylbenzoic acid
e. 1,2,4-Tribromobenzene

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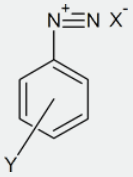
Answer

a. 1. CH_3Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr; 6. $KMnO_4$, H_2O
b. 1. HNO_3, H_2SO_4; 2. Br_2, $FeBr_3$; 3. $SnCl_2$, H_3O^+; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+
c. 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr
d. 1. CH_3Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+
e. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 Br_2; 5. H_2O, NaOH; 6. $NaNO_2$, H_2SO_4; 7. CuBr

Study Notes

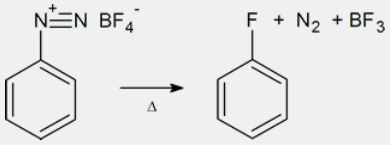
The general process of reacting an aromatic amine with acetic anhydride, substituting it, and then hydrolyzing it is known as “protecting the amino group.”

An “arenediazonium salt” is formed by the reaction of an aromatic amine with nitrous acid at 0–5°C, and has the structure shown below.



Alkanediazonium salts are very unstable; therefore, arenediazonium salts are often simply referred to as diazonium salts.

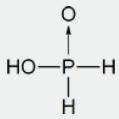
As is mentioned in the textbook, arenediazonium salts are very useful intermediates from which a wide variety of aromatic compounds can be prepared. You should be thoroughly familiar with the use of diazonium salts to prepare each of the classes of compounds. In addition, you should be aware that fluoroarenes can also be prepared from diazonium salts, as follows:



In this case the diazonium salt is prepared using fluoroboric acid, HBF_4, and sodium nitrite. The thermal decomposition of the salt, called the Schiemann reaction, can be quite hazardous.

Note that the IUPAC-preferred name for cuprous chloride is copper(I) chloride; similarly, cuprous cyanide is called copper(I) cyanide.

Hypophosphorous acid has the structure shown below:



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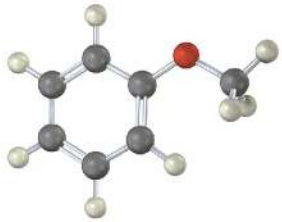
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3.12: Additional Problems

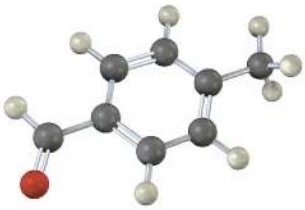
3 • Additional Problems

Visualizing Chemistry

PROBLEM 3-24 Draw the product from the reaction of each of the following substances with (1) Br2, FeBr3, and (2) CH3COCl, AlCl3.

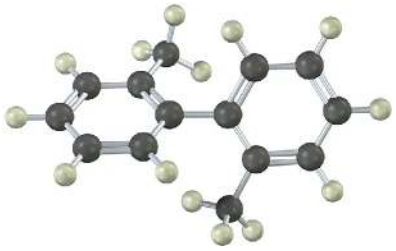


(a)

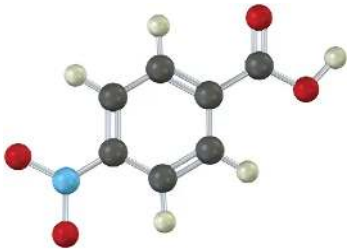


(b)

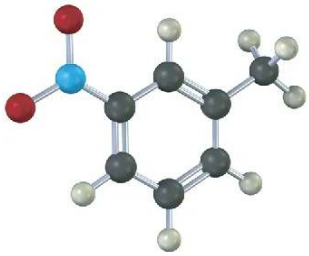
PROBLEM 3-25 The following molecular model of a dimethyl-substituted biphenyl represents the lowest-energy conformation of the molecule. Why are the two benzene rings tilted at a 63° angle to each other rather than being in the same plane so that their *p* orbitals overlap? Why doesn't complete rotation around the single bond joining the two rings occur?



PROBLEM 3-26 How would you synthesize the following compound starting from benzene? More than one step is needed.



PROBLEM 3-27 The following compound can't be synthesized using the methods discussed in this chapter. Why not?



Mechanism Problems

Mechanisms of Electrophilic Substitutions

PROBLEM 3-28 Aromatic iodination can be carried out with a number of reagents, including iodine monochloride, ICl. What is the direction of polarization of ICl? Propose a mechanism for the iodination of an aromatic ring with ICl.

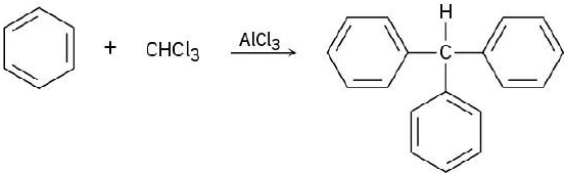
PROBLEM 3-29 The sulfonation of an aromatic ring with SO_3 and H_2SO_4 is reversible. That is, heating benzenesulfonic acid with H_2SO_4 yields benzene. Show the mechanism of the desulfonation reaction. What is the electrophile?

PROBLEM 3-30 The carbocation electrophile in a Friedel–Crafts reaction can be generated by an alternate means than the reaction of an alkyl chloride with $AlCl_3$. For example, reaction of benzene with 2-methylpropene in the presence of H_3PO_4 yields *tert*-butylbenzene. Propose a mechanism for this reaction.

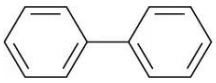
PROBLEM 3-31 The *N*,*N*,*N*-trimethylammonium group, $-\overset{+}{N}(CH_3)_3$, is one of the few groups that is a meta-directing deactivator yet has no electron-withdrawing resonance effect. Explain.

PROBLEM 3-32 The nitroso group, –N=O, is one of the few nonhalogens that is an ortho- and para-directing deactivator. Explain this behavior by drawing resonance structures of the carbocation intermediates in ortho, meta, and para electrophilic reactions on nitrosobenzene, $C_6H_5N{=}O$.

PROBLEM 3-33 Triphenylmethane can be prepared by the reaction of benzene and chloroform in the presence of $AlCl_3$. Propose a mechanism for the reaction.

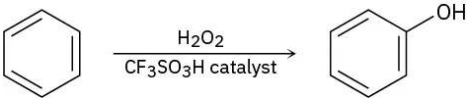


PROBLEM 3-34 Using resonance structures of the intermediates, explain why bromination of biphenyl occurs at ortho and para positions rather than at meta.



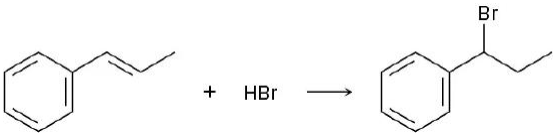
Biphenyl

PROBLEM 3-35 Benzene and alkyl-substituted benzenes can be hydroxylated by reaction with H_2O_2 in the presence of an acidic catalyst. What is the structure of the reactive electrophile? Propose a mechanism for the reaction.

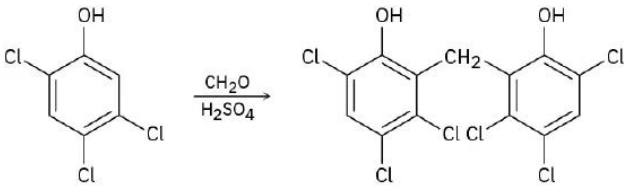


Additional Mechanism Practice

PROBLEM 3-36 Addition of HBr to 1-phenylpropene yields only (1-bromopropyl)benzene. Propose a mechanism for the reaction, and explain why none of the other regioisomer is produced.



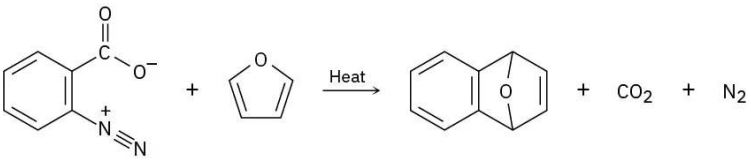
PROBLEM 3-37 Hexachlorophene, a substance used in the manufacture of germicidal soaps, is prepared by reaction of 2,4,5-trichlorophenol with formaldehyde in the presence of concentrated sulfuric acid. Propose a mechanism for the reaction.



Hexachlorophene

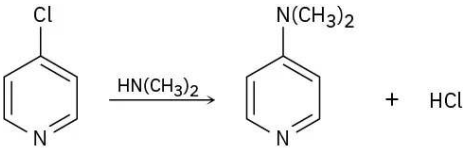
https://chem.libretexts.org/@go/page/507237

PROBLEM 3-38 Benzenediazonium carboxylate decomposes when heated to yield N_2, CO_2, and a reactive substance that can't be isolated. When benzene-diazonium carboxylate is heated in the presence of furan, the following reaction is observed:

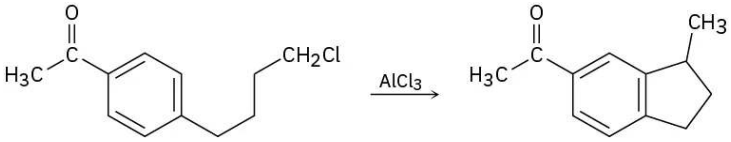


What intermediate is involved in this reaction? Propose a mechanism for its formation.

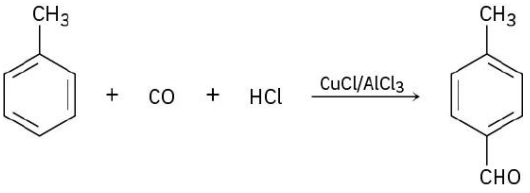
PROBLEM 3-39 4-Chloropyridine undergoes reaction with dimethylamine to yield 4-dimethylaminopyridine. Propose a mechanism for the reaction.



PROBLEM 3-40 Propose a mechanism to account for the following reaction:

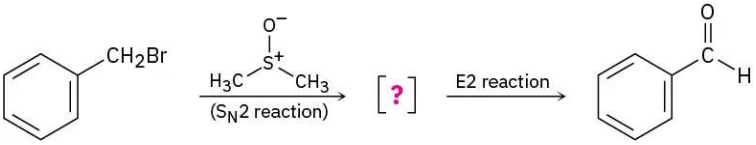


PROBLEM 3-41 In the *Gatterman–Koch reaction*, a formyl group (–CHO) is introduced directly onto a benzene ring. For example, the reaction of toluene with CO and HCl in the presence of mixed $CuCl/AlCl_3$ gives *p*-methylbenzaldehyde. Propose a mechanism.

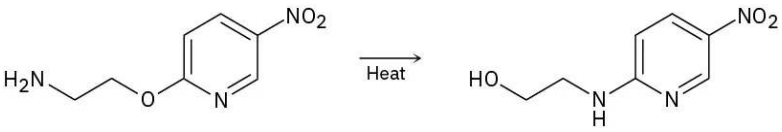


PROBLEM 3-42 Treatment of *p*-*tert*-butylphenol with a strong acid such as H_2SO_4 yields phenol and 2-methylpropene. Propose a mechanism.

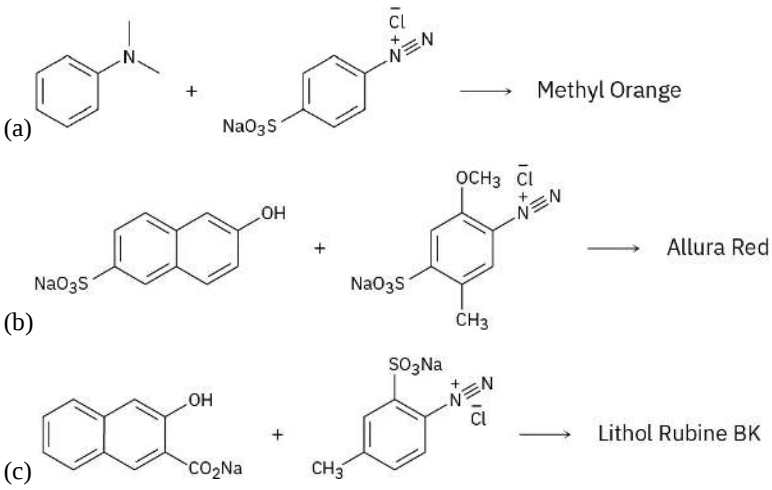
PROBLEM 3-43 Benzyl bromide is converted into benzaldehyde by heating in dimethyl sulfoxide. Propose a structure for the intermediate, and show the mechanisms of the two steps in the reaction.



PROBLEM 3-44 Propose a mechanism for the *Smiles rearrangement* below.

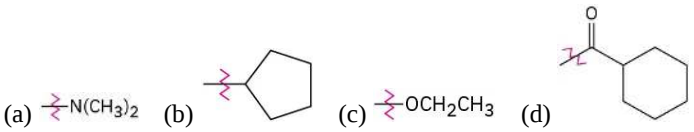


PROBLEM 3-44 Because of their conjugation, azo dyes are highly colored compounds and the major artificial color source for textiles and food. Azo dyes are produced by the reaction of aryl diazonium salts with a second aromatic compound. In the product, the aromatic rings are linked by a diazo bridge (–N=N–). From the reactants provided, propose a structure for each azo dye and draw the electron-pushing mechanism.



Reactivity and Orientation of Electrophilic Substitutions

PROBLEM 3-46 Identify each of the following groups as an activator or deactivator and as an *o*,*p*-director or *m*-director:



PROBLEM 3-47 Predict the major product(s) of nitration of the following substances. Which react faster than benzene, and which slower?

(a) Bromobenzene (b) Benzonitrile (c) Benzoic acid (d) Nitrobenzene (e) Benzenesulfonic acid (f) ethoxybenzene

PROBLEM 3-48 Rank the compounds in each group according to their reactivity toward electrophilic substitution.

- (a) Chlorobenzene, *o*-dichlorobenzene, benzene
- (b) *p*-Bromonitrobenzene, nitrobenzene, phenol
- (c) Fluorobenzene, benzaldehyde, *o*-xylene
- (d) Benzonitrile, *p*-methylbenzonitrile, *p*-methoxybenzonitrile

PROBLEM 3-49 Predict the major monoalkylation products you would expect to obtain from the reaction of the following substances with chloromethane and $AlCl_3$:

(a) Bromobenzene (b) *m*-Bromophenol (c) *p*-Chloroaniline (d) 2,4-Dichloronitrobenzene

(e) 2,4-Dichlorophenol (f) Benzoic acid (g) *p*-Methylbenzenesulfonic acid (h) 2,5-Dibromotoluene

PROBLEM 3-50 Name and draw the major product(s) of electrophilic chlorination of the following compounds:

(a) *m*-Nitrophenol (b) *o*-Xylene (c) *p*-Nitrobenzoic acid (d) *p*-Bromobenzenesulfonic acid

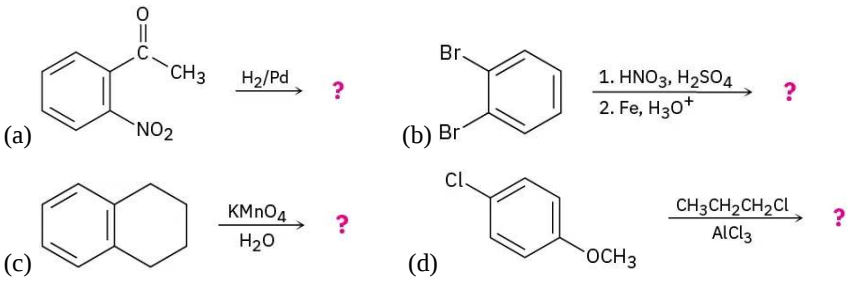
PROBLEM 3-51 Predict the major product(s) you would obtain from sulfonation of the following compounds:

(a) Fluorobenzene (b) *m*-Bromophenol (c) *m*-Dichlorobenzene (d) 2,4-Dibromophenol

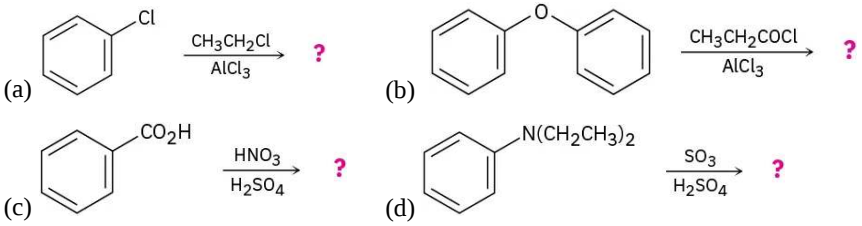
PROBLEM 3-52 Rank the following aromatic compounds in the expected order of their reactivity toward Friedel–Crafts alkylation. Which compounds are unreactive?

(a) Bromobenzene (b) Toluene (c) Phenol (d) Aniline (e) Nitrobenzene (f) *p*-Bromotoluene

PROBLEM 3-53 What product(s) would you expect to obtain from the following reactions:



PROBLEM 3-54 Predict the mayor product(s) of the following reactions:



Organic Synthesis

PROBLEM 3-55 How would you synthesize the following substances starting from benzene or phenol? Assume that ortho- and para-substitution products can be separated. (a) *o*-Bromobenzoic acid (b) *p*-Methoxytoluene (c) 2,4,6-Trinitrobenzoic acid (d) *m*-Bromoaniline

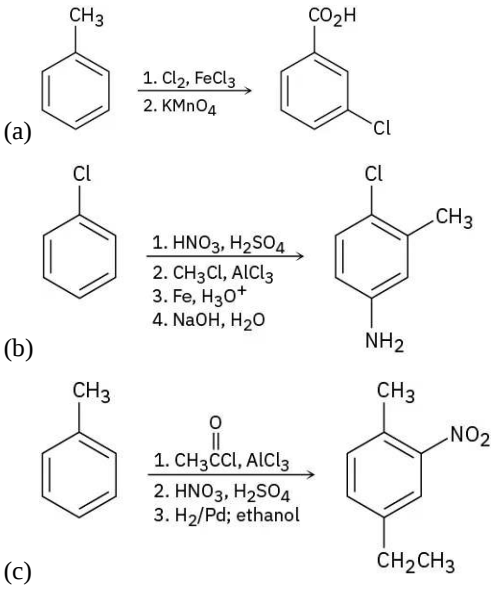
PROBLEM 3-56 Starting with benzene as your only source of aromatic compounds, how would you synthesize the following substances? Assume that you can separate ortho and para isomers if necessary.

(a) *p*-Chloroacetophenone (b) *m*-Bromonitrobenzene (c) *o*-Bromobenzenesulfonic acid (d) *m*-Chlorobenzenesulfonic acid

PROBLEM 3-57 Starting with either benzene or toluene, how would you synthesize the following substances: Assume that ortho and para isomers can be separated.

(a) 2-Bromo-4-nitrotoluene (b) 1,3,5-Trinitrobenzene (c) 2,4,6-Tribromoaniline (d) *m*-Fluorobenzoic acid

PROBLEM 3-58 As written, the following syntheses have flaws. What is wrong with each?

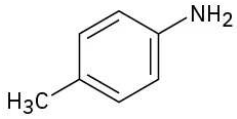


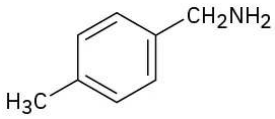
Problem 3-aa How would you prepare aniline from the following starting materials?

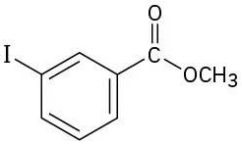
(a) Benzene (b) Benzamide (c) Toluene

Problem 3-ab How would you prepare benzylamine, $C_6H_5CH_2NH_2$, from benzene? More than one step is needed.

Problem 3-ac How would you prepare the following compounds from toluene? A diazonio replacement reaction is needed in some instances.

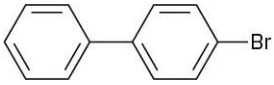
(a) 

(b) 

(c) 

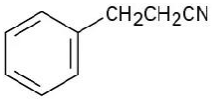
General Problems

PROBLEM 3-59 At what position and on what ring do you expect nitration of 4-bromo-biphenyl to occur? Explain, using resonance structures of the potential intermediates.

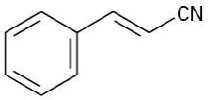


4-Bromobiphenyl

PROBLEM 3-60 Electrophilic substitution on 3-phenylpropanenitrile occurs at the ortho and para positions, but reaction with 3-phenylpropenenitrile occurs at the meta position. Explain, using resonance structures of the intermediates.

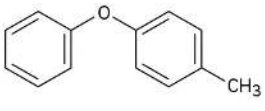


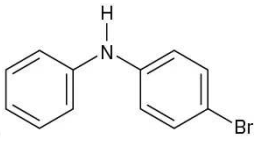
3-Phenylpropanenitrile

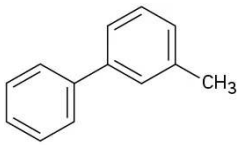


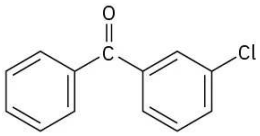
3-Phenylpropenenitrile

PROBLEM 3-61 At what position, and on what ring, would you expect the following substances to undergo electrophilic substitution?

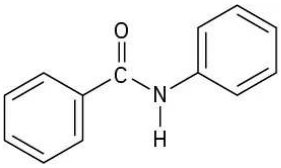
(a) 

(b) 

(c) 

(d) 

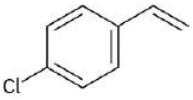
PROBLEM 3-62 At what position, and on what ring, would you expect bromination of benzanilide to occur? Explain by drawing resonance structures of the intermediates.

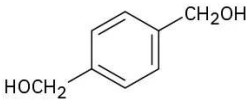


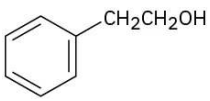
Benzanilide

PROBLEM 3-63 Would you expect the Friedel–Crafts reaction of benzene with (*R*)-2- chlorobutane to yield optically active or racemic product? Explain.

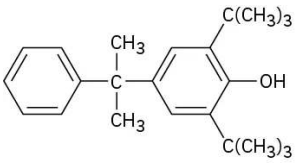
PROBLEM 3-64 How would you synthesize the following substances starting from benzene?

(a) 

(b) 

(c) 

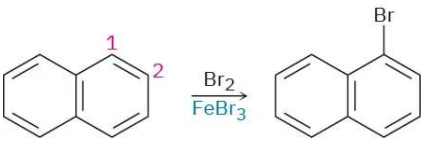
PROBLEM 3-65 The compound MON-0585 is a nontoxic, biodegradable larvicide that is highly selective against mosquito larvae. Synthesize MON-0585 using either benzene or phenol as a source of the aromatic rings.



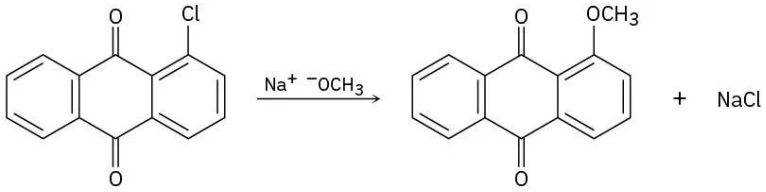
MON-0585

PROBLEM 3-66 Phenylboronic acid, $C_6H_5B(OH)_2$, is nitrated to give 15% ortho- substitution product and 85% meta. Explain the meta-directing effect of the $–B(OH)_2$ group.

PROBLEM 3-67 Draw resonance structures of the intermediate carbocations in the bromination of naphthalene, and account for the fact that naphthalene undergoes electrophilic substitution at C1 rather than C2.



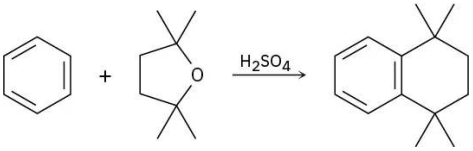
PROBLEM 3-68 Propose a mechanism for the reaction of 1-chloroanthraquinone with methoxide ion to give the substitution product 1-methoxyanthraquinone. Use curved arrows to show the electron flow in each step.



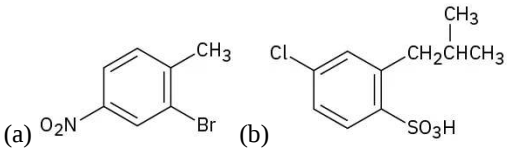
1-Chloroanthraquinone **1-Methoxyanthraquinone**

PROBLEM 3-69 *p*-Bromotoluene reacts with potassium amide to give a mixture of *m*- and *p*-methylaniline. Explain.

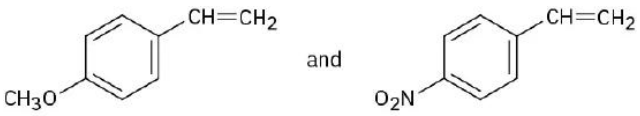
PROBLEM 3-70 Propose a mechanism to account for the reaction of benzene with 2,2,5,5-tetramethyltetrahydrofuran.



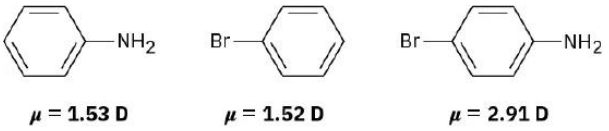
PROBLEM 3-71 How would you synthesize the following compounds from benzene? Assume that ortho and para isomers can be separated.



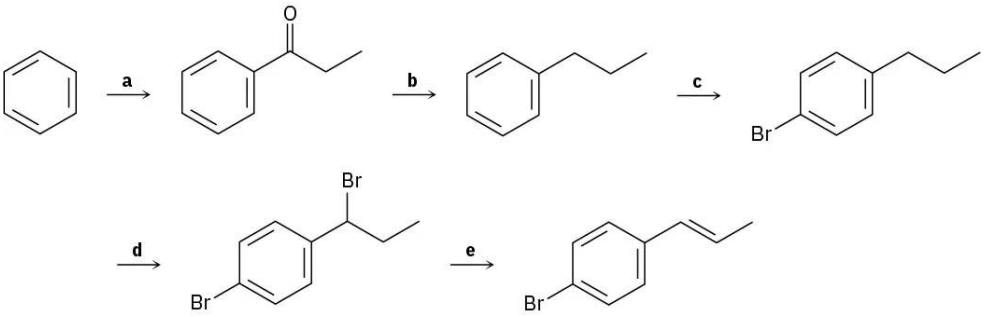
PROBLEM 3-72 You know the mechanism of HBr addition to alkenes, and you know the effects of various substituent groups on aromatic substitution. Use this knowledge to predict which of the following two alkenes reacts faster with HBr. Explain your answer by drawing resonance structures of the carbocation intermediates.



PROBLEM 3-73 Use your knowledge of directing effects, along with the following data, to deduce the directions of the dipole moments in aniline, bromobenzene, and bromoaniline.



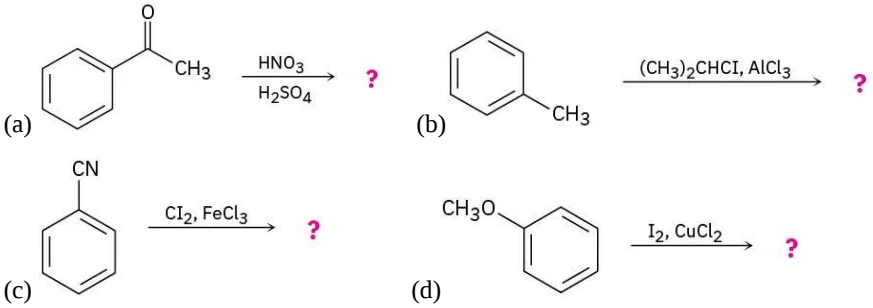
PROBLEM 3-74 Identify the reagents represented by the letters **a**–**e** in the following scheme:



PROBLEM 3-75 Phenols (ArOH) are relatively acidic, and the presence of a substituent group on the aromatic ring has a large effect. The pK_a of unsubstituted phenol, for example, is 9.89, while that of *p*-nitrophenol is 7.15. Draw resonance structures of the corresponding phenoxide anions and explain the data.

PROBLEM 3-76 Would you expect *p*-methylphenol to be more acidic or less acidic than unsubstituted phenol? Explain. (See PROBLEM 3-75.)

PROBLEM 3-77 Predict the product(s) for each of the following reactions. In each case, draw the resonance forms of the intermediate to explain the observed regiochemistry.



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3.S: Chemistry of Benzene - Electrophilic Aromatic Substitution (Summary)

Concepts & Vocabulary

Introduction

- Aromatic compounds don't typically undergo addition reactions.
- Aromatic compounds typically undergo substitution reactions.

3.1 Electrophilic Aromatic Substitution Reactions: Bromination

- Aromatic molecules only react with strong electrophiles.
- The first step in many electrophilic aromatic substitution mechanisms is activation or formation of the electrophile.
- The electrophilic aromatic substitution mechanism occurs in two steps. The first is addition of the electrophile to the ring and the second is elimination of a hydrogen from the ring to re-form the pi bond and restore aromaticity.
- In bromination of an aromatic ring, molecular bromine (Br_2) is reacted with iron tribromide ($FeBr_3$) to form the strongly electrophilic bromine cation and $FeBr_4$. Following this, the aromatic ring is reacted with the bromine cation and adds to the ring to form a benzenonium cation. This molecule then reacts with one of the bromine atoms from $FeBr_4$ to lose a hydrogen forming the product and HBr as well as reforming the iron tribromide.

3.2 Other Aromatic Substitutions

- Aluminum bromide ($AlBr_3$) can be used in place of $FeBr_3$ to create the bromine cation. Also the chlorides of alumnium and iron can also be used to create a chlorine cation which will also undergo electrophilic aromatic substitution.
- Reacting nitric acid and sulfuric acid forms nitronium (NO_2^+), which will react with aromatics for form nitro compounds.
- Sulfonation of aromatics can be accomplished by reacting with sulfur trioxide and sulfuric acid to yield sulfonic acids.

3.3 Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

- Friedel-Crafts reactions incorporate activation of alkyl and acyl halides by reacting them with a Lewis Acid catalyst, $AlCl_3$.
- Friedel-Crafts alkylations allow for adding alkyl chains to aromatic rings.
- After activation with aluminum chloride, alkyl carbocations can undergo rearrangement if it leads to a more stable intermediate.
- Friedel-Crafts acylations add alkyl ketones to aromatic rings.

3.4 Substituent Effects in Substituted Aromatic Rings

- Aromatic inductive effects are caused by differences in electronegativity between atoms bonded to the ring and the ring carbons.
- Most common heteroatoms (N, O, halogens) donate electron density toward the ring inductively.
- Aromatic resonance effects are caused by conjugation of substituents with the pi bonds of the ring.
- Substituents that increase the electron density of the ring activate the ring (make more reactive) toward electrophilic substitution.
- Substituents that decrease the electron density of the ring deactivate the ring (make less reactive) toward electrophilic substitution.

3.5 An Explanation of Substituent Effects

- Steric effects can increase para substitution as ortho/para directors become larger.
- Activating groups are ortho/para (o, p) directors.
- Deactivating groups are meta directors.
- Alkyl groups inductively donate electron density to the ring making them o, p directors.
- Groups with an O or N attached to the aromatic ring are activators and o, p directors due to resonance.
- Groups with a pi bond attached to the aromatic ring are deactivators and m directors due to resonance.
- Halogens are o, p directors, but are deactivators.

3.6 Trisubstituted Benzenes: Additivity of Effects

- When there is more than one group attached to an aromatic ring, these groups may reinforce directing effects (cooperative) or have opposing directing effects (non-cooperative).

3.7 Nucleophilic Aromatic Substitution

- Highly activated aromatic rings can react with strong nucleophiles through a substitution mechanism.
- The mechanism typically begins with addition of a nucleophile followed by elimination of a leaving group.

3.8 Benzyne

- Under highly reactive conditions, a mechanism that begins with elimination for form a benzyne molecule intermediate followed by addition of a nucleophile resulting in nucleophilic aromatic substitution.

3.9 Reduction of Aromatic Compounds

- Catalytic hydrogenation (H_2 and a catalyst) can be used to reduce many aromatic side-chains.
- Nitro groups can be selectively reduced to amines with $SnCl_2$ and HCl or with Fe and HCl.
- Carbonyls adjacent to the ring can be reduced by either Clemmensen reduction (Zn(Hg) and HCl.
- Birch reductions can reduce aromatic rings.

3.10 Synthesis of Polysubstituted Benzenes

- Multistep synthesis requires a combination of forward (from the starting material) and backward (from the target compound) thinking.

3.11 Basicity of Arylamines

- Nitrogen atoms as part of aromatic rings are less basic than methylamine.
- The basic lone pair on the nitrogen is to some extent tied up in – and stabilized by – the aromatic p system.
- This effect is accentuated by the addition of an electron-withdrawing groups.
- Imines are somewhat basic, which can be explained using orbital theory and the inductive effect: the sp^2 orbitals of an imine nitrogen are one part *s* and two parts *p*, meaning that they have about 67% *s* character.

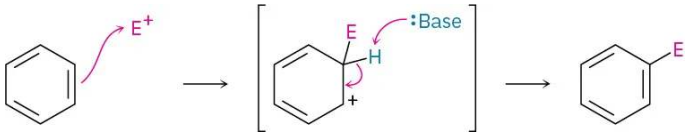
Skills to Master

- Skill 1 Write detailed electrophilic aromatic substitution mechanisms (halogentation, nitration, sulfonation, Friedel-Crafts alkyation and acylation).
- Skill 2 Write detailed mechanisms for formation of reactive electrophiles.
- Skill 3 Predict and explain rearrangements that can occur during Friedel-Crafts alkylation.
- Skill 4 Explain activation and deactivation of aromatic rings toward electrophilic aromatic substitution.
- Skill 5 Explain ortho, para vs. meta directing during electrophilic aromatic substitution reactions.
- Skill 6 Combine activation and deactivation and directing effects to predict products of reactions of substituted aromatic molecules.
- Skill 7 Write detailed nucleophilic aromatic substitution mechanisms through addition-elimination.
- Skill 8 Write detailed nucleophilic aromatic substitution mechanisms through benzyne elimination-addition.
- Skill 9 Draw products of oxidation of aromatic molecules.
- Skill 10 Draw products of reduction of aromatic side-chains.
- Skill 11 Draw mechanisms for reduction of aromatic rings.
- Skill 12 Solve multistep synthesis problems incorporating directing effects and side-chain reactions.
- Skill 13 Propose a synthesis of benzene derivates using diazonium coupling reactions.
- Skill 14 Be able to predict the product formed when pyrrole is subjected to an aromatic electrophilic substitution.
- Skill 15 Write the detailed mechanism for the electrophilic aromatic substitution of pyrrole to account for the fact that substitution takes place at C2 rather than C3.
- Skill 16 Explain why pyridine undergoes electrophilic substitution much less readily than does benzene.

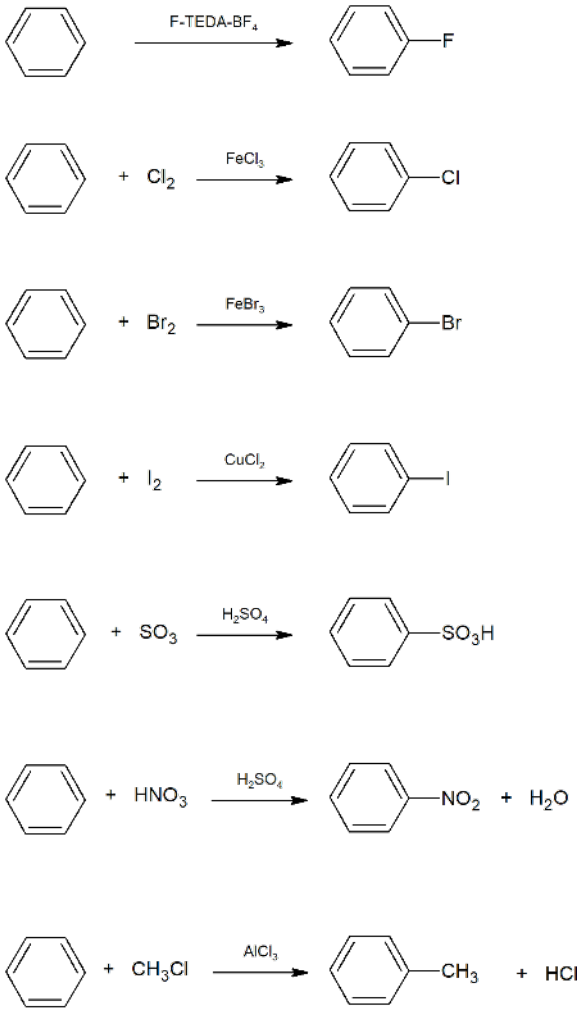
Summary of Reactions

Electrophilic Aromatic Substitution

An **electrophilic aromatic substitution reaction** takes place in two steps-initial reaction of an electrophile, $\mathbf{E}^+$, with the aromatic ring, followed by loss of H^+ from the resonance-stabilized carbocation intermediate to regenerate the aromatic ring.



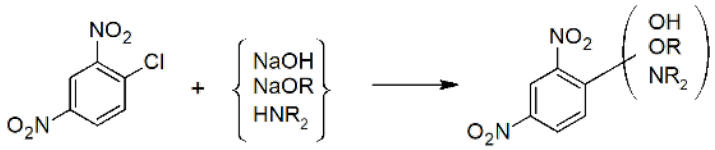
Many variations of the reaction can be carried out, including halogenation, nitration, and sulfonation. **Friedel–Crafts alkylation** and **acylation** reactions, which involve reaction of an aromatic ring with carbocation electrophiles, are particularly useful. They are limited, however, by the fact that the aromatic ring must be at least as reactive as a halobenzene. In addition, polyalkylation and carbocation rearrangements often occur in Friedel–Crafts alkylation.

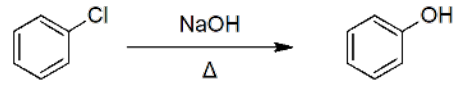


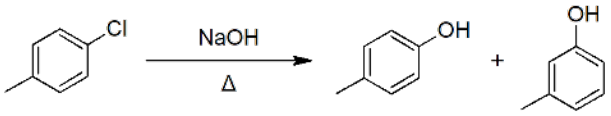
Nucleophilic Aromatic Substitution

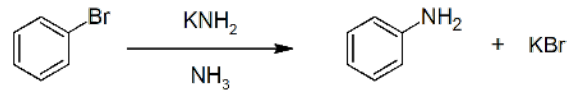
Halobenzenes undergo **nucleophilic aromatic substitution** through either of two mechanisms. If the halobenzene has a strongly electron-withdrawing substituent in the ortho or para position, substitution occurs by addition of a nucleophile to the ring, followed

by elimination of halide from the intermediate anion. If the halobenzene is not activated by an electron-withdrawing substituent, substitution can occur by elimination of HX to form **benzyne**, followed by the addition of a nucleophile.



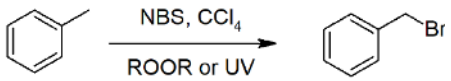




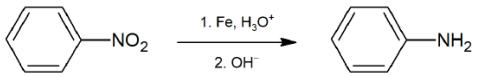


Other Reactions

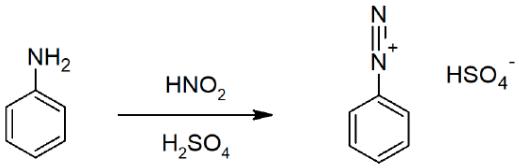
Benzylic Bromination of Alkylbenzene

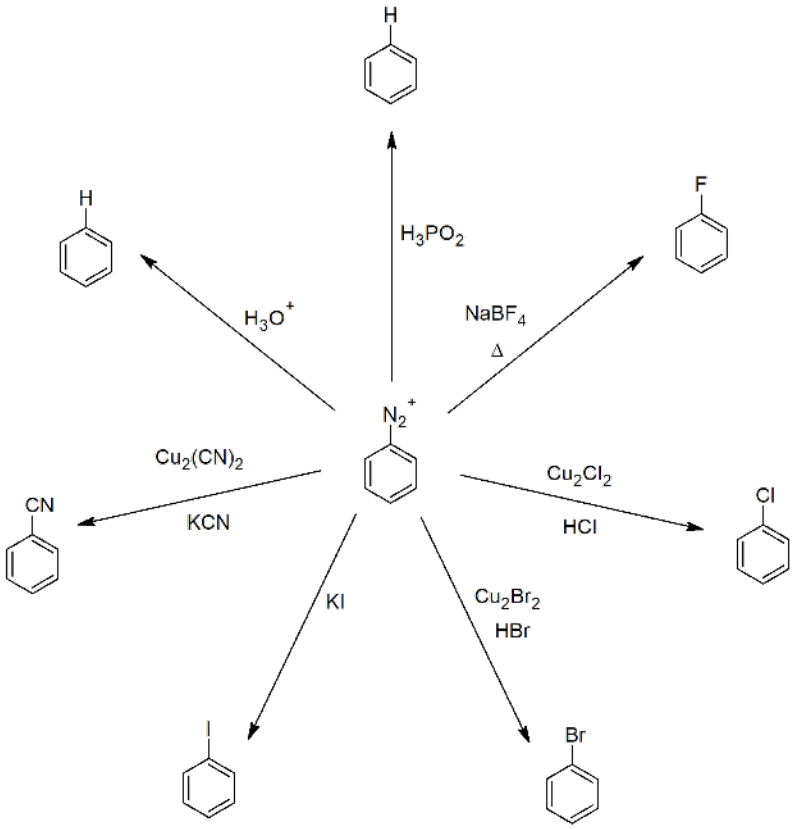


Reduction of Nitro Group



Amine Reactions





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CHAPTER OVERVIEW

4: Ethers and Epoxides; Thiols and Sulfides

We shall begin in a very traditional manner, with a discussion of the nomenclature of ethers. We will then describe how ethers may be prepared in the laboratory, and discuss the relative inertness of these compounds. A discussion of the chemistry of cyclic ethers follows, with particular emphasis on the preparation and reactions of epoxides (cyclic ethers containing a three-membered ring). We will then introduce crown ethers—compounds that consist of large rings containing several oxygen atoms and the spectroscopic properties of ethers. The unit will close with a description of the chemistry of thiols and sulfides, the sulfur-containing analogues of alcohols and ethers.

4.0: Introduction
4.1: Names and Properties of Ethers
4.2: Preparing Ethers
4.3: Reactions of Ethers - Acidic Cleavage
4.4: Reactions of Ethers - Claisen Rearrangement
4.5: Cyclic Ethers - Epoxides
4.6: Reactions of Epoxides - Ring-opening
4.7: Crown Ethers
4.8: Thiols and Sulfides
4.9: Spectroscopy of Ethers and Epoxides
4.10: Interchapter - A Preview of Carbonyl Chemistry
4.11: Additional Problems
4.S: Ethers and Epoxides; Thiols and Sulfides (Summary)

Learning Objectives

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis using one or more of the reactions introduced in this chapter, along with any number of the reactions you have studied to date.
- solve “road-map” problems that may require a knowledge of the chemistry of ethers, epoxides, thiols and sulfides, in addition to any of the material you have studied up to this point in organic chemistry.
- define, and use in context, the key terms introduced in this chapter.

Contributors and Attributions

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4.0: Introduction

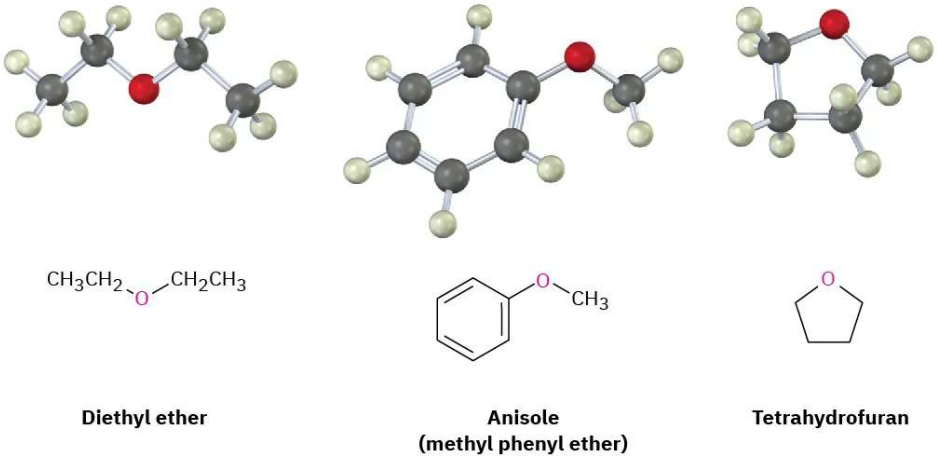
Objectives

After completing this section, you should be able to use the terms “ether,” “diethyl ether ” and “ethyl ether ” appropriately in context.

Ethers and Epoxides

Ethers (R–O–R′), like the alcohols, are organic derivatives of water, but they have two organic groups bonded to the same oxygen atom rather than one. The organic groups might be alkyl, aryl, or vinylic, and the oxygen atom might be in an open chain or a ring.

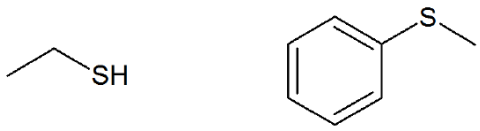
Perhaps the most well-known ether is diethyl ether, which has a long history of medicinal use as an anesthetic and industrial use as a solvent. Other useful ethers include anisole, a pleasant-smelling aromatic ether used in perfumery, and tetrahydrofuran (THF), a cyclic ether often used as a solvent.



Diethyl ether | **Anisole (methyl phenyl ether)** | **Tetrahydrofuran**

Thiols and Sulfides

Thiols (R–S–H, otherwise called thio alcohols or mercaptans) and sulfides (R–S–R′) are sulfur analogs of alcohols and ethers, respectively. Both functional groups are found in various biomolecules, although not as commonly as their oxygen-containing relatives.



ethanethiol | methyl phenyl sulfide



Figure 4.0.1: The appalling and unforgettable odor of skunks is due to a mixture of several simple thiols. (credit: modification of work “Striped Skunk” by Tom Friedel/Wikimedia Commons, CC BY 3.0)

Key Terms

Make certain that you can define, and use in context, the key terms below.

- ether ($\mathrm{R{-}O{-}R'}$)
- sulfide ($\mathrm{R{-}S{-}R'}$)
- thiol ($\mathrm{R{-}S{-}H}$)

Study Notes

As defined in the textbook, an “ether” is a substance with the general formula ($\mathrm{R{-}O{-}R'}$) where R and $\mathrm{R'}$ are alkyl, aryl, vinyl or allyl groups. However, the word “ether” is also commonly used to refer to the specific compound, $\mathrm{CH_3{-}CH_2{-}O{-}CH_2{-}CH_3}$, which is correctly called “diethyl ether.” Further confusion can arise because some chemists refer to “diethyl ether ” as “ethyl ether.” In this course, “ether ” will be used to refer to the class of compounds with the structure ($\mathrm{R{-}O{-}R'}$); diethyl ether will refer to the compound, $\mathrm{CH_3{-}CH_2{-}O{-}CH_2{-}CH_3}$; and “ethyl ether ” will not be used.

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4.1: Names and Properties of Ethers

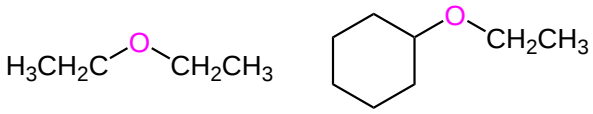
Objectives

After completing this section, you should be able to

1. write two acceptable names for a simple dialkyl ether, given its Kekulé, shorthand or condensed structure.
2. name a complicated ether by the IUPAC system, given its Kekulé, shorthand or condensed structure.
3. draw the Kekulé, condensed or shorthand structure of an ether, given an acceptable name.
4. explain why the boiling point of an ether is generally higher than that of an alkane of similar molecular mass.

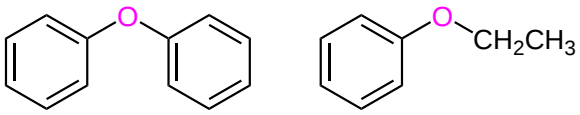
Structure of Ethers

Ethers are a class of organic compounds that contain an sp^3 hybridized oxygen between two alkyl groups and have the formula R-O-R'. These compounds are used in dyes, perfumes, oils, waxes and other industrial uses. Aliphatic ethers have no aryl groups directly attached to the ether oxygen.



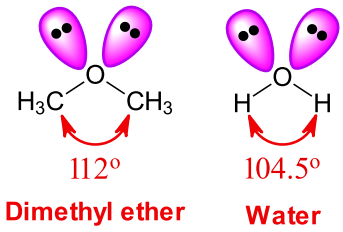
Examples of Aliphatic Ethers

Aromatic ethers have at least one aryl ring directly attached to the ether oxygen. In aryl ethers, the lone pair electrons on oxygen are conjugated with the aromatic ring which significantly changes the properties of the ether.

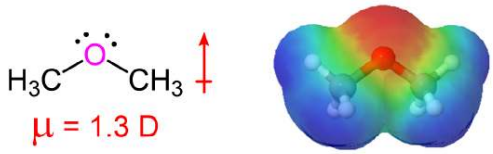


Example of Aromatic Ethers

The sp^3 hybridization of oxygen gives ethers roughly the same geometry as alcohols and water. The R-O-R' bond angle is close to what is expected in a tetrahedral geometry. The bond angle of dimethyl ether is 112° which is larger than the H-O-H bond angle in water (104.5°) due to the steric repulsion of the methyl groups.



The presence of an electronegative oxygen atom gives ethers a small dipole moment with the electron density primarily on oxygen (red and orange in the electrostatic potential map).



Comparisons of Physical Properties of Alcohols and Ethers

Ethers, unlike alcohols, have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore, there is no intermolecular hydrogen bonding between ether molecules, which makes their boiling points much lower than an alcohol with similar mass. Despite the presence of a small dipole moment, ethers have boiling points that are about the same as alkanes of comparable molar mass. (Table 4.1.1).

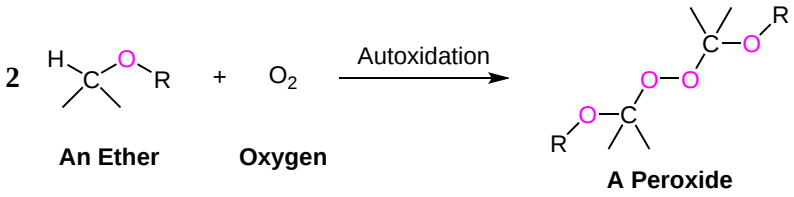
Table 4.1.1 : Comparison of Boiling Points of Alkanes, Alcohols, and Ethers

Condensed Structural Formula	Name	Molar Mass	Boiling Point (°C)	Intermolecular Hydrogen Bonding in Pure Liquid?
$CH_3CH_2CH_3$	propane	44	–42	no
CH_3OCH_3	dimethyl ether	46	–25	no
CH_3CH_2OH	ethyl alcohol	46	78	yes
$CH_3CH_2CH_2CH_2CH_3$	pentane	72	36	no
$CH_3CH_2OCH_2CH_3$	diethyl ether	74	35	no
$CH_3CH_2CH_2CH_2OH$	butyl alcohol	74	117	yes

Ether molecules do have an oxygen atom, however, and engage in hydrogen bonding with water molecules. Consequently, an ether has about the same solubility in water as the alcohol that is isomeric with it. For example, dimethyl ether and ethanol (both having the molecular formula C_2H_6O) are completely soluble in water, whereas diethyl ether and 1-butanol (both $C_4H_{10}O$) are barely soluble in water (8 g/100 mL of water).

Peroxide Formation

Many ethers can react with oxygen to form explosive peroxide compounds n a free radical process called autoxidation. For this reason ethers should not be stored for long periods of time and should not be stored in glass bottles. The danger is particularly acute when ether solutions are distilled to near dryness. The hydroperoxides can become more concentrated during a distillation because they tend to have a slightly higher boiling point than the corresponding ether. Before performing an ether distillation great care should be taken to test for the presence of peroxides.

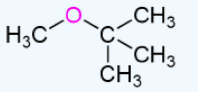


An Ether **Oxygen** **A Peroxide**

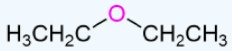
Naming Ethers

When no other functional group is present, simple ethers are often given common functional class names. Both alkyl groups attached to the oxygen atom are named as substituents (in alphabetical order) and then the word *ether* is added. The names for alkyl substituents are used.

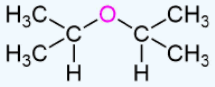
Example 4.1.1



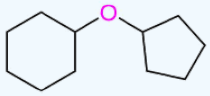
Methyl *tert*-butyl ether



Diethyl ether



Diisopropyl ether



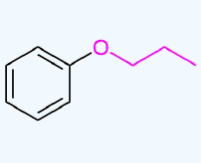
Cyclohexyl cyclopentyl ether

IUPAC nomenclature for ethers should be used for complicated ethers, compounds with more than one ether linkage, and compounds where other functional groups are present with an ether. In these cases, an RO group of the ether is named as an alkoxy substituent. Common alkoxy substituents are given names derived from their alkyl component. The suffix *-yl* is replaced with *-oxy*. (Table 4.1.2):

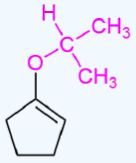
Table 4.1.2 : Common Alkyl and Alkoxy Groups

Alkyl Group	Name		Alkoxy Group	Name
CH_3–	Methyl		CH_3O–	Methoxy
CH_3CH_2–	Ethyl		CH_3CH_2O–	Ethoxy
$(CH_3)_2CH$–	Isopropyl		$(CH_3)_2CHO$–	Isopropoxy
$(CH_3)_3C$–	tert-Butyl		$(CH_3)_3CO$–	tert-Butoxy
C_6H_5–	Phenyl		C_6H_5O–	Phenoxy

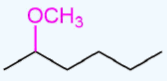
Example 4.1.2



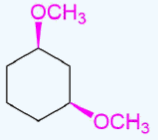
Propoxybenzene



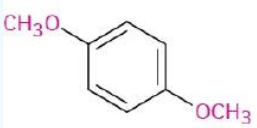
1-Isopropoxycyclopentene



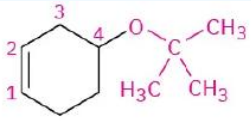
2-Methoxyhexane



Cis-1,3-Dimethoxycyclohexane



p-Dimethoxybenzene

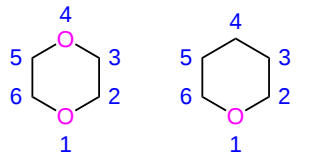


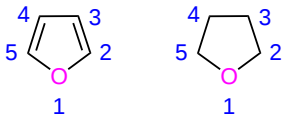
4-*tert*-Butoxy-1-cyclohexene

Cyclic Ethers

Cyclic ethers are a type of heterocycle with one or more oxygens located in the ring. Many cyclic ethers have common names and are often used as solvents due to their inert nature. These ring structures are also found in many biological molecules such as sugars

and DNA. The rings are numbered so that an oxygen gets position 1.



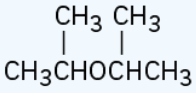


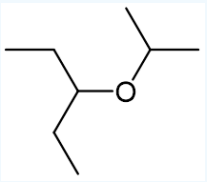
Example 4.1.3

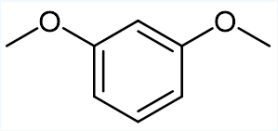


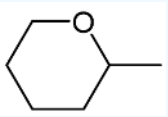
Exercise 4.1.1

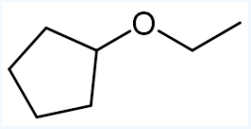
Name the following ethers:

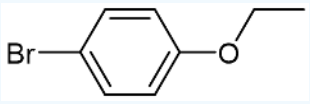
a. 

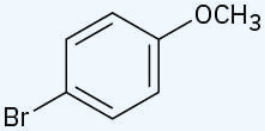
b. 

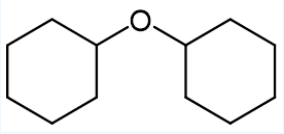
c. 

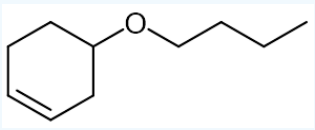
d. 

e. 

f. 

g. 

h. 

i. 

Answers

a. Diisopropyl ether
b. 3-Isopropoxypentane
c. 1,3-Dimethoxybenzene
d. 2-Methyltetrahydropyran
e. Cyclopentyl ethyl ether
f. *p*-Bromoanisole or 4-bromo-1-methoxybenzene
g. 4-Bromo-1-ethoxybenzene
h. Dicyclohexyl ether
i. 4-Butoxycyclohexene

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4.2: Preparing Ethers

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the industrial preparation of simple symmetrical ethers.
2. write an equation to illustrate the Williamson synthesis of ethers.
   a. identify the ether obtained from the reaction of a given alkyl halide with a given alkoxide ion.
   b. identify the reagents needed to prepare a given ether through a Williamson synthesis.
   c. identify the limitations of the Williamson synthesis, and make the appropriate choices when deciding how best to synthesize a given ether.
   d. write an equation to describe the formation of an alkoxide from an alcohol.
   e. identify silver(I) oxide as a reagent which can be used in a Williamson synthesis.
3. write an equation to show how an ether can be prepared by the alkoxymercuration-demercuration of an alkene.
   a. identify the product formed from the alkoxymercuration-demercuration of a given alkene.
   b. identify the alkene, the reagents, or both, needed to prepare a given ether by the alkoxymercuration-demercuration process.
   c. write the detailed mechanism of the reaction between an alkene, an alcohol and mercury(II) trifluoroacetate.

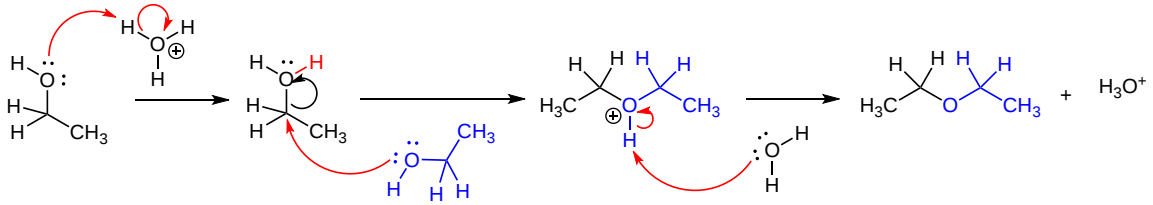
Ether Formation Though Dehydration

Acid-catalyzed dehydration of small 1°-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. This reaction **cannot** be employed to prepare unsymmetrical ethers because a mixture of products is likely to be obtained. Also, 2° and 3° alcohols cannot be used for this reaction because they dehydrate to form alkenes by an E1 mechanism.

$$2\,CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{130\ ^\circ C} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O \tag{4.3.1}$$

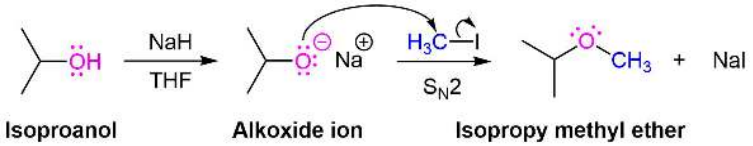
Mechanism

In the first step of the reaction mechanism, one alcohol is protonated to become a good leaving group. In the second step, a second alcohol displaces water from the protonated alcohol during an S_N2 reaction yielding a protonated ether. In the final step, this intermediate is deprotonated to yield the symmetrical ether.



Williamson Ether Synthesis

One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with a primary alkyl halide or tosylate. As previously discussed, alkoxides are commonly created by deprotonating an alcohol with a strong base, such as sodium hydride (NaH). Simple alcohols can be used a solvent during a Williamson ether synthesis and with their alkoxide created through the addition of sodium metal ($Na_{(s)}$).

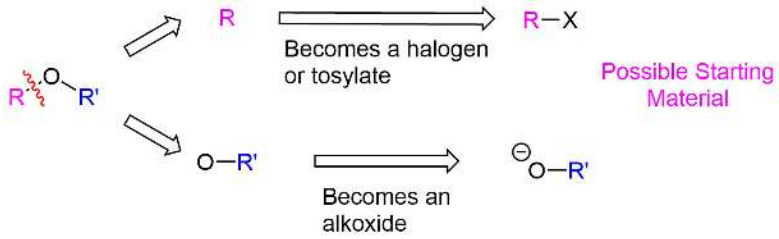


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Planning a Williamson Ether Synthesis

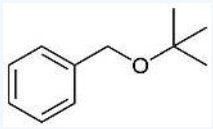
The Williamson ether synthesis has the same limitations as other S_N2 reactions. Since alkoxide anions are strong bases, utilizing 2° or 3° halogen leaving groups could possibly produce an E2 elimination product. When considering the synthesis of an unsymmetrical ether, there are two different combinations of reactants possible and each should be carefully considered. In general, the pathway that utilizes the least sterically hindered halogen will be preferred.

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alkoxide. The other fragment will become a halogen or tosylate.



? Worked Example 4.2.1

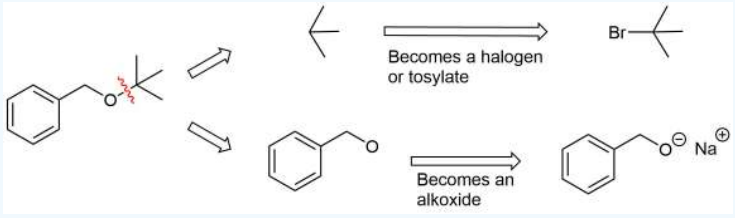
How would you prepare the following molecule using a Williamson Ether Synthesis?



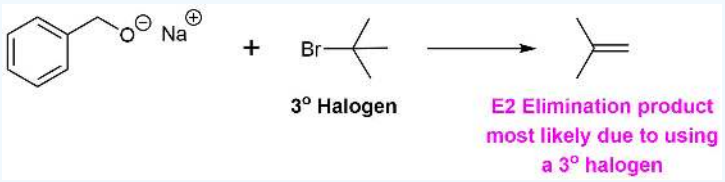
Answer

Analysis: The ether is asymmetrical so each of the C-O bonds can be broken to create a different set of possible reactants. After cleavage of the C-O bond, pathway 1 shows a 3° halogen as the starting material. This reaction will most likely not be effective due to alkoxides reacting with 3° halogens to preferable form an alkenes by E2 elimination. Pathway 2 shows a 1° halogen as a starting material which is favorable for S_N2 reactions.

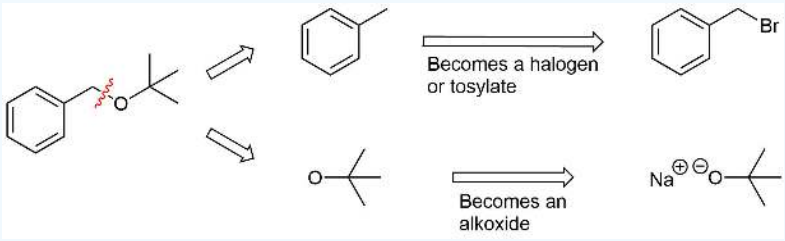
Pathway 1



Solution 1

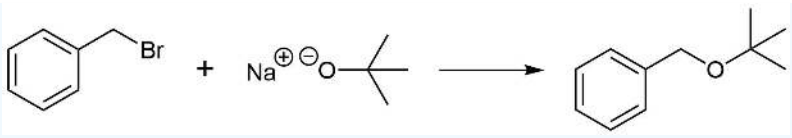


Pathway 2



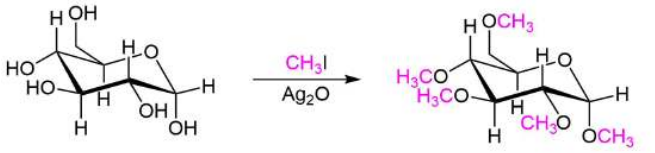
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Solution 2



Ether Synthesis Using Silver Oxide

A variation of the Williamson ether synthesis uses silver oxide (Ag_2O) in the place of the strong base. The conditions of this variation are milder than the typical Willamson synthesis because a strong base and the formation of an alkoxide intermediate are not necessary. This reaction is particularly useful when converting the -OH groups on a sugar into ethers.



α-D-Glucopyranose — Methyl 2,3,4,6-tetra-*O*-methyl-α-D-Glucopyranoside

Mechanism

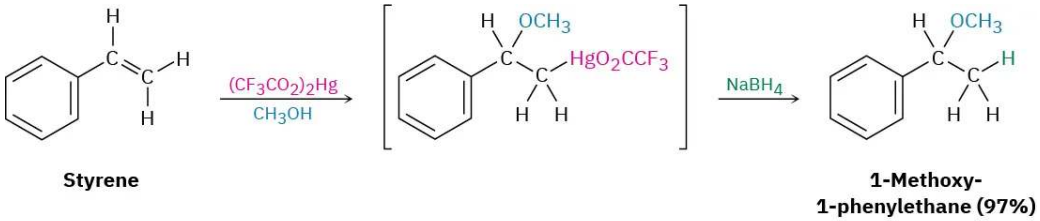
During this reaction, a partial positively charged silver in Ag_2O gives draws electron density from the iodine in CH_3I. This correspondingly removes electron density from the adjacent carbon increasing its partial positive charge which increases its electrophlicity. This allows the alcohol to act as a nucleophile in the subsequent S_N2 reaction.



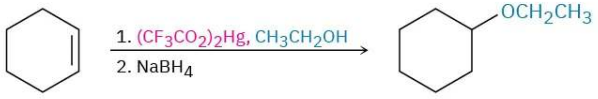
Alcohol — Polarized C-I Bond — Ether

Ether Synthesis Using Alkoxymercuration

Alkoxymercuration, is patterned after the oxymercuration reaction. Reaction of an alkene with an alcohol in the presence of a trifluoroacetate mercury (II) salt [$(CF_3CO_2)_2Hg$] prodcues an alkoxymercuration product. Demercuration using sodium borohydride ($NaBH_4$) yields an ether product. Overall, this reaction allows for the Markovnikov addition of an alcohol to an alkene to create an ether. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the mercuric acetate (trifluoroacetate anion is a poorer nucleophile than acetate). Most 1º, 2º, 3º alcohols can be successfully used for this reaction.



Styrene — 1-Methoxy-1-phenylethane (97%)

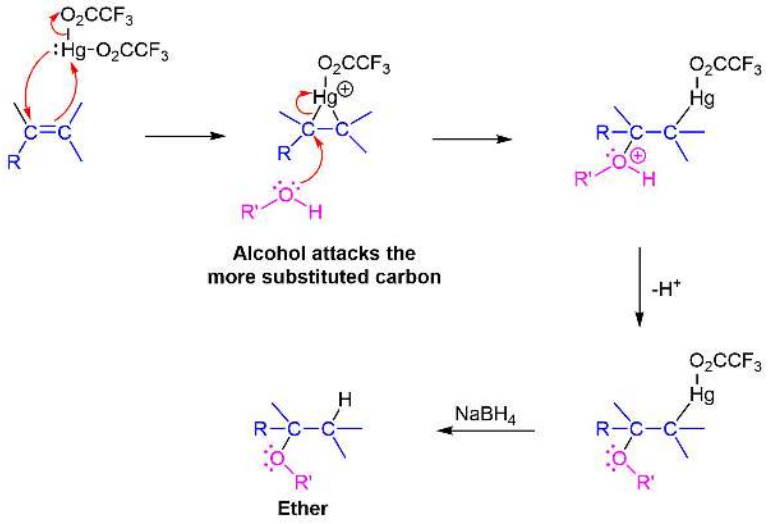


Cyclohexene — Cyclohexyl ethyl ether (100%)

Mechanism

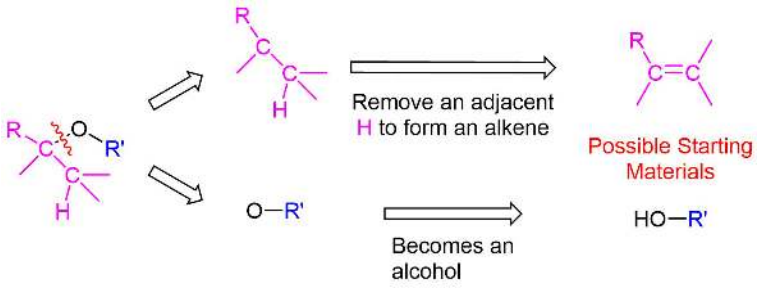
The mechanism of alkoxymercuration is similar to that of oxymercuration, with electrophillic addition of the mercuric species to the alkene. The alcohol nucleophile attacks the more substituted carbon of the three-membered ring via a S_N2 reaction. Finally,

sodium borohydride ($NaBH_4$) provides a reductive demercuration to form the ether product.



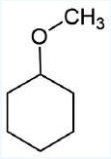
Planning the Synthesis of an Ether using Alkoxymercuration

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alcohol. The alkyl fragment will lose a hydrogen from a adjacent carbon to form an alkene. The main point to consider when choosing a possible synthesis pathways is the ability of the alkyl fragment to form an alkene.



? Worked Example 4.2.2

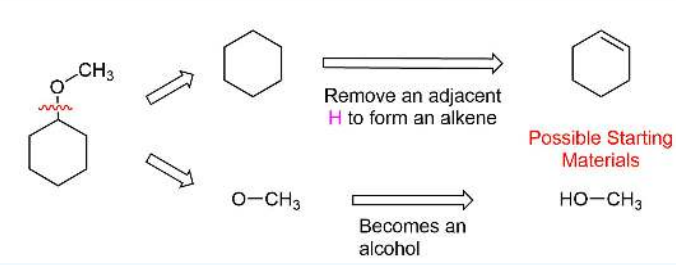
How would you prepare the following molecule using a alkoxymercuration?



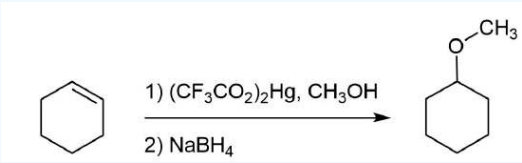
Answer

Analysis: The ether is symmetrical so each C-O bond of the ether can be cleaved to produce a set of starting materials for consideration. Pathway one shows a set of starting material which should work well for this reaction. The alcohol, methanol, can easily be used as a solvent. Although the alkene does not have a defined more and less substituted side, its symmetry will prevent a mixture of product from forming. The fragmentation for pathway 2 shows starting material which are not viable for this reaction. The alkyl fragment only has one carbon which cannot be used to form an alkene starting material. This means pathway 2 is not a viable method for the synthesis of the target molecule.

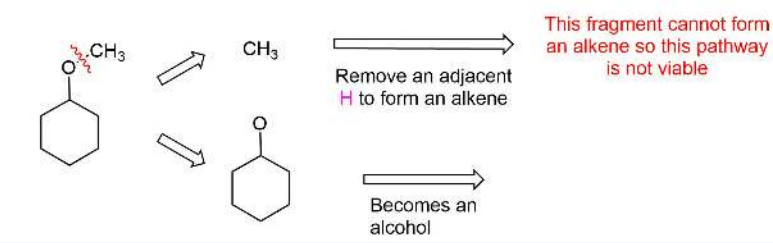
Pathway 1



Solution 1



Pathway 2



Exercises

? Exercise 4.2.1

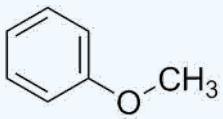
When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

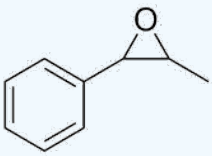
Answer

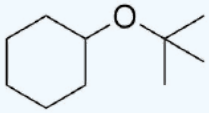
The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions from occurring. The electrophile should have the characteristics of a good S_N2 electrophile, preferably primary to minimize any elimination reactions from occurring.

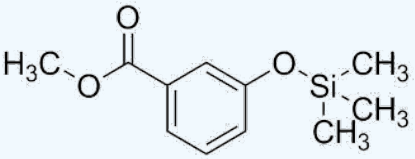
? Exercise 4.2.2

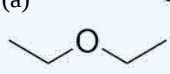
How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a) 

(b) 

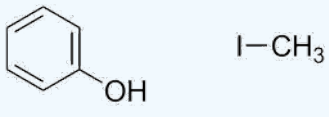
(c) 

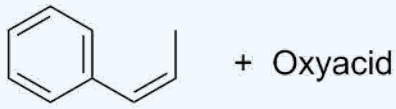
(d) 

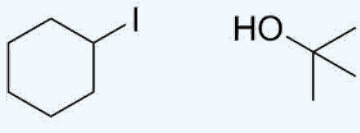
(e) 

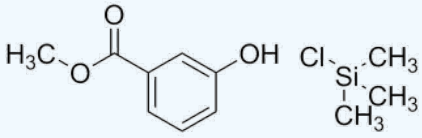
Answer

The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

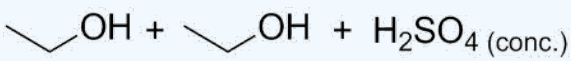
(a) 

(b) 

(c) 

(d) 

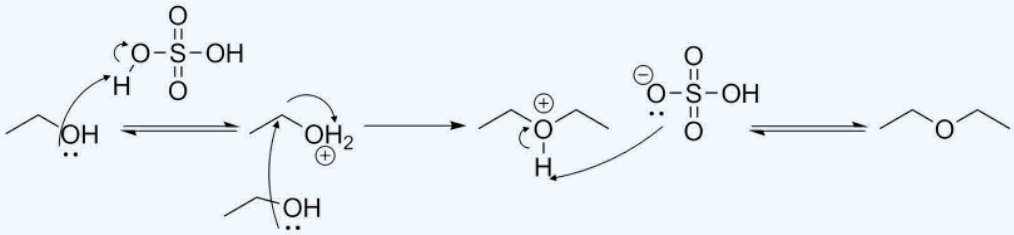
Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e) 

Exercise 4.2.3

Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Answer

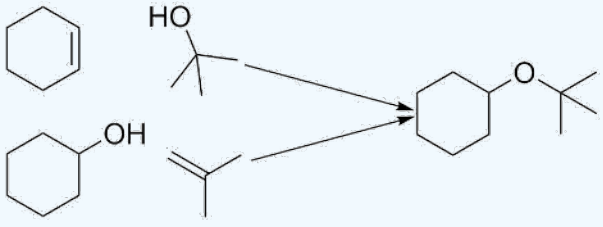


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Exercise 4.2.4

t-butoxycyclohexane can be prepared two different ways from an alkene and an alcohol, draw both possible reactions.

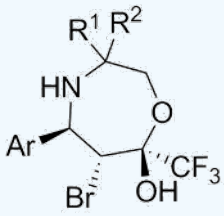
Answer



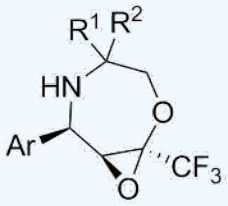
While both are possible, the top route is likely easier because both starting materials are a liquid.

Exercise 4.2.5

Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [*J. Org. Chem.*, **2016**, *81 (20)*, pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)



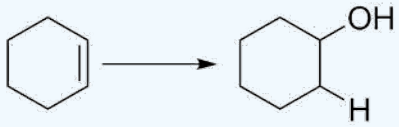
Answer



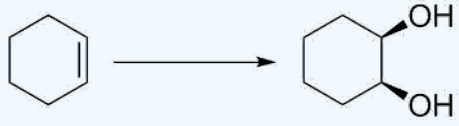
Exercise 4.2.6

What reagents would you use to perform the following transformations?

(a)



(b)

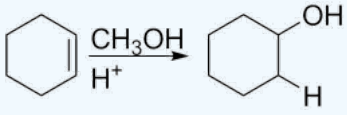


(c)

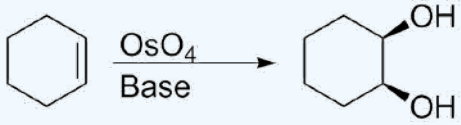


Answer

(a)

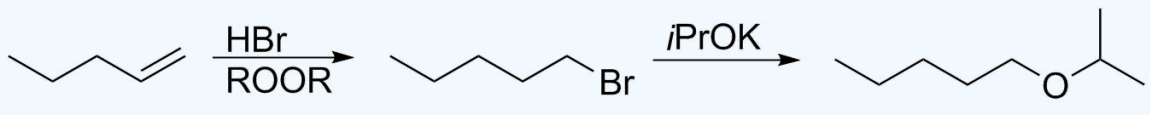


(b)



Note the cis addition

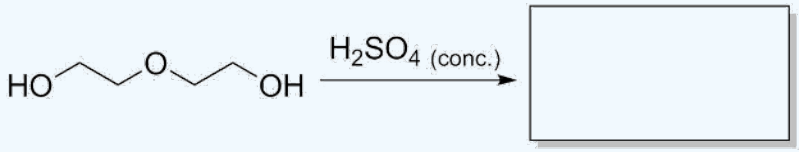
(c)



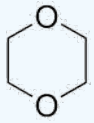
An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.

Exercise 4.2.7

Predict the product of the following.



Answer



The result is the production of dioxane, a common solvent.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- alkoxymercuration
- oxymercuration
- Williamson ether synthesis

Study Notes

We studied oxymercuration as a method of converting an alkene to an alcohol in Section 8.5. "Alkoxymercuration" is a very similar process, except that we are now converting an alkene into an ether. The two processes are compared below.

Description	oxymercuration	alkoxymercuration
we react an	alkene	alkene
with	water	an alcohol
in the presence of	$Hg(O_2CCH_3)_2$	$Hg(O_2CCF_3)_2$
followed by treatment with	$NaBH_4$	$NaBH_4$
to produce an	alcohol	ether

Review the mechanism of the oxymercuration reaction in Section 8.5, paying particular attention to the regiochemistry and the stereochemistry of the reaction. The mechanism is identical to alkoxymercuration.

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4.3: Reactions of Ethers - Acidic Cleavage

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the acidic cleavage of an ether.
2. identify the products formed when a given ether is cleaved by a strong acid.
3. identify the reagent needed to bring about cleavage of a given ether.
4. deduce the structure of an unknown ether, given the products of acidic cleavage of the ether.
5. write the detailed mechanism for the acidic cleavage of a given ether.

Study Notes

There are a number of points in this section that require additional explanations.

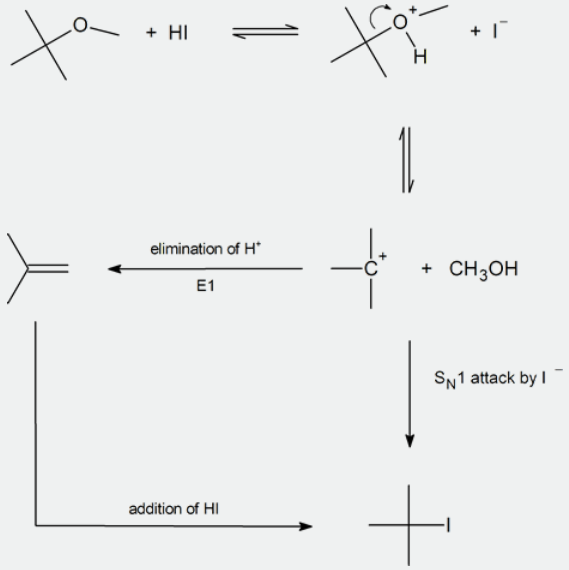
First, if an excess of HI (or HBr) is used in the cleavage reaction, the alcohol formed is converted by a nucleophilic substitution reaction to the appropriate alkyl halide:

$$\mathrm{ROH + HI \longrightarrow RI + H_2O}$$

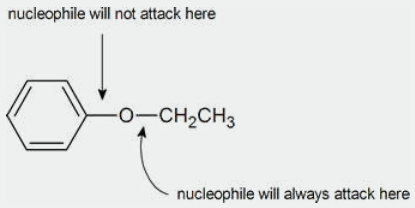
In view of this substitution, some textbooks simplify the overall cleavage process as:

$$\mathrm{R{-}O{-}R' + 2\,HI \longrightarrow RI + R'I + H_2O}$$

Second, we should consider in detail how certain ethers (those containing tertiary alkyl, benzyl or allyl groups) cleave by an S_N1 mechanism:



Finally, notice that an aryl alkyl ether will always produce a phenol and an alkyl halide, never an aryl halide and an alcohol. This is because we rarely see a nucleophile attacking an aromatic ring carbon in preference to an aliphatic carbon:

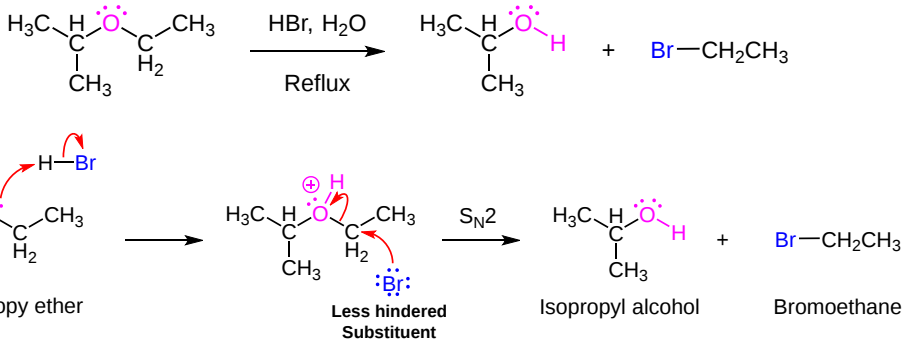


As phenols do not undergo nucleophilic substitution reactions, even if an excess of HX is used, the products from the cleavage of an aryl alkyl ether are a phenol and an alkyl halide. Diaryl ethers are not cleaved by acids.

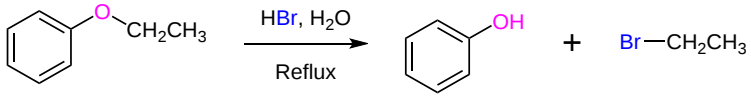
Ethers are known to be unreactive towards most reagents which makes them excellent reaction solvents. The most common reaction of ethers is cleavage of the C–O bond by using strong acids. During acidic cleavage the ether oxygen is protonated to form a good leaving groups which can be eliminated as part of an S_N2, S_N1, or E1 reaction mechanism. The mechanistic pathway is primarily determined by the strong acid used and the type of substituents attached to the ether.

Acidic Cleavage of Ethers

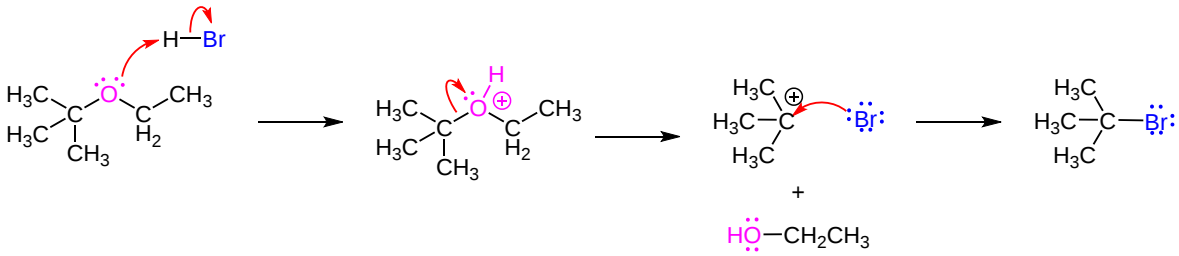
Aqueous solutions of HBr or HI (but not HCl) tend to cleave ethers into alcohol and an alkyl halide product by either an S_N2 or S_N1 mechanism. If the ether is attached to only primary, secondary, or methyl alkyl groups, a selective cleavage will typically take place using an S_N2 mechanism. First, the strong acid protonates the ether oxygen. Then resulting halide conjugate base attacks the protonated ether at the less sterically hindered alkyl substituent forming a halogen product. The ether's more sterically hindered alkyl substituent is ejected as a leaving group and forms an alcohol product. The example below show that when ethyl isopropyl ether is cleaved with hydrobromic acid the products isopropyl alcohol and bromoethane are produced. The bromide nucleophile preferably attacks the ether's ethyl substituent because it is less hindered (1°) than the isopropyl substituent (2°).



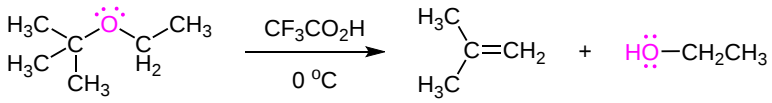
It is important to note that a phenyl substituent on an ether is not capable of participating in the S_N2 reaction of an acidic cleavage. If a phenyl group is present it will become a phenol in the product due to the halide nucleophile preferably attacking the other alkyl substituent.



When using HBr or HI, the acidic cleavage of ethers with tertiary, benzylic, or allylic substituents tend to occur by an S_N1 mechanism. The ability of these substituents to produce relatively stable carbocations promotes the S_N1 mechanism. The change in mechanism causes the tertiary, benzylic, or allyic group to preferably become the halogen product of the acidic cleavage. This makes the ether's other alkyl substituent become the alcohol product.

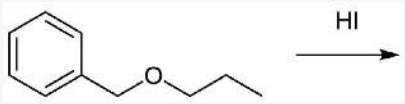


When using a strong acid whose conjugate base is a poor nucleophile, such as trifluoroacetic acid (CF_3CO_2H), for the the acidic cleavage of an ether with a tertiary alkyl substituent, the mechanism will often be E1. In this case the tertiary alkyl substituent will lose an adjacent hydrogen to form an alkene product. The ether's other alkyl substituent will form an alcohol product.



Worked Example 4.3.1

Predict the products of the following reaction:



Answer

Analysis: When considering the acidic cleavage of ethers it is important to realize that S_N2, S_N1, or E1 reactions are possible depending on the conditions. First, identify if the ether has a substituent which can easily form a carbocation: tertiary, benzylic, or allylic substituents. If none of these substituents are present the reaction will most likely be S_N2. However, if one of the substituents is present the reaction will most likely be S_N1 or E1. Next, identify if the reaction conditions will allow for an E1 reaction. These are the presence of a tertiary alkyl substituent on the ether along with the use of a strong acid which has a poor nucleophile as a conjugate base. If this set of conditions is not present the reaction will most likely be S_N1.

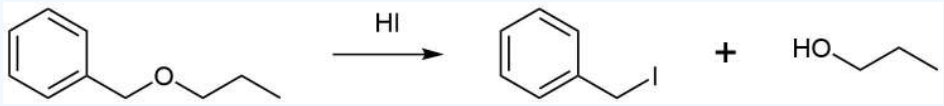
For a S_N2 reaction: The less hindered alkyl substituent of the ether will become a halogen. The other alkyl substituent will become an alcohol.

For a S_N1 reaction: The substituent which easily forms a carbocation will become a halogen and the other alkyl substituent will become an alcohol.

For an E1 reaction: The tertiary alkyl substutent will form an alkene and the other alkyl substiutent will become an alcohol.

For the reaction proposed above, the reactant contains a benzylic substituent so the reaction will most likely be S_N1. Consequently, the benzylic substituent will become and Iodide product and the propyl substituent will become an alcohol.

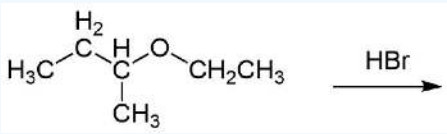
Solution



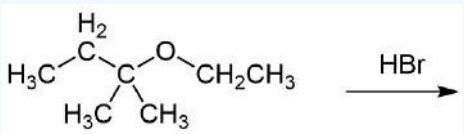
Exercises 4.3.1

1) Predict the product of the following reactions:

a)

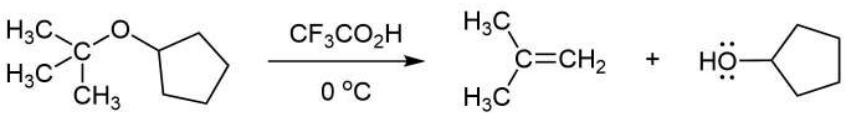


b)



2) Please draw the mechanism for the following reaction:

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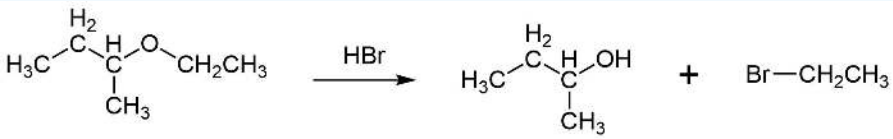


3) Why is HCl less effective at cleaving ethers than HBr or HI?

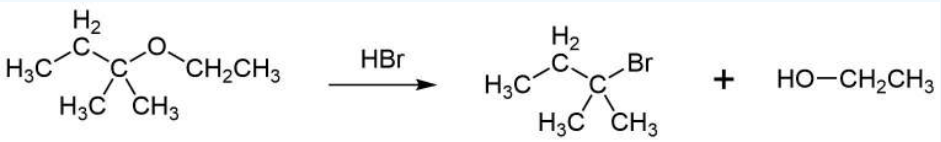
Answer

1)

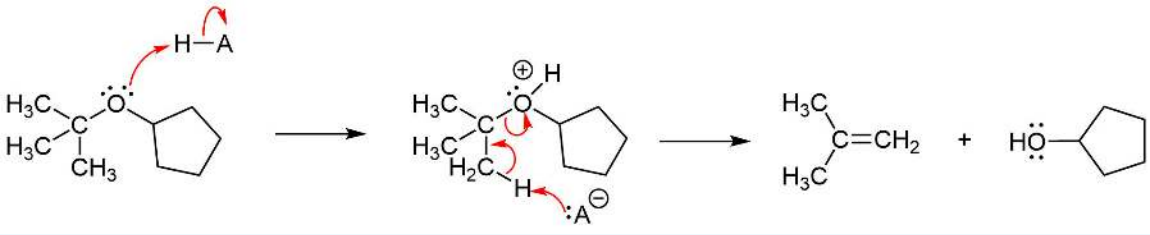
a)



b)



2)



3) HCl's conjugate base Cl^- is a poor nucleophile when compared to Br^- and I^-. The chloride anion is not a strong enough nucleophile to promote the acidic cleavage of ethers.

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4.4: Reactions of Ethers - Claisen Rearrangement

Objectives

After completing this section, you should be able to

1. write an equation to represent the Claisen rearrangement of allyl phenyl ester.
2. account for the formation of a specific product from a Claisen rearrangement, without giving mechanistic details.

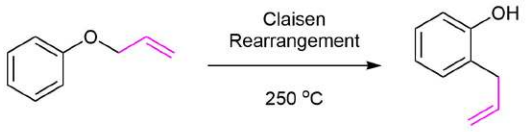
Key Terms

Make certain that you can define, and use in context, the key term below.

- Claisen rearrangement

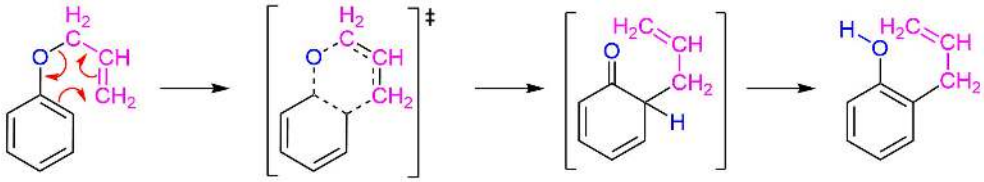
Claisen Rearrangements

The Claisen rearrangement is a key organic reaction that involves the thermal rearrangement of allyl vinyl ethers to form β-aryl allyl ethers. This reaction is specific to ally aryl ethers and allyl vinyl ethers. Heating an allyl aryl ether to 250 °C causes an intramolecular rearrangement to produce an *o*-allylphenol.



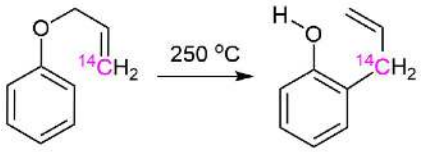
Allyl phenyl ether **o-Allylphenol**

The Claisen rearrangement takes place through a concerted mechanism in which a C-C bond forms between the C3 of the allyl group and the ortho position of the benzene ring at the same time that the C-O bond of the ether breaks. This rearrangement initially produces the non-aromatic 6-allyl-2,4- cyclohexadienone intermediate which quickly undergoes a proton shift to reform the aromatic ring in the *o*-allylphenol product. Claisen rearrangement occurs in a six-membered, cyclic transition state involving the concerted movement of six bonding electrons in the first step. The presence of six electrons in a ring suggests that the transition state may have aromatic characteristics. The Claisen rearrangement is part of a broader class of reactions called sigmatropic rearrangements which will be discussed in more detail in **Section 30-8**.



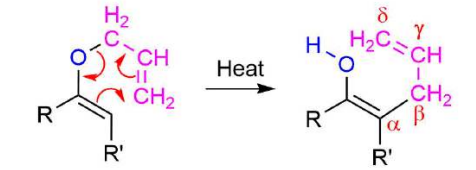
Transition State **Intermediate**

Evidence for this mechanism was provided by performing the rearrangement with allyl group with a ^{14}C label at C3. The product of this reaction was shown to have the ^{14}C labeled carbon exclusively bonded to the ring.

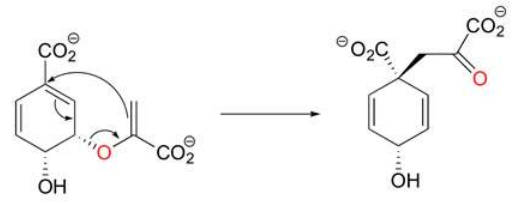


Only Product

Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



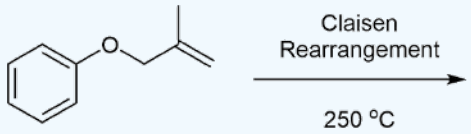
Claisen rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.



Exercise 4.4.1

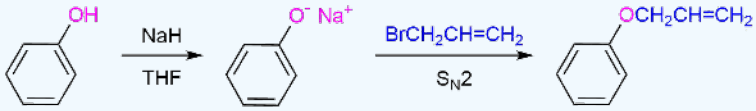
1) Show how you could synthesize allyl phenyl ether from allyl bromide and phenol.

2) What would be the expected product of the following Claisen rearrangement?

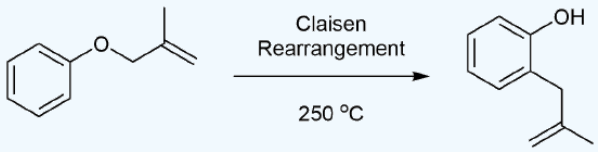


Answer

1)



2)



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4.5: Cyclic Ethers - Epoxides

Objectives

After completing this section, you should be able to

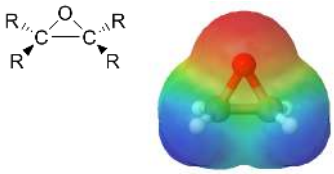
- write an equation to describe the industrial preparation of ethylene oxide.
- list two important industrial uses of ethylene oxide.
- write an equation to describe the normal laboratory preparation of an epoxide.
- identify the epoxide produced from the reaction of a given alkene with a peroxyacid.
- identify the alkene, the reagent, or both, needed to prepare a given epoxide.
- write an equation to describe the preparation of an epoxide from an alkene via a halohydrin.

Key Terms

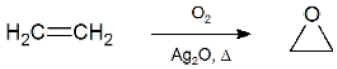
Make certain that you can define, and use in context, the key term below.

- epoxide (oxirane)

Epoxides (also known as **oxiranes**) are three-membered ring structures in which one of the vertices is an oxygen and the other two are carbons. Epoxides behave differently than other ethers due to the strain created by the three-membered ring.



The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air. Ethylene oxide is used as an important chemical feedstock in the manufacturing of ethylene glycol, which is used as antifreeze, liquid coolant and solvent. In turn, ethylene glycol is used in the production of polyester and polyethylene terephthalate (PET) the raw material for plastic bottles.



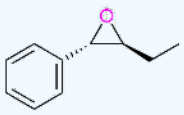
Nomenclature of Epoxides

The name ethylene oxide is not systematic but common. Epoxides are systematically named as an oxirane ring system much like the other cyclic ethers discussed in **Section 4.2**. The oxygen is numbered in the 1 position.

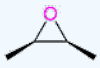


Oxirane

Example 4.5.1



trans-2-Ethyl-3-phenyloxirane



cis-2,3-Dimethyloxirane

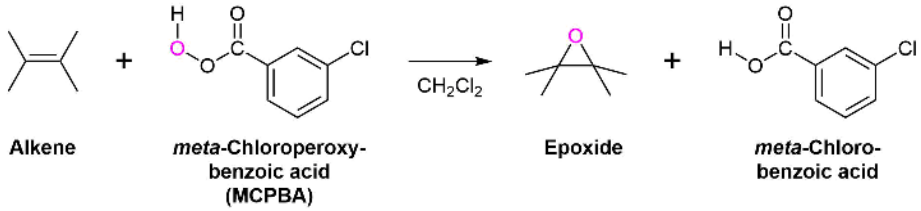


2,2-Dimethyloxirane

Synthesis of Epoxides

As discussed in CHEM 231, epoxides are typically prepared by the reaction of an alkene and a peroxycarboxylic acid (RCO_3H), such as *meta*-chloroperbenzoic acid (MCPBA). The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the CO_3H group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the CO_3H group becomes CO_2H.

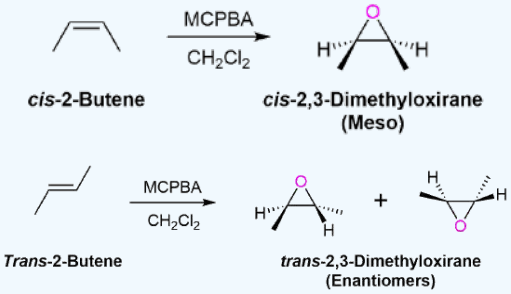
General Reaction



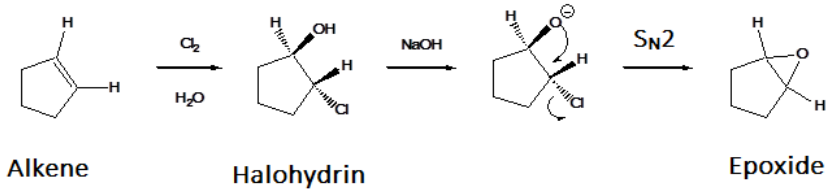
Stereochemical Consideration

The oxygen addition to the alkene is a syn addition and is stereospecific. The substituents of a *cis*-alkene will appear in the *cis* configuration on the epoxide ring. Likewise, Substituents of a *trans*-alkene will appear in the *trans* configuration on the epoxide ring. During this reaction the sp^2 hybridized carbons of the alkene are converted to sp^3 hybridized carbons in the epoxide. Thus, there is the possibility of two new chiral carbons forming in the epoxide product. In most cases, epoxidation of an alkene will product a mixture of enantiomers in the product, due to the electrophilic oxygen being able to attack from above or below the plane of the alkene. One major exception is the epoxidation of symmetrical cis-alkene which produces a meso compound product.

Example 4.5.2



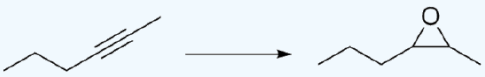
Treatment of an alkene with X_2 & H_2O creates a halohydrin. When a halohydrin is treated with a base the alcohol is deprotonated to from an alkoxide. This causes an intramolecular Williamson ether synthesis to produce an epoxide along with the elimination of HX. Note, that this reaction generally forms a mixture of enantiomeric products unless a meso compound is produced.



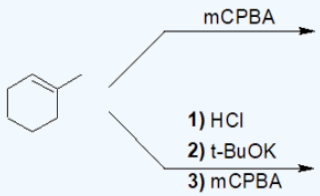
Exercise 4.5.1

1) What reagents would you use to perform the following transformation?

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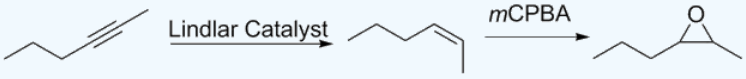
2) Predict the products of the following reactions:



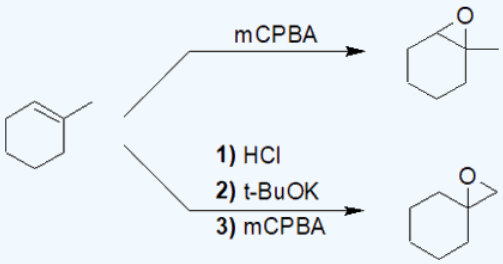
3) Predict the product of the following reaction. Be sure to include proper stereochemistry.

Answer

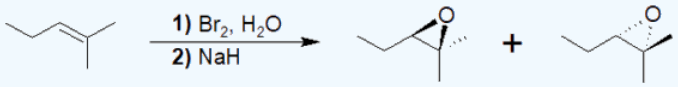
1) Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.



2)



3)



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4.6: Reactions of Epoxides - Ring-opening

Objectives

After completing this section, you should be able to

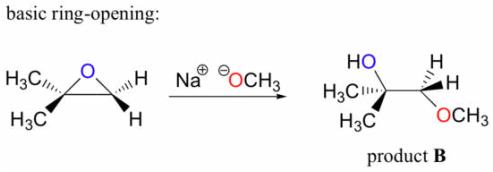
1. write an equation to describe the opening of an epoxide ring under mildly acidic conditions.
   a. identify the product formed from the hydrolysis of an epoxide.
   b. write the mechanism for the opening of an epoxide ring by an aqueous acid, paying particular attention to the stereochemistry of the product.
   c. identify the product formed when an epoxide ring is opened by a hydrogen halide under anhydrous conditions.
2. predict the major product from the acidic cleavage of a given unsymmetrical epoxide.
3. write an equation to illustrate the cleavage of an epoxide ring by a base.
   a. identify the product formed from the reaction of a given epoxide with given base.
   b. explain why epoxides are susceptible to cleavage by bases, whereas other cyclic ethers are not.

Study Notes

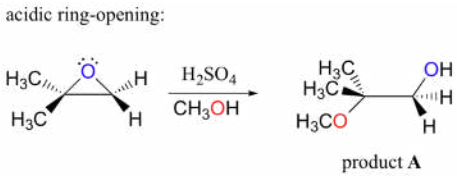
In the discussion on base-catalyzed epoxide opening, the mechanism is essentially S_N2. While oxygen is a poor leaving group, the ring strain of the epoxide really helps to drive this reaction to completion. Indeed, larger cyclic ethers would not be susceptible to either acid-catalyzed or base-catalyzed cleavage under the same conditions because the ring strain is not as great as in the three-membered epoxide ring.

Epoxide Ring-Opening by Alcoholysis

The ring-opening reactions of epoxides provide a nice overview of many of the concepts discussed in earlier chapters of this book. Ring-opening reactions can proceed by either S_N2 or S_N1 mechanisms, depending on the nature of the epoxide and on the reaction conditions. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes alcoholysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic attack, leading to what we will refer to as product B:



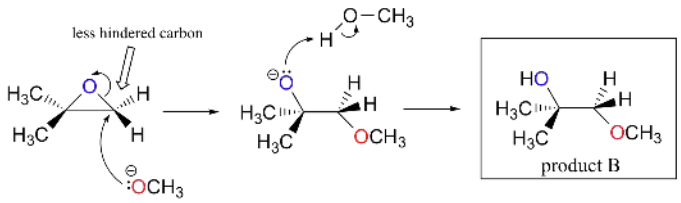
Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon is the site of attack. As a result, product A predominates.



These are both good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively).

Basic Epoxide Ring-Opening by Alcoholysis

In the basic, S_N2 reaction, the leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group (**Section 11-3**), and thus the ring is unlikely to open without a 'push' from the nucleophile.

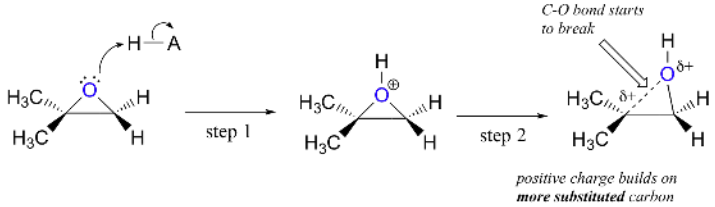


The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

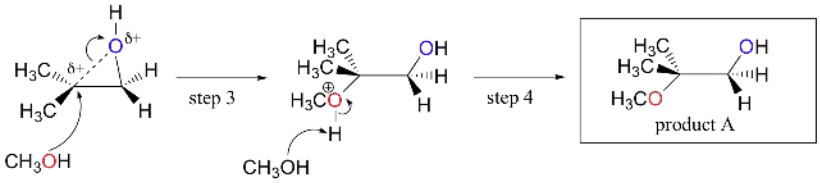
There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an S_N2 reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other S_N2 reactions, nucleophilic attack takes place from the backside, resulting in inversion at the electrophilic carbon.

Acid-Catalyzed Epoxide Ring-Opening by Alcoholysis

The best way to depict the acid-catalyzed epoxide ring-opening reaction is as a hybrid, or cross, between an S_N2 and S_N1 mechanism. First, the oxygen is protonated, creating a good leaving group (step 1 below). Then the carbon-oxygen bond begins to break (step 2) and positive charge begins to build up on the more substituted carbon. Recall that alkyl substituents can donate electron density through hyper conjugation and stabilize a positive charge on a carbon.



Unlike in an S_N1 reaction, the nucleophile attacks the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

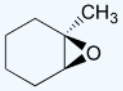


Attack takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile attacks the more substituted carbon because it is this carbon that holds a greater degree of positive charge.

Example 18.6.1

Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

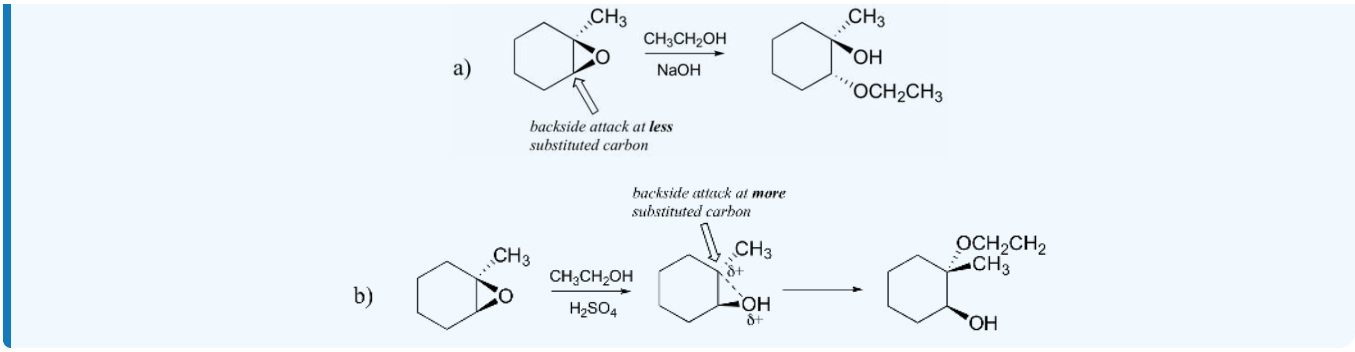
a. ethanol and a small amount of sodium hydroxide
b. ethanol and a small amount of sulfuric acid



Hint: be sure to consider both regiochemistry **and** stereochemistry!

Answer

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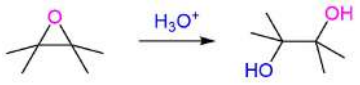
Epoxide Ring-Opening by Hydrolysis

Epoxides may be cleaved by hydrolysis to give ***trans*-1,2-diols** (1,2 diols are also called **vicinal diols or vicinal glycols)**. The reaction can be preformed under acidic or basic conditions which will provide the same regioselectivity previously discussed.

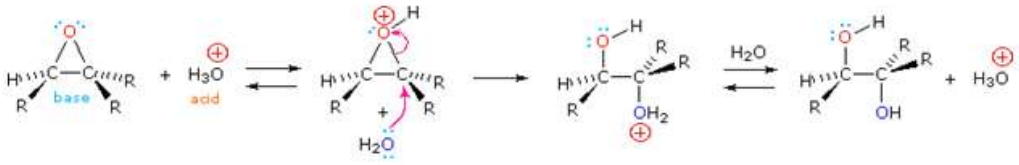
Acid Catalyzed Hydrolysis

Under aqueous acidic conditions the epoxide oxygen is protonated and is subsequently attacked by a nucleophilic water. After deprotonation to reform the acid catalyst a 1,2-diol product is formed. If the epoxide is asymmetric, the incoming water nucleophile will preferably attack the more substituted epoxide carbon. The epoxide ring is opened by an S_N2 like mechanism so the two -OH groups will be *trans* to each other in the product.

General Reaction



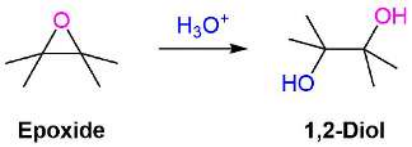
Mechanism



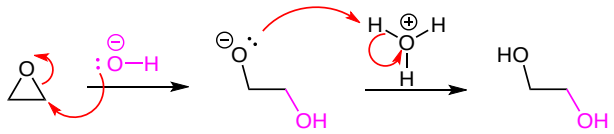
Basic Hydrolysis

Under aqueous basic conditions the epoxide is opened by the attack of hydroxide nucleophile during an S_N2 reaction. The epoxide oxygen forms an alkoxide which is subsequently protonated by water forming the 1,2-diol product. If the epoxide is asymmetric the incoming hydroxide nucleophile will preferable attack the less substituted epoxide carbon. Because the reaction takes place by an S_N2 mechanism the two -OH groups in the product will be *trans* to each other.

General Reaction



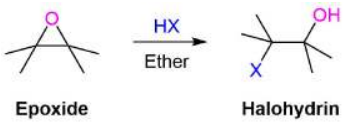
Mechanism



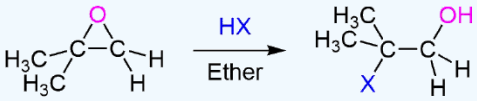
Epoxide Ring-Opening by HX

Epoxides can also be opened by anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will attack the less substituted carbon through an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in an S_N1 like reaction.

General Reaction

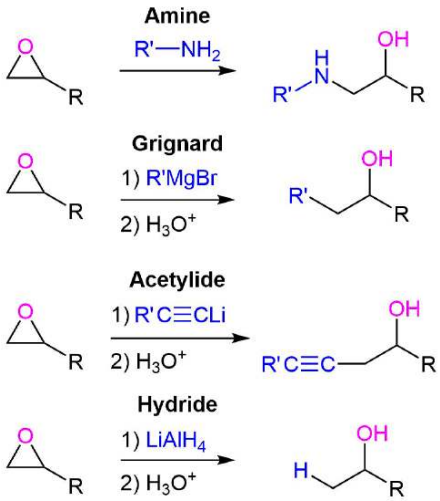


Example 18.6.2

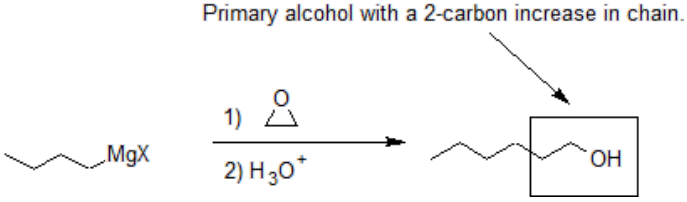


Epoxide Ring-Opening by Other Basic Nucleophiles

A wide variety of basic nucleophiles can be used for the ring opening of an epoxide including, amines, hydrides, Grignard reagents, acetylide anions, and hydride. These ring openings generally take place by an S_N2 mechanism.

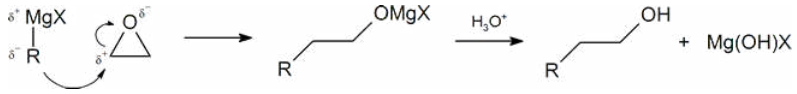


Reacting Grignard reagents with ethylene oxide is a particularly useful reaction because it produces a primary alcohol containing two more carbon atoms than the original Grignard reagent.



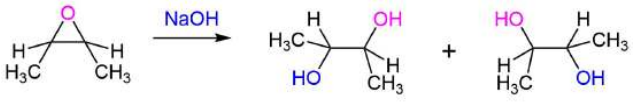
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This reaction follows the same S_N2 mechanism as the opening of epoxide rings under basic conditions since Grignard reagents are both strong nucleophiles and strong bases. The first step of the mechanism of this reaction involves the S_N2 attack of the Grignard reaction to open the epoxide to form an alkoxide. The second step of the mechanism involves the protonation of the alkoxide to form an alcohol.



Additional Stereochemical Considerations of Ring-Opening

During the ring-opening of an asymmetrical epoxide, the regiochemical control of the reaction usually allows for one stereoisomer to be produced. However, if the epoxide is symmetrical, each epoxide carbon has roughly the same ability to accept the incoming nucleophile. When this occurs the product typically contains a mixture of enantiomers.



Symmetrical Epoxide **Enantiomers**

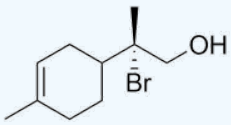
Exercises

Exercise 4.6.1

Given the following, predict the product assuming only the epoxide is affected. (Remember to show stereochemistry)



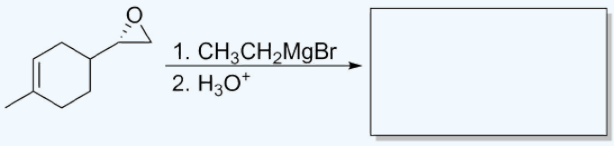
Answer



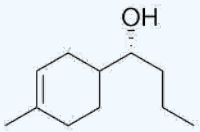
Note that the stereochemistry has been inverted

Exercise 4.6.2

Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

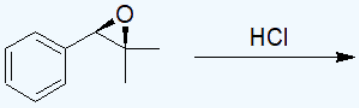


Answer

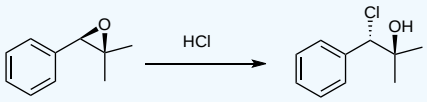


Exercise 4.6.3

Provide the structure of the product of the following reaction. Be sure to include proper stereochemistry.



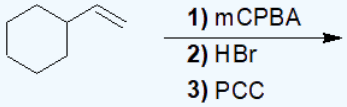
Answer



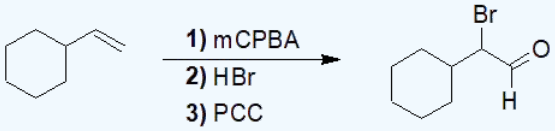
The ring side of the protonated epoxide intermediate will better stabilize a partial positive charge, so would be the more likely carbon for the chloride ion to attack.

Exercise 4.6.4

Predict the product of the following reaction.

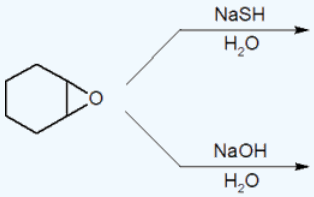


Answer



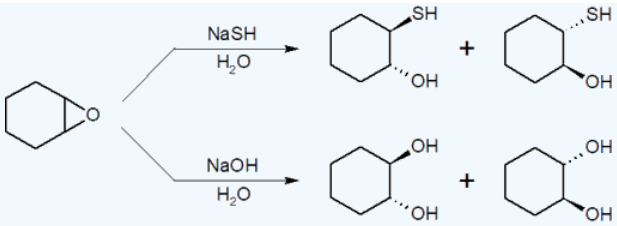
Exercise 4.6.5

Provide the final products of the following reactions.



Answer

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4.7: Crown Ethers

Objectives

After completing this section, you should be able to

1. write the normally accepted name for a crown ether, given its structure.
2. draw the structure of a crown ether, given its normally accepted name.
3. describe, briefly, the uses of crown ethers.

Key Terms

Make certain that you can define, and use in context, the key term below.

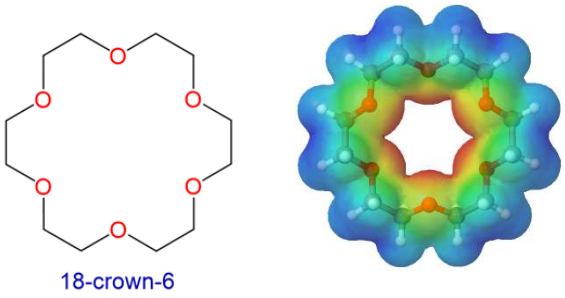
- crown ether

Study Notes

A “crown ether ” is a cyclic ether containing several (i.e., 4, 5, 6 or more) oxygen atoms. As we have indicated in the objectives above, a detailed knowledge of these compounds is not required in this course.

Crown Ethers

Crown ethers are cyclic polyethers with four or more oxygen atoms each separated by two or three carbon atoms. Crown ethers have the general formula of $(OCH_2CH_2)_n$ or $(OCH_2CH_2CH_2)_n$ and are named using both the total number of atoms in the ring and the number of oxygen atoms. Thus 18-crown-6 is an 18-membered ring with six oxygen atoms. All crown ethers have a cavity in the center this is lined with oxygen atoms and can accommodate a alkali metal ion, such as K^+. The cation is stabilized by interacting with lone pairs of electrons on the surrounding oxygen atoms. The negative character of center cavity of 18-crown-6 can be seen by looking at its electrostatic potential map shown below. The presence of high electron density is shown by a red color.



Crown ethers are useful for dissolving ionic substances in organic solvents, such as $KMnO_4$ dissolving in toluene, by sequestering the cations inside a hydrophilic cavity, whereas the outer shell, consisting of C–H bonds, is hydrophobic.

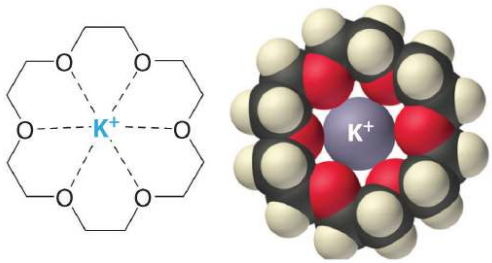
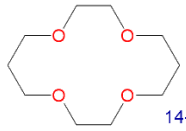
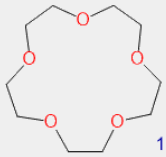
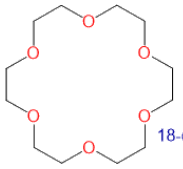
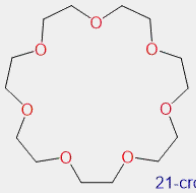


Figure 4.7.1: Potassium complex of the crown ether 18-crown-6. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

The availability of crown ethers with cavities of different sizes allows specific cations to be solvated with a high degree of selectivity. Crown ethers prefer to bind alkali metal cations with sizes that match that of their binding cavity. For instance, as shown

in Table 4.7.1, 14-crown-4 preferentially binds to Li^+, 15-crown-5 preferentially binds to Na^+, 18-crown-6 preferentially binds to K^+, and 21-crown-7 preferentially binds to Cs^+.

Table 4.7.1: Crown ethers preferentially bind cations with sizes that match the cavity size of their crown-shaped conformers.

Crown Ether	Cavity Diameter (A˚)	Preferred Cation	Cation Diameter (A˚)
 14-crown-4	1.2-1.5	Li^+	1.36
 15-crown-5	1.7-2.2	Na^+	1.94
 18-crown-6	2.6-3.2	K^+	2.66
 21-crown-7	3.4-4.3	Cs^+	3.34

Cryptands

Cryptands (from the Greek *kryptós*, meaning “hidden”) are variations of crown ethers comprised of two nitrogens connected by three polyether strands. A common nomenclature is used where the numbers preceding the word cryptan indicate the number of oxygen atoms in each strand of the molecule.

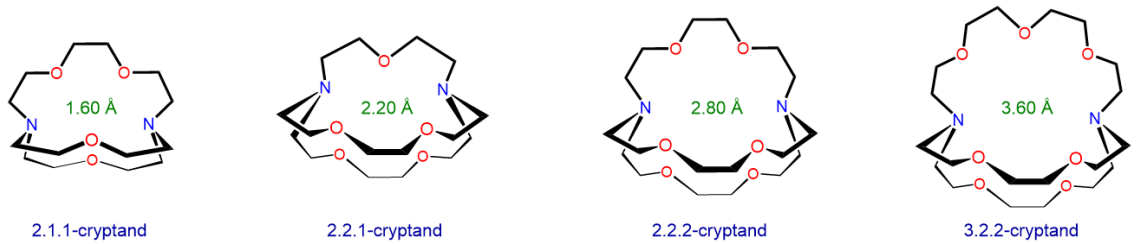


Figure 4.7.2: Structures and approximate binding cavity diameters for several cryptands.

Like crown ethers, cryptands are compounds that contains a central cavity that can completely surround a cation with lone pair electrons from oxygen and nitrogen atoms. Also, cryptands can be used to prepare solutions of ionic compounds in solvents that are otherwise too nonpolar to dissolve them. Similar to crown ethers, cryptands prefer to bind with alkali metal cations whose diameter matches the size of their binding cavity.

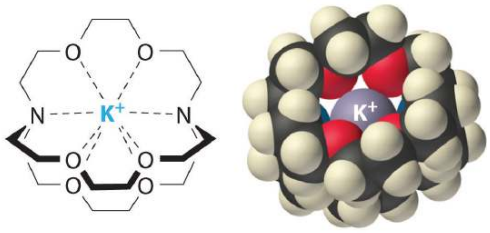


Figure 4.7.3: Potassium complex of 2,2,2-cryptand. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

Exercise 4.7.1

Cryptand ligands also preferentially bind alkali metal ions with sizes that match the size of their binding cavities. The structure and approximate cavity sizes of several cryptands are shown above. Use the information in Table 4.7.1 to predict which alkali metal ion each cryptand will preferentially bind.

Answer

The cryptands might be expected to selectively bind the largest ion which fits within the cavity. Predicted selectivity of crown ethers for alkali metal cations based on the hypothesis that they will selectively bind the largest ion which fits their binding cavity are listed below.

Cryptand	Cavity Diameter of (Å)	Preferred Cation	Cation Diameter (Å)
2.1.1-cryptand	1.60	Li^+	1.36
2.2.1-cryptand	2.20	Na^+	1.96
2.2.2-cryptand	2.80	K^+	2.66
3.2.2-cryptand	3.60	Cs^+	3.34

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4.8: Thiols and Sulfides

Objectives

After completing this section, you should be able to

1. a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   d. write an equation to illustrate the preparation of a thiol by the reaction of thiourea with an alkyl halide.
2. write an equation to show the interconversion between thiols and disulfides.
3. a. write the name of a sulfide, given its structure.
   b. draw the structure of a sulfide, given its name.
   c. write an equation showing how a sulfide may be prepared by the reaction of a thiolate anion on an alkyl halide.
   d. identify the product from the reaction of a given alkyl halide with a given thiolate anion.
   e. identify the reagents necessary to prepare a given sulfide.
   f. write an equation to illustrate the formation of a trialkylsulfonium salt from a sulfide and an alkyl halide.

Key Terms

Note: All of these terms are defined in the "Study Notes," below.

- disulfide
- mercapto group
- (organic) sulfide
- sulfone
- sulfoxide
- thiol
- thiolate anion
- trialkylsulfonium ion (trialkylsulfonium salt)

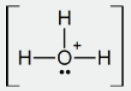
Study Notes

The chemistry of sulfur-containing organic compounds is often omitted from introductory organic chemistry courses. However, we have included a short section on these compounds, not for the sake of increasing the amount of material to be digested, but because much of the chemistry of these substances can be predicted from a knowledge of their oxygen-containing analogues.

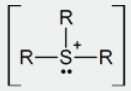
A thiol is a compound which contains an SH functional group. The SH group itself is called a mercapto group. A disulfide is a compound containing an S-S linkage.

(Organic) sulfides have the structure R-S-R′, and are therefore the sulfur analogues of ethers. The nomenclature of sulfides can be easily understood if one understands the nomenclature of the corresponding ethers. Notice that the term "thio" is also used in inorganic chemistry. For example, SO_4^{2-} is the sulfate ion; while $S_2O_3^{2-}$, in which one of the oxygen atoms of a sulfate ion has been replaced by a sulfur atom, is called thiosulfate. Thiolate anions, RS^-, are analogous to alkoxy anions, RO^-. Thiolate anions are better nucleophiles than are alkoxy anions.

If you have trouble understanding why trialkylsulfonium ions are formed, think of them as being somewhat similar to the hydronium ions that are formed by protonating water:



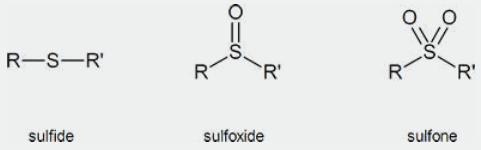
hydronium ion



trialkylsulfonium ion

Later we shall see examples of tetraalkylammonium ions, R_4N^+, which again may be regarded as being similar to hydronium ions.

Sulfoxides and sulfones are obtained by oxidizing organic sulfides. You need not memorize the methods used to carry out these oxidations.



sulfide sulfoxide sulfone

Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

Table 4.8.1: Comparison of compounds containing oxygen and sulfur

Oxygen-containing Compound	Sulfur Analogue
ether, R-O-R′	sulfide, R-S-R′
alkoxy anion, RO^-	thiolate anion, RS^-
alcohol, ROH	thiol, RSH
hydroxy group, OH^-	mercapto group, SH^-
peroxide, R-O-O-R′	disulfide, R-S-S-R′

Note that when we name thiols, we include the “e” of the alkane name. Thus, CH_3CH_2SH is called “ethanethiol,” not “ethanthiol.”

Thiols and sulfides are the "sulfur equivalent" of alcohols and ethers. You can replace the oxygen atom of an alcohol with a sulfur atom to make a thiol; similarly, you can replace the oxygen atom in an ether with S to make the corresponding alkyl sulfide. This is because thiols contain the C-S-H functional group, while sulfides contain the C-S-C group.

Oxidation States of Sulfur Compounds

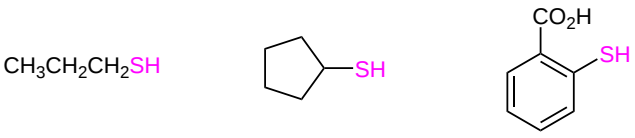
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

Sulfur Oxidation States in Organic Compounds

-2	-1	0	+2	+4	+6
H_2S R–S–H thiols R–S–R sulfides R–S–R (R) sulfonium ions	R–S–S–R disulfides	S elemental R–S(=O)–R sulfoxides R–S–OH sulfenic acids	R–S(=O)(=O)–R sulfones R–S(=O)–OH sulfinic acids	SO_2 R–S(=O)(=O)–OH sulfonic acids R–O–S(=O)–O–R sulfite esters	SO_3 R–O–S(=O)(=O)–O–R sulfate esters

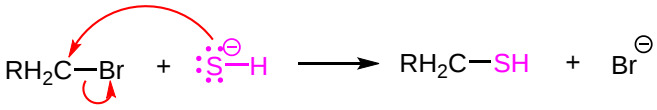
Thiols

Thiols are often called “mercaptans,” a reference to the Latin term mercurium captans (capturing mercury), since the -SH group forms strong bonds with mercury and its ions. Thiols are analogous to alcohols. Thiols are weakly acidic (pK_a ~ 10) and are much stronger acids than alcohols (pKa ~ 16). However, thiols usually do not form hydrogen bonds due to the sulfur atom not have sufficient electronegativity. Thiols named using the same rules as alcohols except the parent chain is named as alkane with the suffix -thiol added. As a substituent the -SH group is called a **mercapto** group.



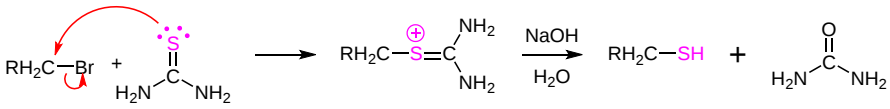
Propanethiol **Cyclopentanethiol** ***o*-Mercaptobenzoic acid**

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a nucleophile in an S_N2 reaction with alkyl halides.



Hydrosulfide ion **Thiol**

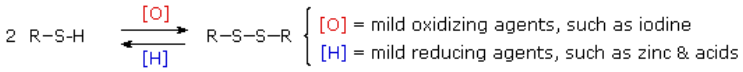
One problem with this reaction is that the thiol product can deprotonate and undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C{=}S$, as the nucleophile. The S_N2 reaction first produces an alkyl isothiourea salt as an intermediate. This salt is then hydrolyzed to form the thiol by a reaction with aqueous base.



Thiourea **Thiol** **Urea**

Disulfides

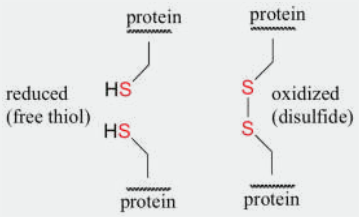
Thiols (R-S-H) can be oxidized to form disulfides (R-S-S-R') through reaction with Br_2 or I_2. Note, an equivalent oxidation of alcohols (R-O-H) to peroxides (R-O-O-R') is not normally observed. The reasons for this different behavior becomes clear when looking at bond strengths. The S–S single bond in disulfides is nearly twice as strong as the O–O bond in peroxides. Also, the O–H bond in alcohols is more than 25 kcal/mole stronger than the S–H bond in thiols. Thus, thermodynamics favors disulfide formation over peroxide. Disulfides can easily be reduced back to a thiols through reaction with zinc and acid.



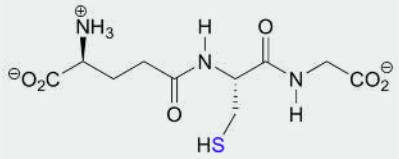
Thiol **Disulfide**

Disulfide bridges in proteins

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.

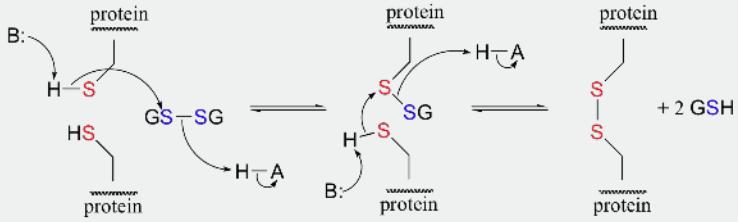


Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme. Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

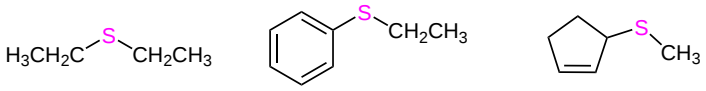
In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'. A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSG, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.



In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

Sulfides

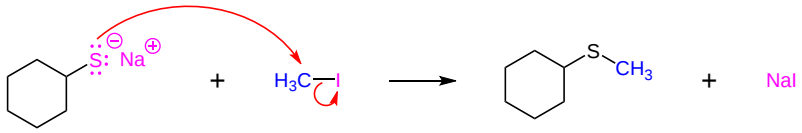
Sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substances, alkylthio is used in place of alkoxy.



Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

Sulfur analogs of ethers are called **sulfides**. Sulfides are less common than thiols as naturally occurring compounds. However, sulfides—especially disulfides (C-S-S-C)—have important biological functions, mainly in reducing agents (antioxidants).

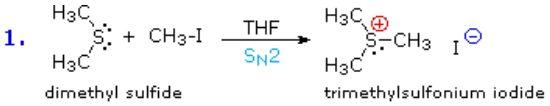
Since thiols are weakly acidic their conjugate bases, called thiolate ions, can be easily formed through reaction with a strong base such as NaH. Thiolates have proven to be excellent nucleophiles and easily undergo S_N2 reactions with primary and secondary alkyl halides to form sulfides. The reaction is analogous to the Williamson ether synthesis previously discussed in this chapter (**Section 3**)



Cyclohexanethiolate **Cyclohexyl methyl sulfide**

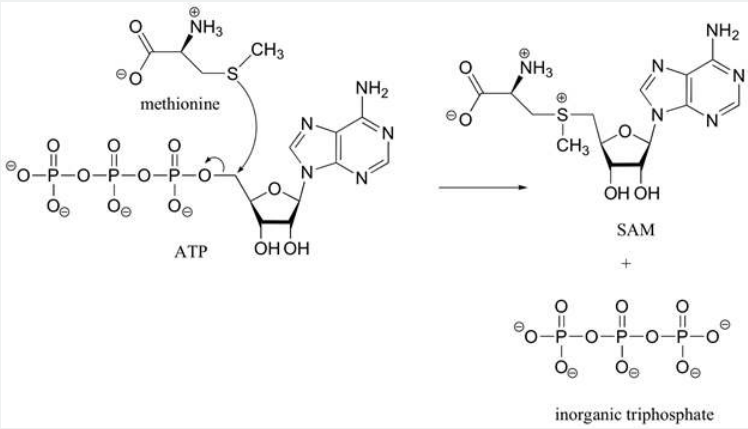
The chemical behavior of sulfides contrasts with that of ethers in some important ways. Because sulfur's valence electrons involve 3P orbitals they are further away and less tightly held than the valence electrons on oxygen which involve 2P orbitals. This makes the nucleophilicity of sulfur atoms much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. For instance, sulfides, unlike ethers, easily react with primary

alkyl halides through an S_N2 mechanism to give ternary sulfonium ions (R_3S^+) in the same manner that 3º-amines can be alkylated to form quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

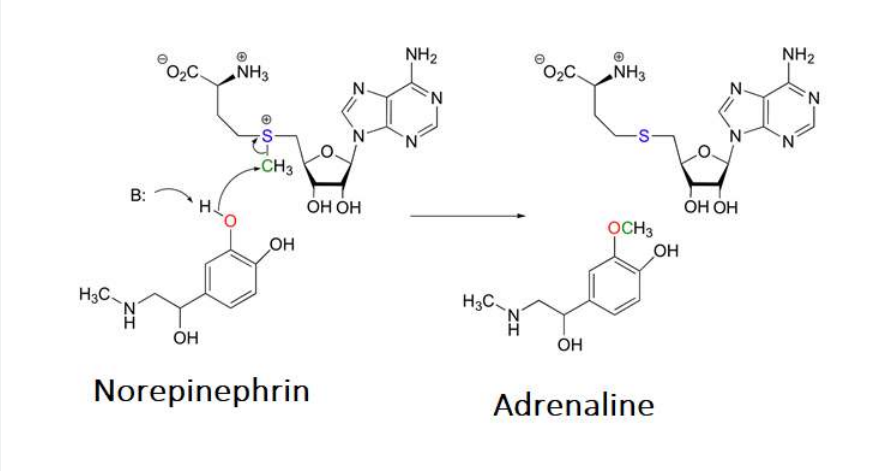


Biological Sulfonium Ion Formation

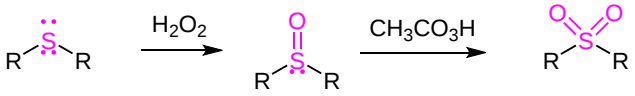
In biological systems the sulfonium ion, *S*-adenosylmethionine (SAM), is formed by a S_N2 reaction between the nucleophilic sulfur atom of the amino acid methionine and the electrophilic methene (CH_2) carbon of adenosine triphosphate (ATP). This reaction is unusually in that the triphosphate ion is removed from ATP as a leaving group. In most cases biological nucleophiles attack an electrophilic phosphorus on ATP causing a diphosphate ion to be removed as the leaving group.



The sulfonium ion in SAM is an effective methylating agent. Through an S_N2 reaction, biological nucleophiles can attack the electrophilic methyl group bonded to the positively charged sulfonium ion and cause the removal of a neutral sulfide as a leaving group. An example of this reaction is the catechol-O-methyltransferase catalyzed O-methylation of norepinephrin by SAM to produce adrenaline.

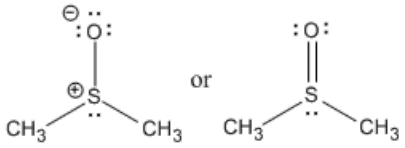


Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room temperature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid, such as peracetic acid (CH_3CO_3H), to produce the sulfone (R_2SO_2).



Sulfide **Sulfoxide** **Sulfone**

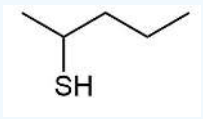
A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is considered a polar aprotic solvent.

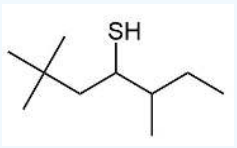


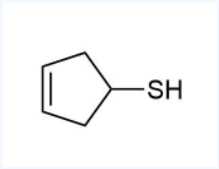
DMSO is a very polar, aprotic solvent

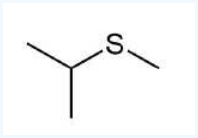
Exercise 4.8.1

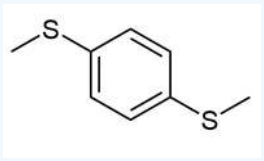
Give IUPAC names the following compounds:

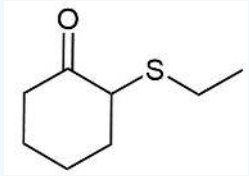
a) 

b) 

c) 

d) 

e) 

f) 

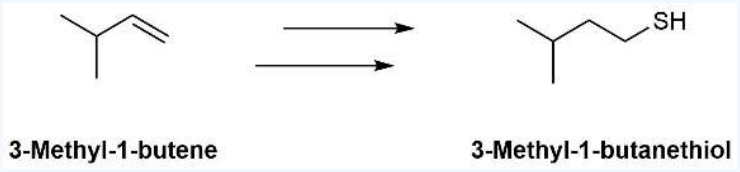
Answer

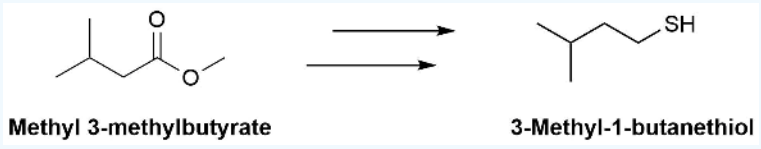
a) 2-Pentanethiol. b) 2,2,5-Trimethyl-4-heptanethiol. c) 3-Cyclopentene-1-thiol

d) Methyl isopropyl sulfide. e) *p*-Di(methylthio)benzene. f) 2-(Ethylthio)cyclohexanone

Exercise 4.8.2

The molecule 3-methyl-1-butanethiol has been shown to be one of the components of skunk spray. How would make the following conversions?

a) 

b) 

Answers

a) 1) HBr & Peroxides, 2) $(NH_2)_2C=S$, 3) NaOH & H_2O

b) 1) $LiAlH_4$, 2) PBr_3, 3) $(NH_2)_2C=S$, 4) NaOH & H_2O

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4.9: Spectroscopy of Ethers and Epoxides

Objectives

After completing this section, you should be able to

1. use the ^{1}H NMR spectrum of an unknown ether or epoxide to determine its identity.
2. identify the approximate chemical shift expected for protons attached to the carbon atoms that are bonded to oxygen in an ether or an epoxide.

Infrared Spectroscopy

Ethers are difficult to identify by IR spectroscopy. Although they show an absorption due to C–O single-bond stretching in the range 1050 to 1150 cm^{-1}, many other kinds of absorptions occur in the same range. Figure 4.9.1 shows the IR spectrum of diethyl ether and identifies the C–O stretch. Phenyl alkyl ethers show two strong absorbances for C–O stretching at 1050 and 1250 cm^{-1}. Figure 4.9.2 shows the IR spectrum of anisole.

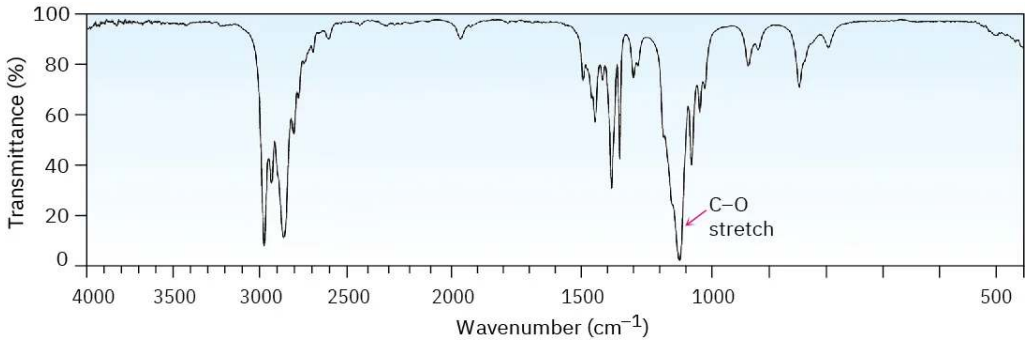


Figure 4.9.1: The infrared spectrum of diethyl ether, $CH_3CH_2OCH_2CH_3$.

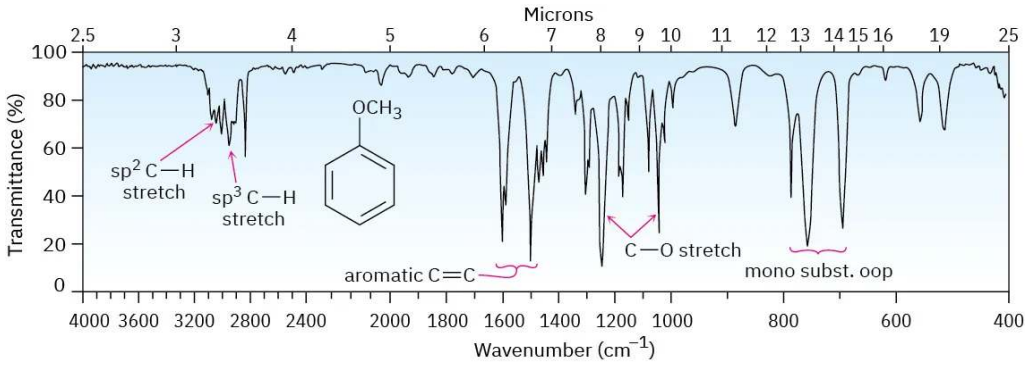


Figure 4.9.2: The infrared spectrum of anisole.

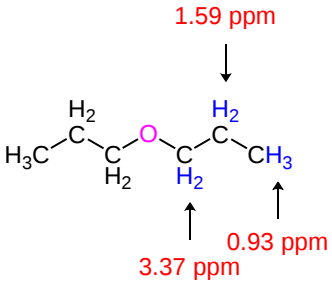
Nuclear Magnetic Resonance Spectroscopy

^{1}H NMR Spectroscopy

Ethers

- Hydrogens on carbon adjacent to the ether show up in the region of 3.4-4.5 ppm.

The ^{1}H NMR spectrum of dipropyl ether, Figure 4.9.3, shows three signals with the triplet at 3.37 ppm (B) assigned to the -CH_2- beside the ether and the other two signals upfield (1.59 and 0.93 ppm). Notice the protons closer to the electron-withdrawing oxygen atom are further downfield, indicating some deshielding. Protons at (A) and (C) are each coupled to two equivalent (B) protons. So, each of these signals appears as a triplet. The (B) protons in turn are coupled to a set of two and three equivalent protons and appears as a sextet.



Dipropyl ether

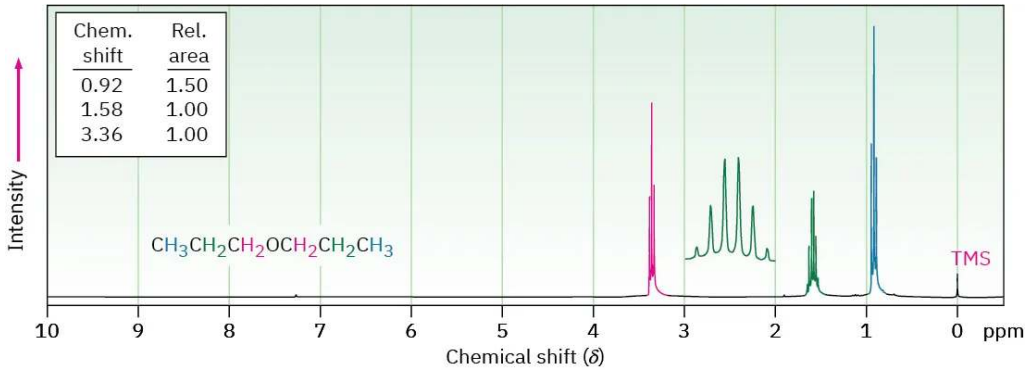
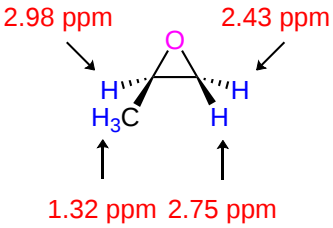


Figure 4.9.3: The ^{1}H NMR spectrum of dipropyl ether. Protons on carbon next to oxygen are shifted downfield to 3.36 δ.

Epoxides

- Peaks in epoxides are shifted to a slightly higher field than other ethers. Hydrogens on carbons in and epoxide appear in the region of 2.5 to 3.5 ppm.

Epoxides absorb at a slightly higher field than other ethers and show characteristic resonances at 2.5 to 3.5 δ in their ^{1}H NMR spectra, as indicated for 1,2-epoxypropane (**2-Methyloxirane**) in Figure 4.9.4. The methylene protons of this epoxide are diastereotopic, and display complex splitting (Review NMR Chapter).



2-Methyloxirane

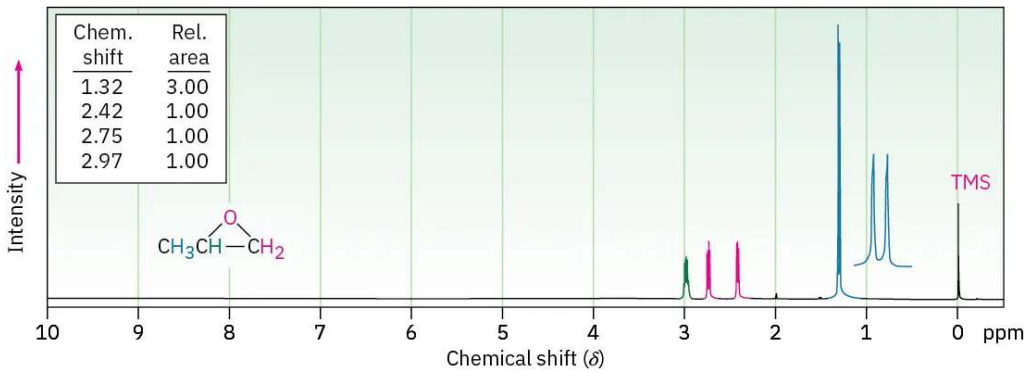


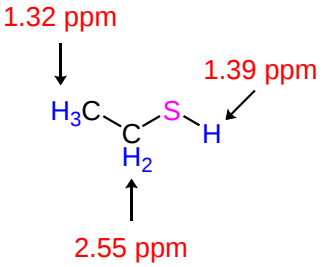
Figure 4.9.4: The ^{1}H NMR spectrum of 1,2-epoxypropane (**2-Methyloxirane**).

The methylene protons of this epoxide are diastereotopic and appear as two separate peak. When looking at the 3D structure of 2-methyloxirane it is clear that each methylene hydrogen is distinctly different. Also, hydrogens attached to the carbons in eposxides tend to display complex splitting patterns.

Thiols

- Hydrogens on carbons adjacent to the sulfur in sulfides and thiols appear in the region of 2.0 to 2.5 ppm.
- The SH hydrogen of a thiol typically appears in the region of 1.3-1.5 ppm.

As Sulfur is not as electronegative as Oxygen, the SH proton is actively involved in splitting in this ^{1}H NMR spectra. In Ethanethiol, Figure 4.9.5, the SH proton peak at 1.39 ppm is split into a triplet, and the methylene peak at 2.55 ppm is split into a quintet.



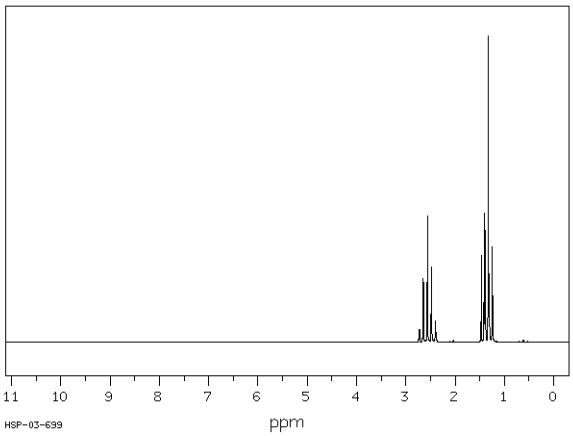
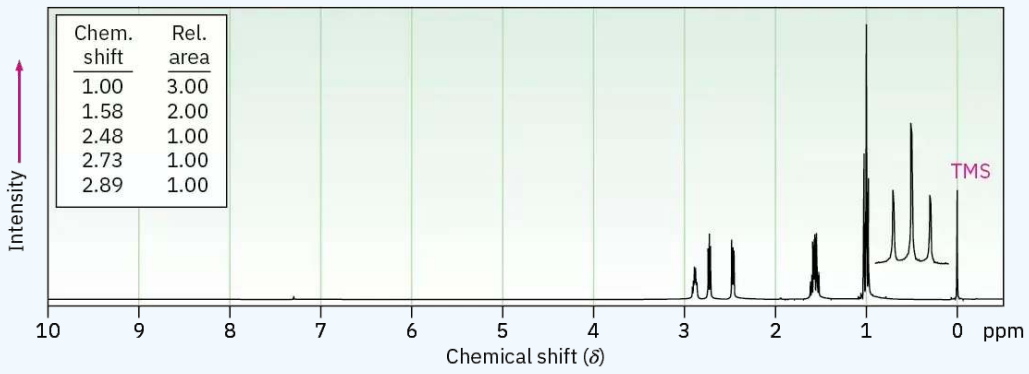


Figure \(\PageIndex{5}\): The ^{1}H NMR spectrum of Ethanethiol. Source: SDBSWeb http://sdbs.db.aist.go.jp

? Exercise 4.9.1

The ^{1}H NMR spectrum shown is that of a cyclic ether with the formula C_4H_8O. Propose a structure.



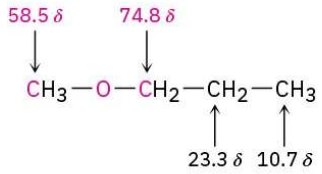
Answer

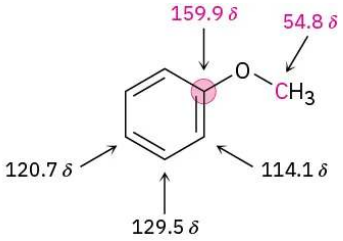
1,2-Epoxybutane

^{13}C NMR Spectra

Ethers

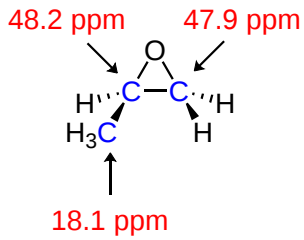
Ether carbon atoms also exhibit a downfield shift in the ^{13}C NMR spectrum, where they usually absorb in the 50 to 80 δ range. For example, the carbon atoms next to oxygen in methyl propyl ether absorb at 58.5 and 74.8 δ. Similarly, the methyl carbon in anisole absorbs at 54.8 δ.





Epoxides

Carbons that are part of the epoxide appear in the 40-60 ppm region. For example, in Figure 4.9.6, the carbon atoms next to oxygen in **2-Methyloxirane** absorb at 48.2 δ for CH, and 47.9 δ. for CH_2.



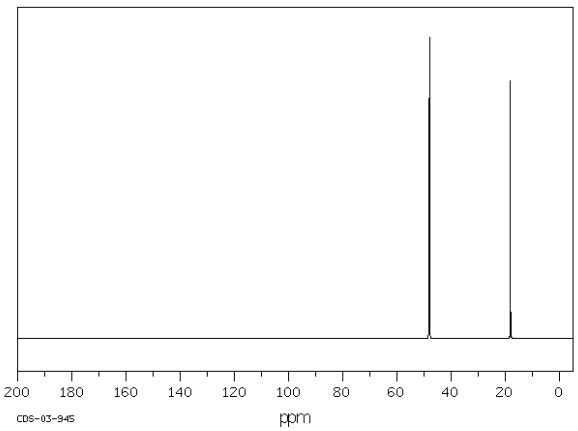
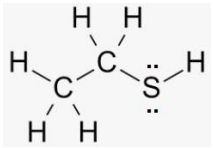


Figure 4.9.6: The ^{13}C NMR spectrum of 1,2-epoxypropane (**2-Methyloxirane**). Source: SDBSWeb : http://sdbs.db.aist.go.jp'

Thiols

As Sulfur is not as electronegative as Oxygen, carbon adjacent to the sulfur in sulfides and thiols appear in the region of 20-40 ppm. For example, in Figure 4.9.7, the carbon atoms next to sulfur in ethanethiol absorb at 19.71 and 19.20 δ.



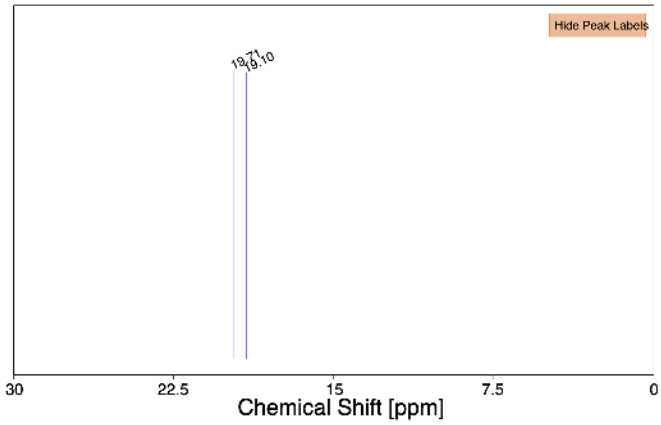
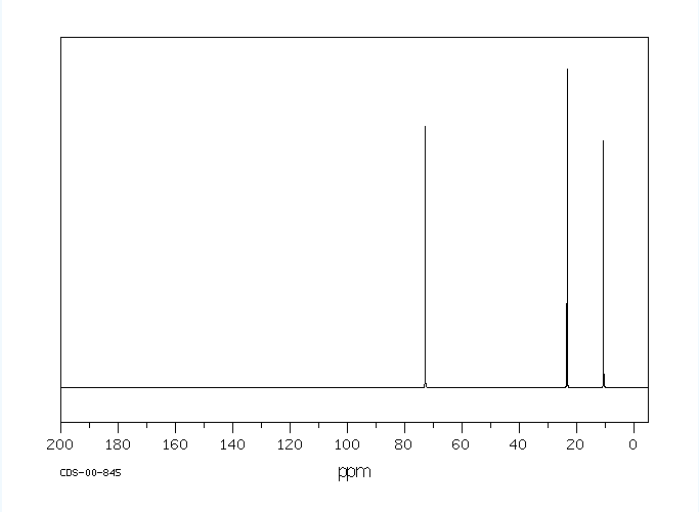


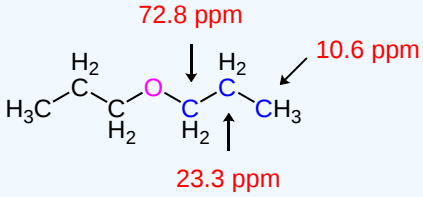
Figure 4.9.7: The ^{13}C NMR spectrum of **Ethanethiol**. Source: https://pubchem.ncbi.nlm.nih.gov/

Exercise 4.9.2

The ^{1}C NMR spectrum shown is that of a linear ether with the formula $C_6H_{14}O$. Propose a structure.



Answer



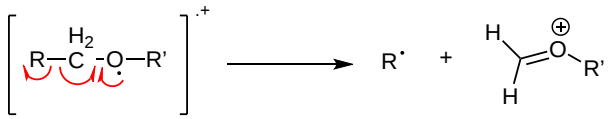
Dipropyl ether. Source: SDBSWeb : http://sdbs.db.aist.go.jp

Mass Spectra

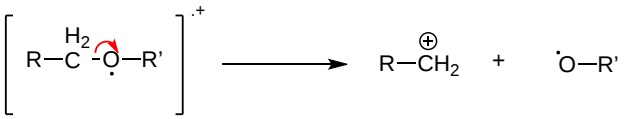
Ethers, sulfides, and epoxides all have similar fragmentation patterns in mass spectra with a few subtle variations.

Fragmentation Patterns for Ethers

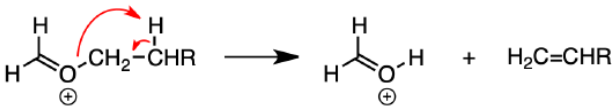
- The M^+ is may be weak or absent, but usually stronger than the corresponding alcohol.
- They primarily undergo alpha-cleavage to produce $[H_2C{=}O\text{-}R]^+$
- They can also undergo an inductive cleavage to produce R^+
- Rearrangement with loss of CHR=CHR'. This fragmentation happens after an alpha-cleavage.



alpha-cleavage



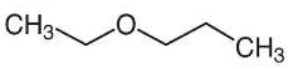
inductive cleavage



rearrangement

For Example, the primary fragmentation pattern for ethyl propyl ether (M^+= 88) in mass spectrometry involves:

1. **Alpha-cleavage at the carbon-carbon bond adjacent to the oxygen atom**, leading to the formation of prominent fragment ion m/z = 59, corresponding to the loss of an ethyl radical (m = 29). The fragment m/z = 73, corresponding to the loss of a methyl radical (m= 43), is not as prominent as the previous one because the methyl radical is not as stable as larger ones.
2. **Inductive** cleavage, the fragment ion m/z = 29 corresponds to the ethyl cation, and the fragment m/z = 43 corresponds to the propyl cation.
3. **Rearrangement** of fragment ion m/z = 59 leads to the formation of prominent fragment ion m/z = 31, corresponding to the loss of the alkene ethene (m = 28).



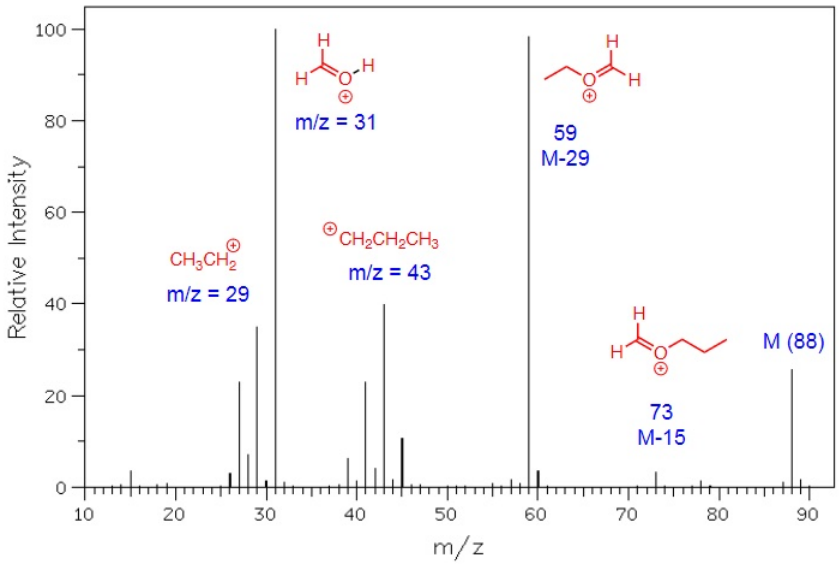


Figure 4.9.8: The Mass spectra of **Ethyl Propyl Ether**. Source: https://pubchem.ncbi.nlm.nih.gov/

Epoxides

- The M^+ is typically weak or absent
- They primarily undergo alpha-cleavage to produce an alkyl radical

Sulfides

- The M^+ is typically stronger than the corresponding ether
- They primarily undergo alpha-cleavage to produce an alkyl radical
- They can also undergo an inductive cleavage to produce R^+

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4.10: Interchapter - A Preview of Carbonyl Chemistry

So far, in our survey of the oxygen-containing organic compounds, we have studied the chemistry of ethers and alcohols. Now we turn our attention to a much larger group of compounds—those containing a carbonyl group:



The variety of carbonyl compounds is so wide, and their chemistry so extensive, that we shall need the next five chapters to discuss them thoroughly. One advantage of this course is that we have divided up the discussion of carbonyl compounds so that this large amount of factual material can be studied in small, readily digestible blocks.

The purpose of this chapter is to provide a general outline of what is to follow in the next five chapters: the various types of carbonyl compounds are introduced, the nature of the carbonyl group is explained, and the four most common mechanisms by which carbonyl groups react are described in general terms.

Chapter Objectives

When you have completed this chapter, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. identify the various types of carbonyl compounds.
3. write the mechanism of each of the four general types of reactions discussed in the chapter.
4. define, and use in context, the key terms introduced in this chapter.

Introduction

Objectives

After completing this section, you should be able to give examples of the wide variety of biologically important, pharmaceutical and industrial compounds that contain one or more carbonyl groups.

Key Terms

Make certain that you can define, and use in context, the key term below.

- carbonyl group

Study Notes

A “carbonyl group” consists of an sp^2-hybridized carbon atom that is joined to an oxygen atom by a double bond.

Natural Occurrence of Aldehydes and Ketones

Aldehydes and ketones are widespread in nature and are often combined with other functional groups. Examples of naturally occurring molecules which contain a aldehyde or ketone functional group are shown in the following two figures. The compounds in the figure 1 are found chiefly in plants or microorganisms and those in the figure 2 have animal origins. Many of these molecular structures are chiral.

When chiral compounds are found in nature they are usually enantiomerically pure, although different sources may yield different enantiomers. For example, carvone is found as its levorotatory (R)-enantiomer in spearmint oil, whereas, caraway seeds contain the dextrorotatory (S)-enantiomer. In this case the change of the stereochemistry causes a drastic change in the perceived scent. Aldehydes and ketones are known for their sweet and sometimes pungent odors. The odor from vanilla extract comes from the molecule vanillin. Likewise, benzaldehyde provides a strong scent of almonds and is this author’s favorite chemical smell. Because of their pleasant fragrances aldehyde and ketone containing molecules are often found in perfumes. However, not all of the fragrances are pleasing. In particular, 2-heptanone provides part of the sharp scent from blue cheese and (R)-Muscone is part of the

musky smell from the Himalayan musk deer. Lastly, ketones show up in many important hormones such as progesterone (a female sex hormone) and testosterone (a male sex hormone). Notice how subtle differences in structure can cause drastic changes in biological activity. The ketone functionality also shows up in the anti-inflammatory steroid, Cortisone.

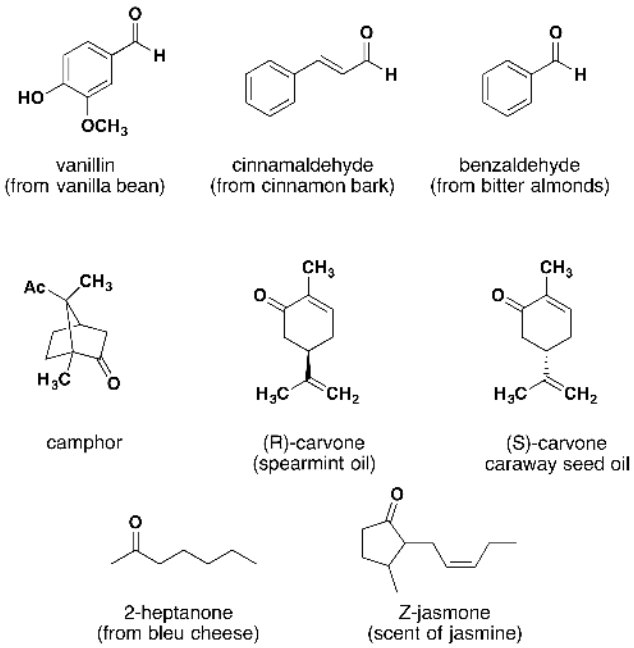


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

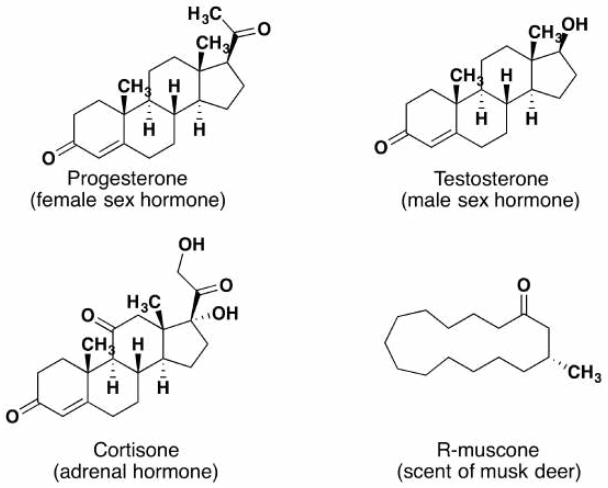


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

I Kinds of Carbonyl Compounds

Objectives

After completing this section, you should be able to

1. identify the following types of compounds as containing carbonyl groups: aldehydes, ketones, carboxylic acids, acid chlorides, acid anhydrides, esters, lactones, amides and lactams.
2. identify the important difference between aldehydes and ketones, and the other types of compounds listed under Objective 1, above.

Key Terms

Make certain that you can define, and use in context, the key term below.

- acyl fragment or acyl group

Study Notes

The idea of an “acyl group”

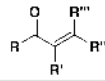
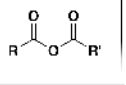


is not really new. Recall that in Chapter 16 we discussed the introduction of acyl groups into benzene rings by means of the Friedel-Crafts acylation reaction.

Note the use of the word “moiety” as an alternative to “group” or “fragment.”

Study the different types of carbonyl compounds listed in the table so that you can immediately recognize to which type a given compound belongs.

Some Carbonyl Compounds

Compound	Aldehyde	Ketone	Formaldehyde	Carboxylic Acid	Ester	Amide	Enone	Acyl Halide	Acid Anhydride
Structure									
General Formula	RCHO	RCOR'	CH_2O	RCOOH	RCOOR'	RCONR'R''	RC(O)C(R')CR''R'''	RCOX	$(RCO)_2O$

One should also add to this list lactones (cyclic esters) and lactams (cyclic amides).

II Nature of the Carbonyl Group

Objectives

After completing this section, you should be able to describe the electronic structure, polarity, and geometry of the carbonyl group.

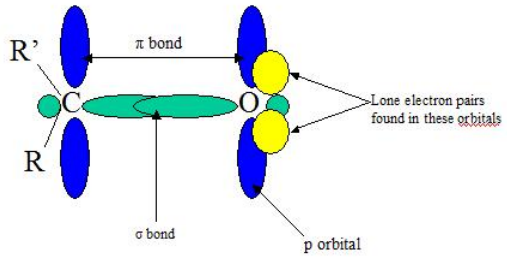
A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom --> [**C=O**] The simplest carbonyl groups are aldehydes and ketones usually attached to another carbon compound. These structures can be found in many aromatic compounds contributing to smell and taste.

Introduction

Before going into anything in depth be sure to understand that the **C=O** entity itself is known as the "Carbonyl group" while the members of this group are called "carbonyl compounds" --> **X**-C=O. The carbon and oxygen are usually sp^2 hybridized and planar.

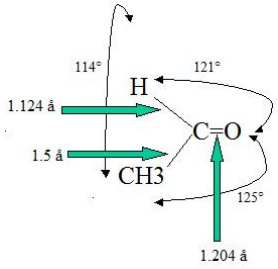
Carbonyl Group Double Bonds

The double bonds in alkenes and double bonds in carbonyl groups are VERY different in terms of reactivity. The C=C is *less* reactive due to C=O electronegativity attributed to the oxygen and its two lone pairs of electrons. One pair of the oxygen lone pairs are located in 2s while the other pair are in 2p orbital where its axis is directed perpendicular to the direction of the pi orbitals. The Carbonyl groups properties are directly tied to its electronic structure as well as geometric positioning. For example, the electronegativity of oxygen also polarizes the pi bond allowing the single bonded substituent connected to become electron withdrawing.



**Note: Both the pi bonds are in phase (top and botom blue ovals)*

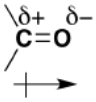
The double bond lengths of a carbonyl group is about 1.2 angstroms and the strength is about 176-179 kcal/mol). It is possible to correlate the length of a carbonyl bond with its polarity; the longer the bond meaing the lower the polarity. For example, the bond length in C=O is larger in acetaldehyde than in formaldehyde (this of course takes into account the inductive effect of CH_3 in the compound).



Polarization

As discussed before, we understand that oxygen has two lone pairs of electrons hanging around. These electrons make the oxygen more electronegative than carbon. The carbon is then partially postive (electrophillic) and the oxygen partially negative (nucleophillic). The polarizability is denoted by a lowercase delta and a positive or negative superscript depending. For example, carbon would have d+ and oxygen delta^(-). The polarization of carbonyl groups also effects the boiling point of aldehydes and ketones to be higher than those of hydrocarbons in the same amount. The larger the carbonyl compound the less soluble it is in water. If the compound exceeds six carbons it then becomes insoluble.

**For more information about carbonyl solubility, look in the "outside links" section*



**Amides are the most stable of the carbonyl couplings due to the high-resonance stabilization between nitrogen-carbon and carbon-oxygen.*

III General Reactions of Carbonyl Compounds

Objectives

After completing this section, you should be able to

1. list the four general reaction mechanisms that dominate the chemistry of carbonyl compounds.
2. discuss nucleophilic addition reactions of aldehydes and ketones (Chapter 19).
    a. write a general mechanism for nucleophilic addition to a carbonyl compound.

b. write a detailed mechanism for the addition of a given nucleophile (e.g., a Grignard reagent) to an aldehyde or ketone.

3. discuss nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21).
   a. write a general mechanism to illustrate nucleophilic acyl substitution reactions.
   b. write a detailed mechanism for the reaction of a given carbonyl-containing compound with a given nucleophile through a nucleophilic acyl substitution.
4. discuss alpha substitution reactions (Chapter 22).
   a. write a general mechanism to illustrate alpha-substitution of a carbonyl compound through the formation of an enol or enolate anion.
   b. explain the stability and ease of formation of enolate anions.
   c. write the detailed mechanism for the formation of an alpha-substituted carbonyl compound from the overall reaction of a carbonyl compound with a primary alkyl halide.
5. discuss carbonyl condensation reactions (Chapter 23).
   a. write a general mechanism to illustrate the condensation reaction that can occur between two molecules of a carbonyl compound; for example, the reaction of two molecules of acetaldehyde to form one molecule of aldol.

Key Terms

Note: All of these terms are defined in the "Study Notes," below.

- aldol reaction
- alkylation
- alpha substitution
- carbonyl condensation
- enol
- enolate anion
- nucleophilic acyl substitution
- nucleophilic addition reaction

Study Notes

A "nucleophilic addition reaction" (of a carbonyl compound) involves the initial attack of a nucleophile on the slightly positive carbonyl-carbon atom to form a tetrahedral intermediate.

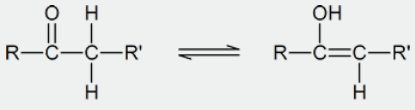
In a "nucleophilic acyl substitution reaction," a nucleophile attacks the carbonyl carbon of a carboxylic acid derivative



and initially produces a tetrahedral intermediate. The intermediate then reacts by expelling the leaving group, X, thereby forming a new carboxylic acid derivative.

In an "alpha substitution reaction" of a carbonyl compound, one of the hydrogen atoms attached to a carbon atom adjacent to the carbonyl group is removed and replaced by some other group.

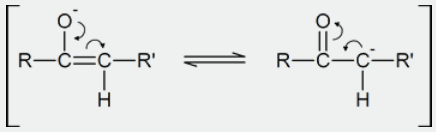
Alpha substitution reactions of carbonyl compounds involve the "enol" form of the compound. Keto-enol tautomerism was briefly introduced in Section 9.4. Review this section if necessary.



keto form enol form

As you can see from the above diagram, the enol form has a hydroxyl group attached to one of the sp^2 hybridized carbon atoms of a carbon-carbon double bond. Removal of the proton from the hydroxyl group produces a resonance-stabilized "enolate

anion":



A "carbonyl condensation reaction" is one in which two carbonyl- containing molecules condense together (i.e., join together), often with the elimination of water. The reaction involves the formation of an enolate anion from one carbonyl-containing molecule, followed by the subsequent nucleophilic attack by this enolate anion on the carbonyl carbon atom of the second molecule.

Nucleophilic Addition to a Carbonyl Group

C=O is prone to additions and nucleophillic attack because or carbon's positive charge and oxygen's negative charge. The resonance of the carbon partial positive charge allows the negative charge on the nucleophile to attack the Carbonyl group and become a part of the structure and a positive charge (usually a proton hydrogen) attacks the oxygen. Just a reminder, the nucleophile is a good acid therefore "likes protons" so it will attack the side with a positive charge.



**Remember: due to the electronegative nature of oxygen the carbon is partially positive and oxygen is partially negative*

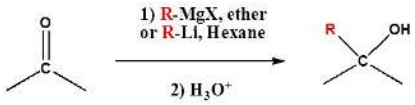


1 2 3

1. The Nucleophile (Nu) attacks the positively charged carbon and pushes one of the double bond electrons onto oxygen to give it a negative charge.
2. The Nucleophile is now a part of the carbon structure with a negatively charged oxygen and a Na^+ "floating" around.
3. The negatively charged oxygen attacks the proton (H^+) to give the resulting product above.

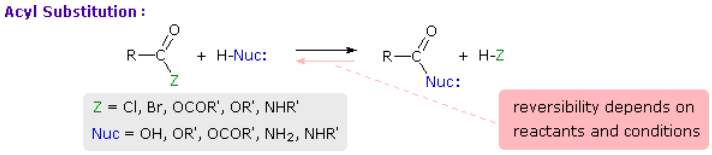
An Organometallic Example

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.

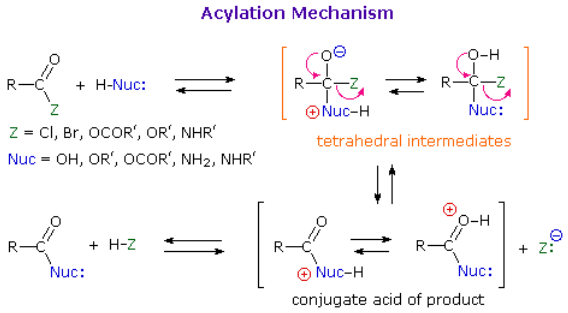


Nucleophilic Acyl Substitution

This is probably the single most important reaction of carboxylic acid derivatives. The overall transformation is defined by the following equation, and may be classified either as **nucleophilic substitution at an acyl group** or as **acylation of a nucleophile**. For certain nucleophilic reagents the reaction may assume other names as well. If Nuc-H is water the reaction is often called **hydrolysis**, if Nuc–H is an alcohol the reaction is called **alcoholysis**, and for ammonia and amines it is called **aminolysis**.



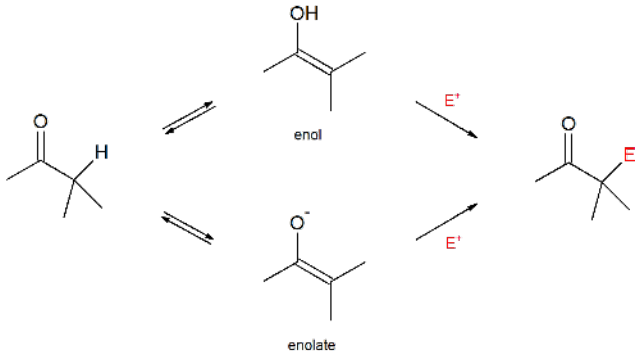
As illustrated in the following diagram, acylation reactions generally take place by an **addition-elimination process** in which a nucleophilic reactant bonds to the electrophilic carbonyl carbon atom to create a tetrahedral intermediate. This tetrahedral intermediate then undergoes an elimination to yield the products. In this two-stage mechanism bond formation occurs before bond cleavage, and the carbonyl carbon atom undergoes a hybridization change from sp^2 to sp^3 and back again. The facility with which nucleophilic reagents add to a carbonyl group was noted earlier for aldehydes and ketones.



Mechanism Toggle

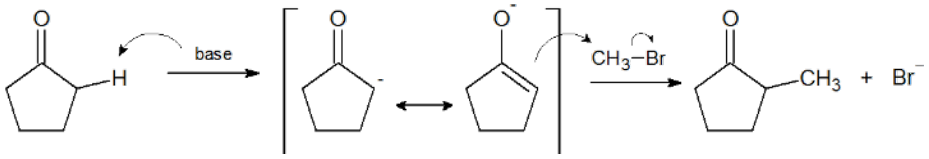
Alpha-Substitution Reactions

Now we will investigate reactions which occur a the carbon alpha to the carbonyl groups. These reactions involve two new nucleophilic species the enol and the enolate.



Note! The electrophile replaces the hydrogen on the alpha carbon.

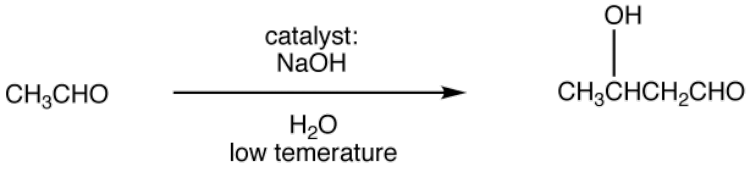
The following is a specific example of this type of reaction. Here we methylate the carbon alpha to the carbonyl group through an enolate intermediate. The hydrogen on the alpha carbon is acidic because of the presence of the C=O group and is therefore preferentially abstracted by the base.



Carbonyl Condensation Reactions

Enolizable aldehydes and enolizable ketones, in the presence of an acid or base catalyst usually in aqueous medium at low temperature, undergo a reaction, giving an aldol as the major product. This reaction is known as aldol reaction. The base-catalyzed

aldol reaction, in which the catalyst is usually the hydroxide ion, is more common. Careful control of reaction temperature is critical because high temperatures promote aldol condensation. The optimum temperature depends on the nature of the aldehyde or ketone. Typically, heating the reaction mixture results in aldol condensation. For example:

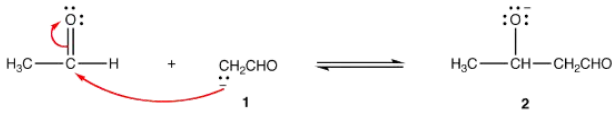


Mechanism:

Step 1: The hydroxide ion deprotanates the aldehyde reversibly.



Step 2: Enolate ion 1 adds to the unreacted aldehyde.



Step 3: Alkoxide ion 2 is protonated by water.



Since all three steps are reversible, the overall reaction is reversible and its equilibrium constant depends on the nature of the aldehyde or ketone. The reactions of aldehydes in which the α-carbon is a secondary carbon usually have large equilibrium constants; those of other aldehydes and ketones have small equilibrium constants. These observations suggest that the equilibrium constant of aldol reaction is sensitive to steric hindrance at the carbonyl carbon in the aldehyde or ketone.

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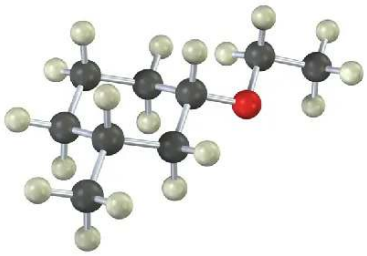
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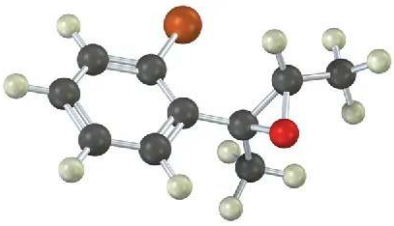
4.11: Additional Problems

4 • Additional Problems

Visualizing Chemistry

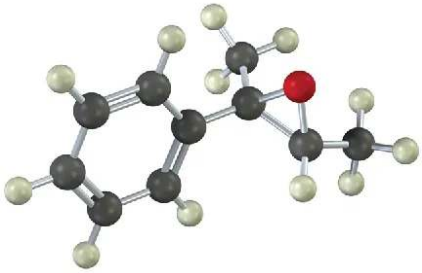
PROBLEM 4-19 Give IUPAC names for the following compounds (red = O; reddish brown = Br; yellow = S):

(a) 

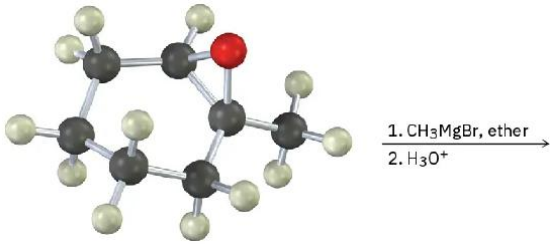
(b) 

(c) 

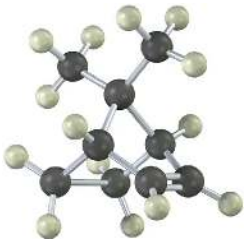
PROBLEM 4-20 Show the product, including stereochemistry, that would result from the reaction of the following epoxide with HBr:



PROBLEM 4-21 Show the product, including stereochemistry, of the following reaction:

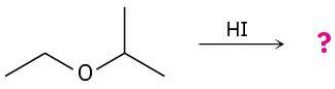


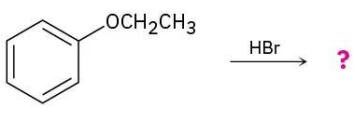
PROBLEM 4-22 Treatment of the following alkene with a peroxyacid yields an epoxide different from that obtained by reaction with aqueous Br_2 followed by base treatment. Propose structures for the two epoxides, and explain the result.



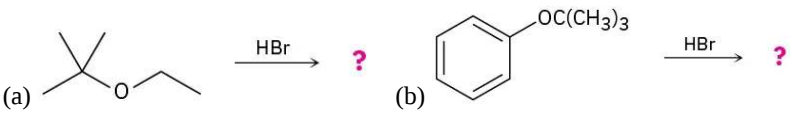
Mechanism Problems

PROBLEM 4-23 Predict the product(s) and provide the mechanism for each of the following reactions.

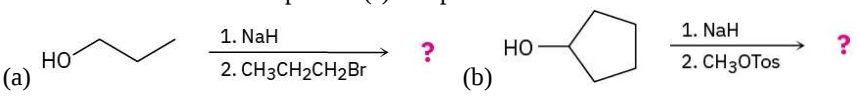
(a) 

(b) 

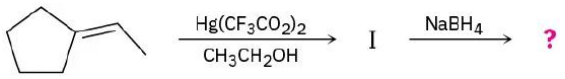
Problem 4-24 Predict the product(s) and provide the mechanism for each of the following reactions.



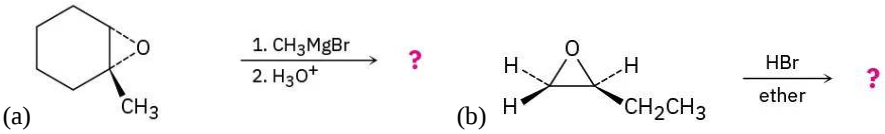
Problem 18-25 Predict the product(s) and provide the mechanism for each of the following two-step processes.



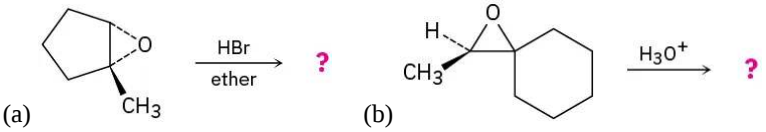
Problem 4-26 The alkoxymercuration of alkenes involves the formation of an organomercury intermediate (I), which is reduced with $NaBH_4$ to give an ether product. Predict the ether product and provide the mechanism for the following reaction.



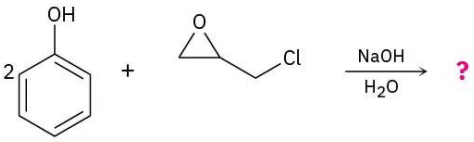
PROBLEM 4-27 Predict the product(s) and provide the mechanism for the following reactions:



Problem 4-28 Predict the product(s) and provide the mechanism for each of the following reactions.

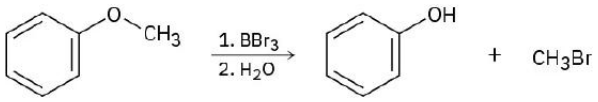


Problem 4-29 In the formation of the prepolymer used to make epoxy resins, a bisphenol reacts with epichlorohydrin in the presence of a base. Show the product and mechanism when two moles of phenol react with epichlorohydrin.

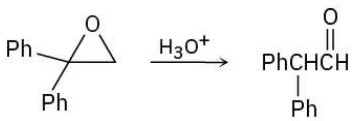


Epichlorohydrin

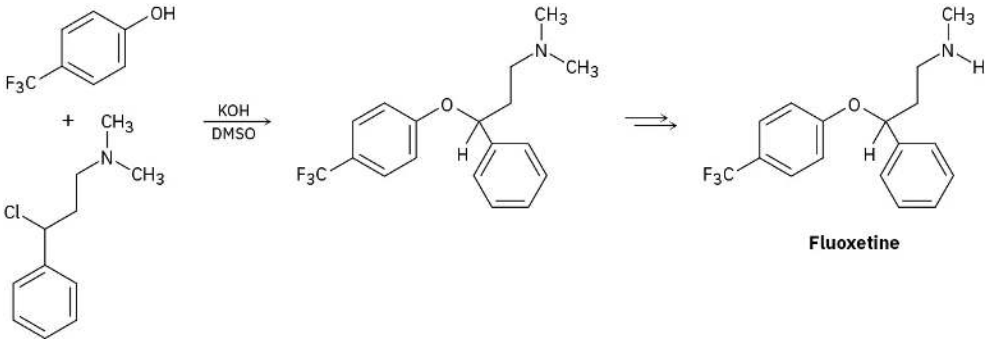
PROBLEM 4-30 Ethers undergo an acid-catalyzed cleavage reaction when treated with the Lewis acid BBr_3 at room temperature. Propose a mechanism for the reaction.



PROBLEM 4-31 Treatment of 1,1-diphenyl-1,2-epoxyethane with aqueous acid yields diphenyl acetaldehyde as the major product. Propose a mechanism for the reaction.



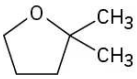
PROBLEM 4-32 Fluoxetine, a heavily prescribed antidepressant marketed under the name Prozac, can be prepared by a route that begins with reaction between a phenol and an alkyl chloride.



Fluoxetine

- (a) The rate of the reaction depends on both phenol and alkyl halide. Is this an S_N1 or an S_N2 reaction? Show the mechanism.
- (b) The physiologically active enantiomer of fluoxetine has (*S*) stereochemistry. Based on your answer in part **(a)**, draw the structure of the alkyl chloride you would need, showing the correct stereochemistry.

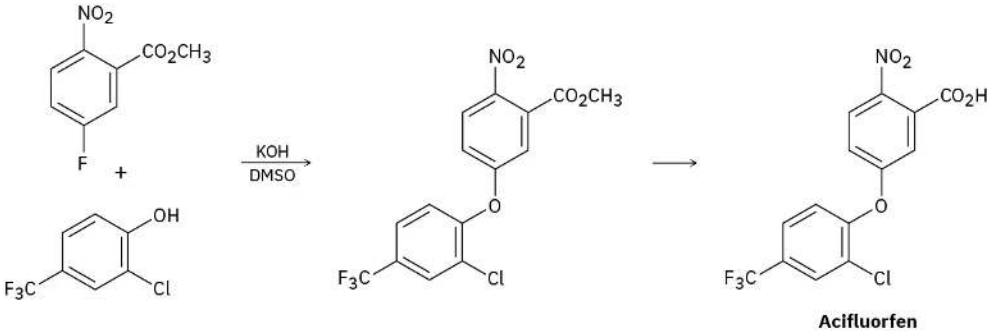
PROBLEM 4-33 When 2-methyl-2,5-pentanediol is treated with sulfuric acid, dehydration occurs and 2,2-dimethyltetrahydrofuran is formed. Suggest a mechanism for this reaction. Which of the two oxygen atoms is most likely to be eliminated, and why?



2,2-Dimethyltetrahydrofuran

PROBLEM 4-34 Methyl aryl ethers, such as anisole, are cleaved to iodomethane and a phenoxide ion by treatment with LiI in hot DMF. Propose a mechanism for this reaction.

PROBLEM 4-35 The herbicide acifluorfen can be prepared by a route that begins with a reaction between a phenol and an aryl fluoride. Propose a mechanism.



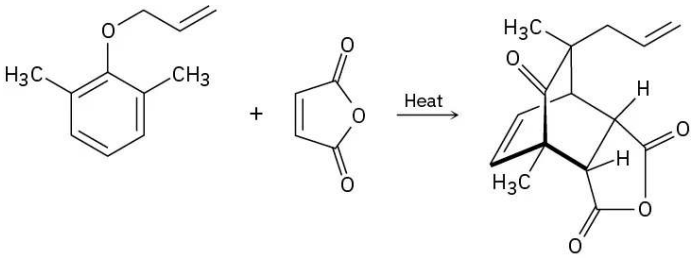
Acifluorfen

PROBLEM 4-36 Aldehydes and ketones undergo acid-catalyzed reaction with alcohols to yield *hemiacetals*, from aldehydes or ketals with ketones compounds that have one alcohol-like oxygen and one ether-like oxygen bonded to the same carbon. Further reaction of a hemiacetal with alcohol then yields an *acetal*, a compound that has two ether-like oxygens bonded to the same carbon.

(a) Show the structures of the hemiketal and ketal you would obtain by reaction of cyclohexanone with ethanol.

(b) Propose a mechanism for the conversion of a hemiacetal into a ketal.

PROBLEM 4-37 Propose a mechanism to account for the following transformation. What two kinds of reactions are occurring?



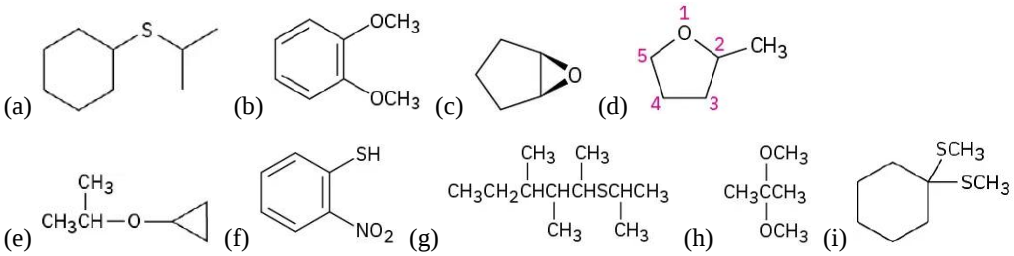
Naming Ethers

PROBLEM 4-38 Draw structures corresponding to the following IUPAC names:

(a) Ethyl 1-ethylpropyl ether (b) Di(*p*-chlorophenyl) ether (c) 3,4-Dimethoxybenzoic acid

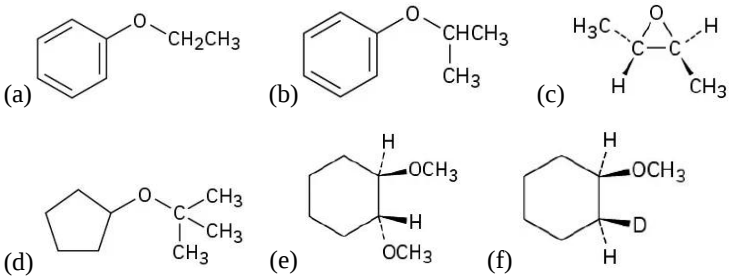
(d) Cyclopentyloxycyclohexane (e) 4-Allyl-2-methoxyphenol (eugenol; from oil of cloves)

PROBLEM 4-39 Give IUPAC names for the following structures:



Synthesizing Ethers

PROBLEM 4-40 How would you prepare the following ethers?



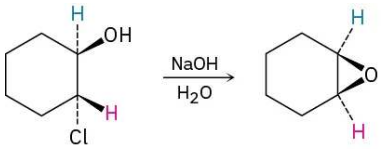
Problem 4-41 How would you prepare the following compounds from 1-phenylethanol?

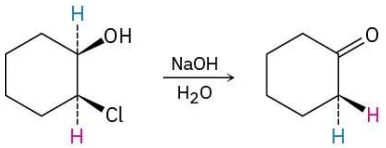
(a) Methyl 1-phenylethyl ether (b) Phenylepoxyethane

(c) *tert*-Butyl 1-phenylethyl ether (d) 1-Phenylethanethiol

PROBLEM 4-42 *tert*-Butyl ethers can be prepared by the reaction of an alcohol with 2-methylpropene in the presence of an acid catalyst. Propose a mechanism for this reaction.

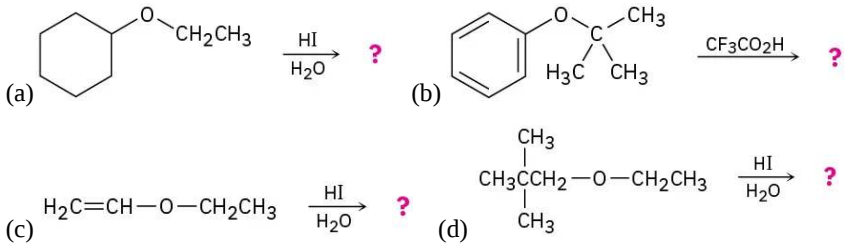
PROBLEM 4-43 Treatment of *trans*-2-chlorocyclohexanol with NaOH yields 1,2-epoxycyclohexane, but reaction of the cis isomer under the same conditions yields cyclohexanone. Propose mechanisms for both reactions, and explain why the different results are obtained.



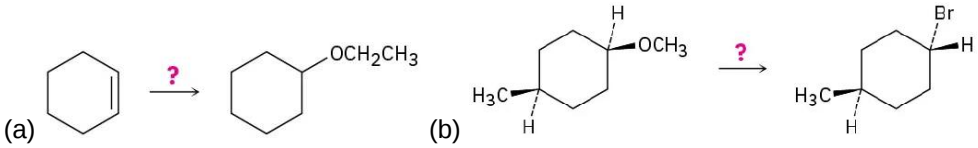


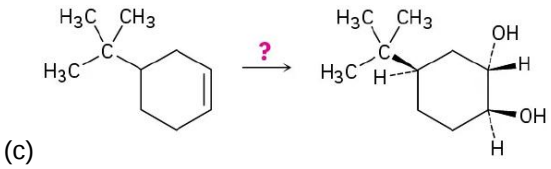
Reactions of Ethers and Epoxides

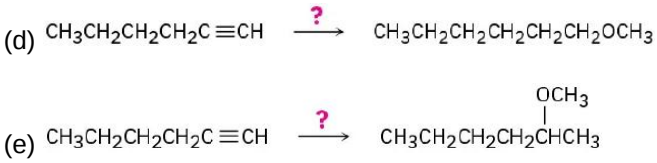
PROBLEM 4-44 Predict the products of the following ether cleavage reactions:



PROBLEM 4-45







Problem 4-46 What product would you expect from the cleavage of tetrahydrofuran with HI?

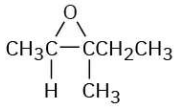
PROBLEM 4-47 Write the mechanism of the hydrolysis of *cis*-5,6-epoxydecane by reaction with aqueous acid. What is the stereochemistry of the product, assuming normal backside S_N2 attack?

PROBLEM 4-48 What is the stereochemistry of the product from acid-catalyzed hydrolysis of *trans*-5,6-epoxydecane? How does the product differ from that formed in Problem 18-47?

PROBLEM 4-49 Acid-catalyzed hydrolysis of a 1,2-epoxycyclohexane produces a trans-diaxial 1,2-diol. What product would you expect to obtain from acidic hydrolysis of *cis*-3-*tert*-butyl-1,2-epoxycyclohexane? (Recall that the bulky *tert*-butyl group locks the cyclohexane ring into a specific conformation.)

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PROBLEM 4-50 Imagine that you have treated (2*R*,3*R*)-2,3-epoxy-3-methylpentane with aqueous acid to carry out a ring-opening reaction.

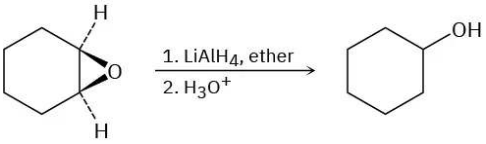


2,3-Epoxy-3-methylpentane
(no stereochemistry implied)

(a) Draw the epoxide, showing stereochemistry. (b) Draw and name the product, showing stereochemistry.

(c) Is the product chiral? Explain. (d) Is the product optically active? Explain.

PROBLEM 4-51 Epoxides are reduced by treatment with lithium aluminum hydride to yield alcohols. Propose a mechanism for this reaction.



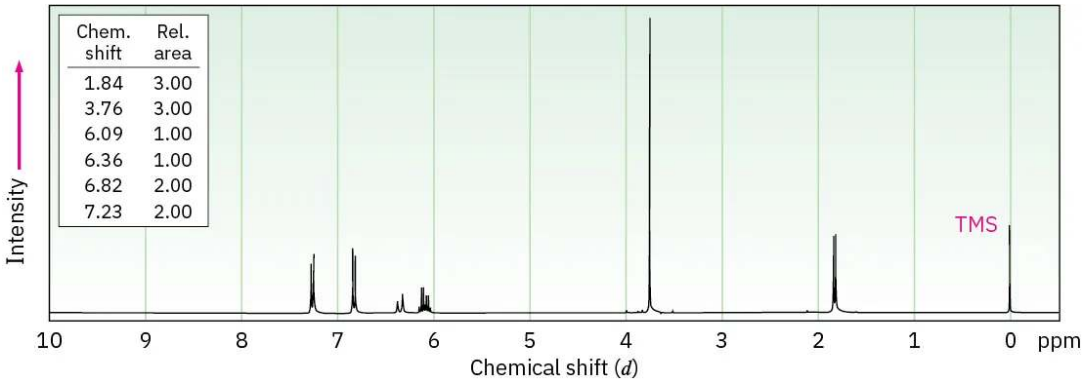
PROBLEM 4-52 Show the structure and stereochemistry of the alcohol that would result if 1,2-epoxycyclohexane were reduced with lithium aluminum deuteride, $LiAlD_4$ (Problem 4-51).

Spectroscopy

PROBLEM 4-53 The red fox *(Vulpes vulpes)* uses a chemical communication system based on scent marks in urine. One component of fox urine is a sulfide whose mass spectrum has $M^+ = 116$. IR spectroscopy shows an intense band at 890 cm^{-1}, and ^1H NMR spectroscopy reveals the following peaks:

Propose a structure consistent with these data. [Note: $(CH_3)_2S$ absorbs at 2.1 δ].

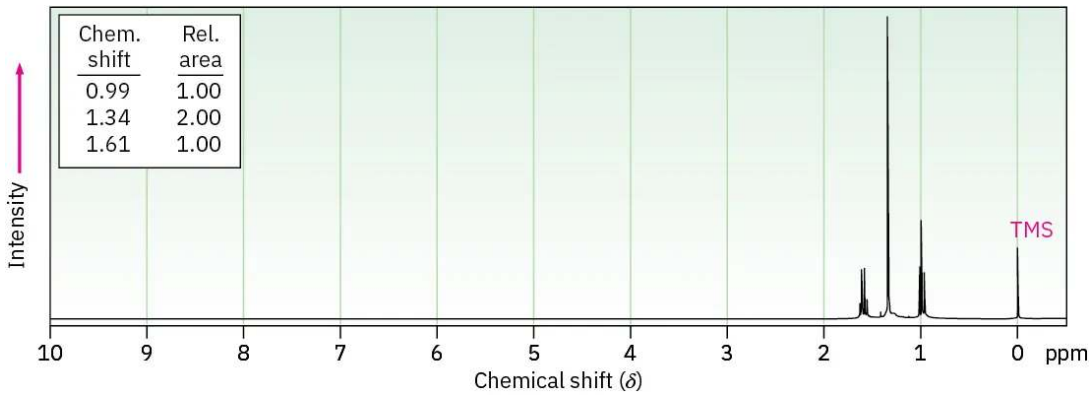
PROBLEM 4-54 Anethole, $C_{10}H_{12}O$, a major constituent of the oil of anise, has the ^1H NMR spectrum shown. On careful oxidation with $Na_2Cr_2O_7$, anethole yields *p*-methoxybenzoic acid. What is the structure of anethole? Assign all peaks in the NMR spectrum, and account for the observed splitting patterns.



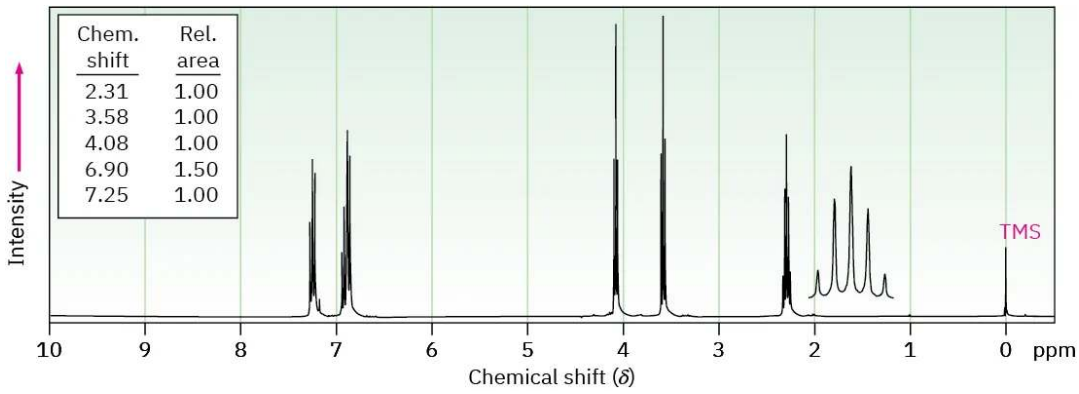
PROBLEM 4-55 Propose structures for compounds that have the following 1H NMR spectra:

(a) $C_5H_{12}S$ (An –SH proton absorbs near 1.6 δ.)

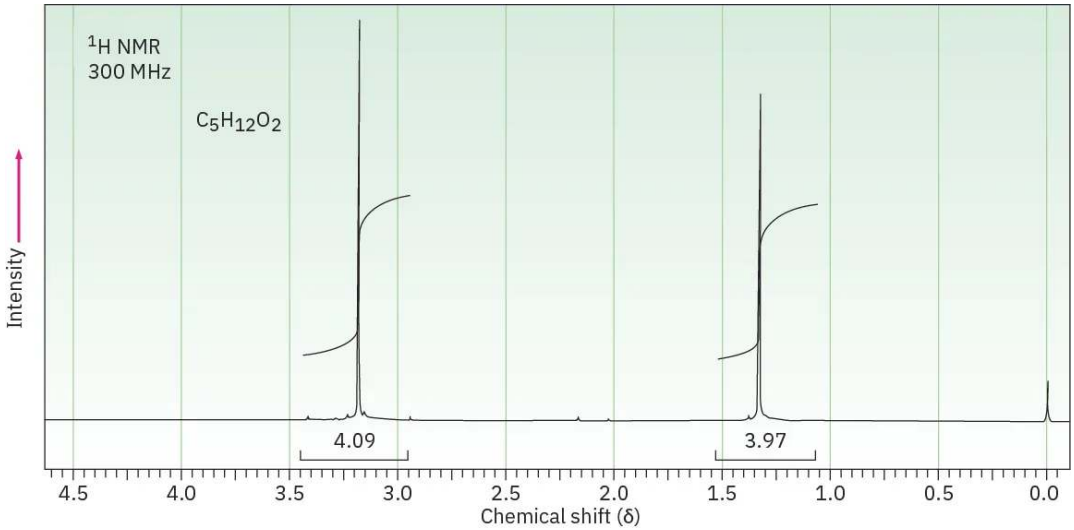
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(b) $C_9H_{11}BrO$

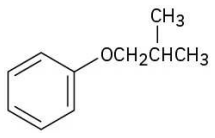


(c) $C_5H_{12}O_2$

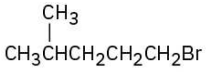


General Problems

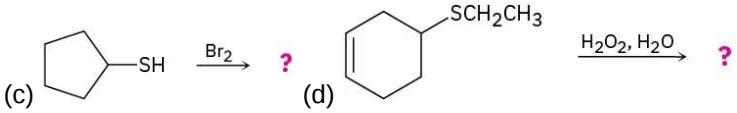
PROBLEM 4-56 Predict the products of the following reactions:

(a) 

HBr → ?

(b) 

1. $(NH_2)_2C{=}S$ 2. $NaOH, H_2O$ → ?



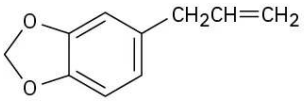
PROBLEM 4-57 How would you synthesize anethole (Problem 4-54) from phenol?

PROBLEM 4-58 How could you prepare benzyl phenyl ether from benzene and phenol? More than one step is required.

PROBLEM 4-59 *Meerwein's reagent*, triethyloxonium tetrafluoroborate, is a powerful ethylating agent that converts alcohols into ethyl ethers at neutral pH. Show the reaction of Meerwein's reagent with cyclohexanol, and account for the fact that trialkyloxonium salts are much more reactive alkylating agents than alkyl iodides.

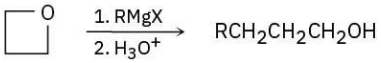
$(CH_3CH_2)_3O^+\ BF_4^-$ **Meerwein's reagent**

PROBLEM 4-60 Safrole, a substance isolated from oil of sassafras, is used as a perfumery agent. Propose a synthesis of safrole from catechol (1,2-benzenediol).



Safrole

PROBLEM 4-61 Grignard reagents react with oxetane, a four-membered cyclic ether, to yield primary alcohols, but the reaction is much slower than the corresponding reaction with ethylene oxide. Suggest a reason for the difference in reactivity between oxetane and ethylene oxide.



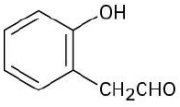
Oxetane

PROBLEM 4-62 The *Zeisel method* is an old analytical procedure for determining the number of methoxyl groups in a compound. A weighed amount of the compound is heated with concentrated HI, ether cleavage occurs, and the iodomethane product is distilled off and passed into an alcohol solution of $AgNO_3$, where it reacts to form a precipitate of silver iodide. The AgI is then collected and weighed, and the percentage of methoxyl groups in the sample is thereby determined. For example, 1.06 g of vanillin, the material responsible for the characteristic odor of vanilla, yields 1.60 g of AgI. If vanillin has a molecular weight of 152, how many methoxyl groups does it contain?

PROBLEM 4-63 Disparlure, $C_{19}H_{38}O$, is a sex attractant released by the female spongy moth, *Lymantria dispar*. The ^1H NMR spectrum of disparlure shows a large absorption in the alkane region, 1 to 2 δ, and a triplet at 2.8 δ. Treatment of disparlure, first with aqueous acid and then with $KMnO_4$, yields two carboxylic acids identified as undecanoic acid and 6-methylheptanoic acid. ($KMnO_4$ cleaves 1,2-diols to yield carboxylic acids.) Neglecting stereochemistry, propose a structure for disparlure. The actual compound is a chiral molecule with 7*R*,8*S* stereochemistry. Draw disparlure, showing the correct stereochemistry.

PROBLEM 4-64 How would you synthesize racemic disparlure (Problem 4-63) from compounds having ten or fewer carbons?

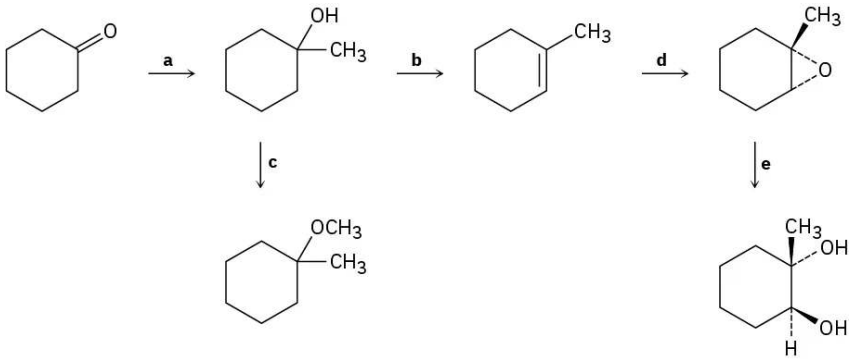
PROBLEM 4-65 How would you prepare *o*-hydroxyphenylacetaldehyde from phenol? More than one step is required.



***o*-Hydroxyphenylacetaldehyde**

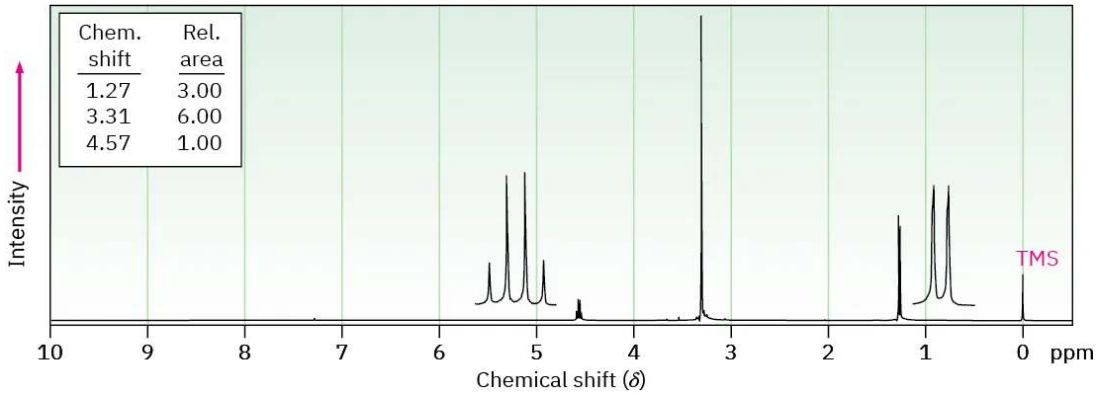
PROBLEM 4-66 Identify the reagents **a**–**e** in the following scheme:

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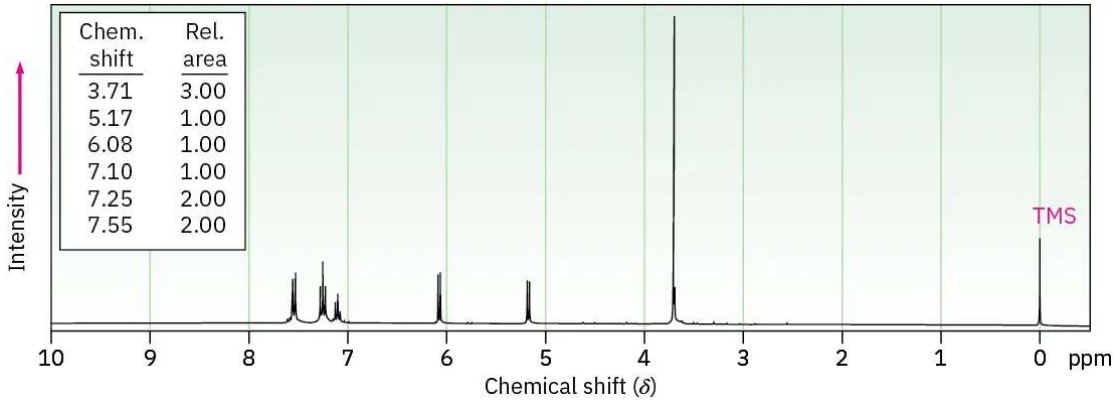


PROBLEM 4-67 Propose structures for compounds that have the following ^{1}H NMR spectra:

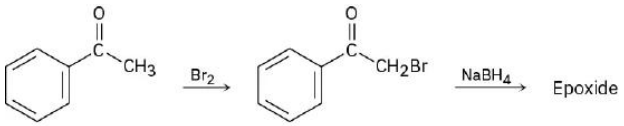
(a) $C_4H_{10}O_2$



(b) $C_9H_{10}O$



PROBLEM 4-68 We saw in **Section 3.5** that ketones react with $NaBH_4$ to yield alcohols. We'll also see in **Section 8.4** that ketones react with Br_2 to yield α-bromo ketones. Perhaps surprisingly, treatment with $NaBH_4$ of the α-bromo ketone from acetophenone yields an epoxide rather than a bromo alcohol. Show the structure of the epoxide, and explain its formation.



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4.S: Ethers and Epoxides; Thiols and Sulfides (Summary)

Concepts & Vocabulary

4.0 Introduction

- Ethers are molecules containing oxygen which is bonded to two carbon groups.
- Thiols are sulfur analogues of alcohols with an SH group instead of OH.
- Sulfides are sulfur analogues of ethers with sulfur bonded to two carbon groups instead of oxygen.

4.1 Names and Properties of Ethers

- Ether groups are named as alkoxy groups.
- Ethers do not have intramolecular hydrogen bonding (unlike alcohols), therefore ethers have significantly reduced intermolecular forces causing boiling points that are much lower than similar sized alcohols.

4.2 Preparing Ethers

- Alkoxymercuration can be used to prepare an ether from an alkene.

4.3 Reactions of Ethers: Acidic Cleavage

- The carbon-oxygen bonds of ethers can be cleaved with strong acids through either nucleophilic substitution or elimination reactions.

4.4 Reactions of Ethers: Claisen Rearrangement

- The Claisen rearrangement is a [3, 3] sigmatropic rearrangement reaction that converts aryl or enol ethers into carbonyl compounds (though the aromatic version rearranges into a phenol to re-establish aromaticity.

4.5 Cyclic Ethers: Epoxides

- Epoxides, also called oxiranes, have a three-membered ring structure with one oxygen and two carbon atoms.
- Epoxides can be formed from alkenes by reaction with peroxy acids (MCPBA for example).
- Epoxides can be formed from halohydrin molecules by reaction with a base, which causes an intramolecular Williamson ether synthesis.

4.6 Reactions of Epoxides: Ring Opening

- When epoxides are ring opened under basic conditions, they follow S_N2 mechanism leading to the nucleophile adding to the less substituted side of the epoxide.
- When epoxides are ring opened under acidic conditions, they follow S_N1 mechanism leading to the nucleophile adding to the more substituted side of the epoxide.
- When epoxides are ring opened in aqueous reactions, the result is an anti-diol.
- Halo acids can be added to epoxides to form anti-halohydrins.

4.7 Crown Ethers

- Crown ethers are cyclic ethers containing several oxygen atoms.
- Crown ethers are named by the number of total atoms in the ring, followed by the word crown and finally the number of oxygen atoms (18-crown-6 for example).

4.8 Thiols and Sulfides

- Thiols can be prepared from alkyl halides through reaction with hydrosulfide ion (SH^-) or through a more complicated series of reactions including thiourea.
- Thiols can be oxidized with mild oxidizing agents to form disulfides.
- Disulfide bridges link cysteine residues in protein structures.
- Sulfides are sulfur analogues of ether, though are much better nucleophiles with sulfur in place of oxygen.

4.9 Spectroscopy of Ethers

- Ethers show standard C-H stretches and bends in IR along with a strong C-O stretch around 1000 cm^{-1}.
- In ^1H NMR, hydrogens on carbons adjacent to the oxygen typically appear between 3.4-4.5 ppm.
- Hydrogens on carbons of an epoxide ring typically appear between 2.5-3.5 ppm in ^1H NMR.

4.10 Interchapter: A Preview of Carbonyl Chemistry

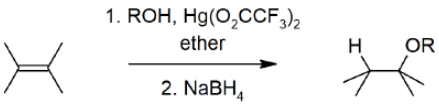
- Carbonyl groups are one of the most important features in organic chemistry and consist of a sp^2 carbon double-bonded to oxygen.
- Carbonyl groups are present in ~10 different functional groups.
- Carbonyl groups are polarized with a partial positive charge on carbon and partial negative charge on oxygen. This makes the carbon atom an electrophile, while the oxygen can act as a nucleophile.
- Carbonyl groups can react through several mechanisms including nucleophilic addition and nucleophilic acyl substitution, alpha substitution and condensation.

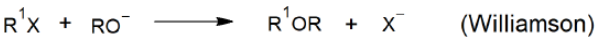
Skills to Master

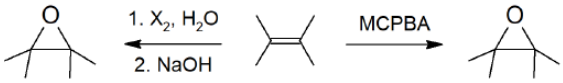
- Skill 1 Name ethers using common naming and IUPAC.
- Skill 2 Write reaction equations for preparation of ethers.
- Skill 3 Write mechanisms for reactions of ethers with strong halogen acids.
- Skill 4 Draw mechanisms for Cope and Claisen rearrangements.
- Skill 5 Draw mechanisms for ring-opening epoxides under acidic and basic conditions.
- Skill 6 Draw and name crown ethers.
- Skill 7 Explain how disulfide bridges contribute to protein structure.
- Skill 8 Give an example of S-adenosyl methionine activity in biological systems.
- Skill 9 Use IR and NMR spectra to identify ethers.

Summary of Reactions

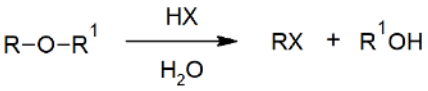
Ether and Epoxide Preparation



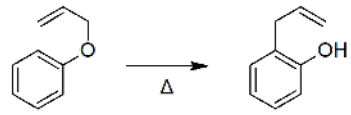




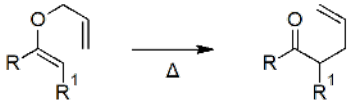
Ether Reactions



Claisen Rearrangement

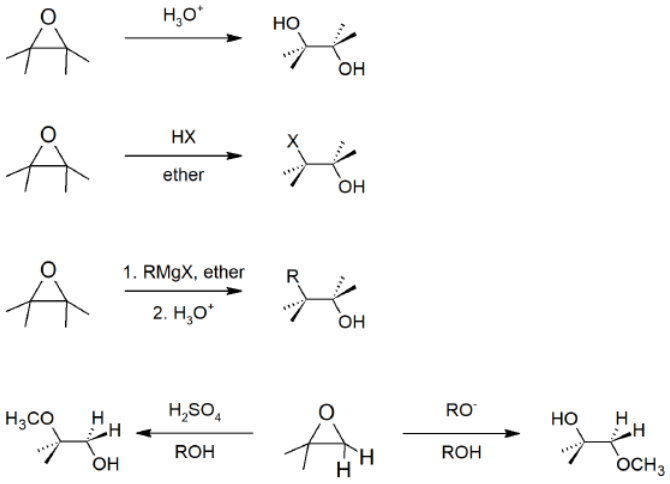


(Claisen rearrangement)

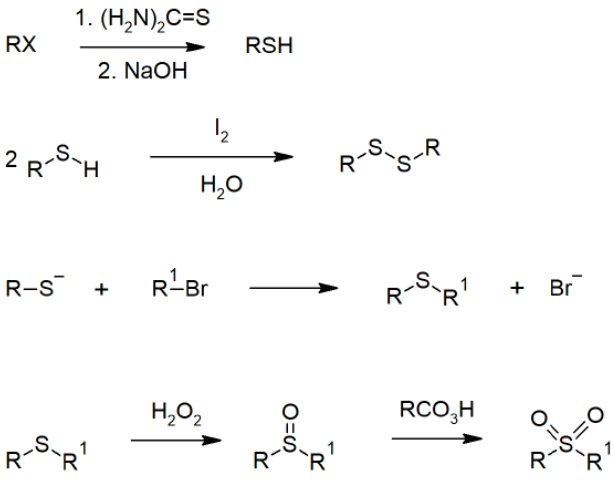


(Claisen rearrangement)

Epoxide Reactions



Sulfur Compound Reactions



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CHAPTER OVERVIEW

5: Aldehydes and Ketones - Nucleophilic Addition Reactions

5.0: Chapter Objectives and Preview of Carbonyl Chemistry
5.1: Naming Aldehydes and Ketones
5.2: Preparing Aldehydes and Ketones
5.3: Oxidation of Aldehydes and Ketones
5.4: Nucleophilic Addition Reactions of Aldehydes and Ketones
5.5: Nucleophilic Addition of Hydride - Alcohol Formation
5.6: Nucleophilic Addition via Organometallic Reactions - Alcohol Formation
5.7: Nucleophilic Addition of HCN - Cyanohydrin Formation
5.8: Nucleophilic Addition of Phosphorus Ylides - The Wittig Reaction
5.9: Nucleophilic Addition of Water- Hydration
5.10: Nucleophilic Addition of Alcohols - Acetal Formation
5.11: Nucleophilic Addition of Amines - Imine and Enamine Formation
5.12: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction
5.13: Biological Reductions
5.14: Conjugate Nucleophilic Addition to α, β-unsaturated Aldehydes and Ketones
5.15: Spectroscopy of Aldehydes and Ketones
5.16: Additional Problems
5.S: Aldehydes and Ketones (Summary)

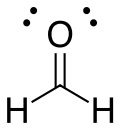
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5.0: Chapter Objectives and Preview of Carbonyl Chemistry

Objectives

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis in which you may have to use any of the reactions discussed in this chapter together with any number of reactions from previous chapters.
- solve “road-map” problems that require a knowledge of the chemistry of aldehydes and ketones.
- use evidence from any combination of infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectroscopy and chemical reactions to determine the structure of an unknown aldehyde or ketone.
- define, and use in context, the key terms introduced in this chapter.

In 1969 the molecule formaldehyde was discovered to be the first polyatomic organic molecule present in interstellar space by the National Radio Astronomy Observatory. The reactivity of formaldehyde gives it a wide variety of uses from embalming fluid to finger nail polish. Formaldehyde contain a C=O bond called a carbonyl, which is fundamental to study of organic chemistry. In this chapter we will begin a multi-chapter discussion on the chemistry of the carbonyl bond starting with aldehyde and ketone functional groups.



formaldehyde

In Chapter 19, we make a comprehensive study of the chemistry of aldehydes and ketones. Aldehydes and ketones are discussed together because their chemistry is very similar. However, as you work through the chapter, be sure to look for specific instances where the chemistry of these two classes of compounds differs.

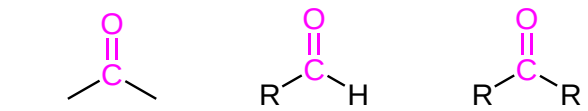
As usual, we begin the chapter with a discussion of nomenclature. This introduction is followed by descriptions of the methods used to prepare aldehydes and ketones in the laboratory. You will notice that a number of these reactions have already appeared in previous units. Note that an important difference between aldehydes and ketones is the resistance of ketones to oxidation.

A large part of this chapter is concerned with the addition of various nucleophiles to the carbonyl group of aldehydes and ketones. In particular, we discuss the addition of a variety of nitrogen-containing compounds, alcohols and phosphorus ylides. Many of these reactions are important to chemists concerned primarily with the synthesis of new organic compounds.

We also describe the Cannizzaro reaction and conjugate addition to α, β-unsaturated carbonyl compounds. We mention the occurrence of nucleophilic addition reactions in biological systems, and conclude the unit with a look at the use of spectroscopic techniques in the analysis of aldehydes and ketones.

Preview of Carbonyl Chemistry

Aldehydes and ketones are organic compounds which incorporate a carbonyl functional group, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an aldehyde. If both are carbons, the compound is a ketone.

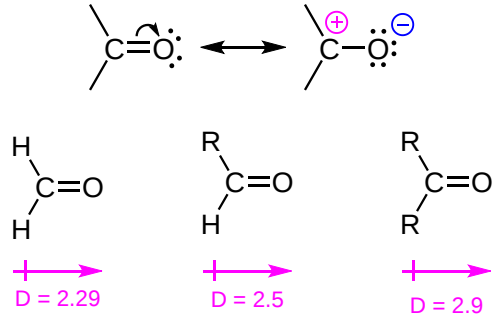


Carbonyl Group Aldehyde Ketone

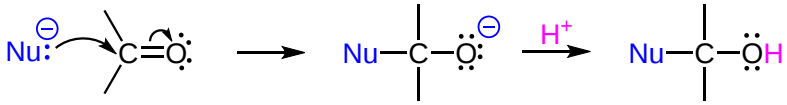
Because of the greater electronegativity of oxygen, the carbonyl group is polar, and aldehydes and ketones have larger molecular dipole moments (D) than do alkenes. The resonance structures below illustrate this polarity, and the relative dipole moments of

https://chem.libretexts.org/@go/page/500403

formaldehyde, other aldehydes and ketones.



This polarity causes the carbonyl carbon to be partially positive (electrophillic) and the oxygen partially negative (nucleophillic). The C=O bond is prone to nucleophillic attack because or carbon's positive charge and oxygen's negative charge. In general, nucleophiles attack the electrophilic carbon and become a part of the structure while the oxygen is protonated forming a hydroxyl group.



Aldehydes and ketones are widespread in nature and are often combined with other functional groups. Examples of naturally occurring molecules which contain an aldehyde or ketone functional group are shown in the following two figures. The compounds in the **figure 1** are found chiefly in plants or microorganisms and those in the **figure 2** have animal origins. Many of these molecular structures are chiral.

When chiral compounds are found in nature they are usually enantiomerically pure, although different sources may yield different enantiomers. For example, carvone is found as its levorotatory (R)-enantiomer in spearmint oil, whereas, caraway seeds contain the dextrorotatory (S)-enantiomer. In this case the change of the stereochemistry causes a drastic change in the perceived scent. Aldehydes and ketones are known for their sweet and sometimes pungent odors. The odor from vanilla extract comes from the molecule vanillin. Likewise, benzaldehyde provides a strong scent of almonds and is this author’s favorite chemical smell. Because of their pleasant fragrances aldehyde and ketone containing molecules are often found in perfumes. However, not all of the fragrances are pleasing. In particular, 2-heptanone provides part of the sharp scent from blue cheese and (R)-muscone is part of the musky smell from the Himalayan musk deer. Lastly, ketones show up in many important hormones such as progesterone (a female sex hormone) and testosterone (a male sex hormone). Notice how subtle differences in structure can cause drastic changes in biological activity. The ketone functionality also shows up in the anti-inflammatory steroid, cortisone.

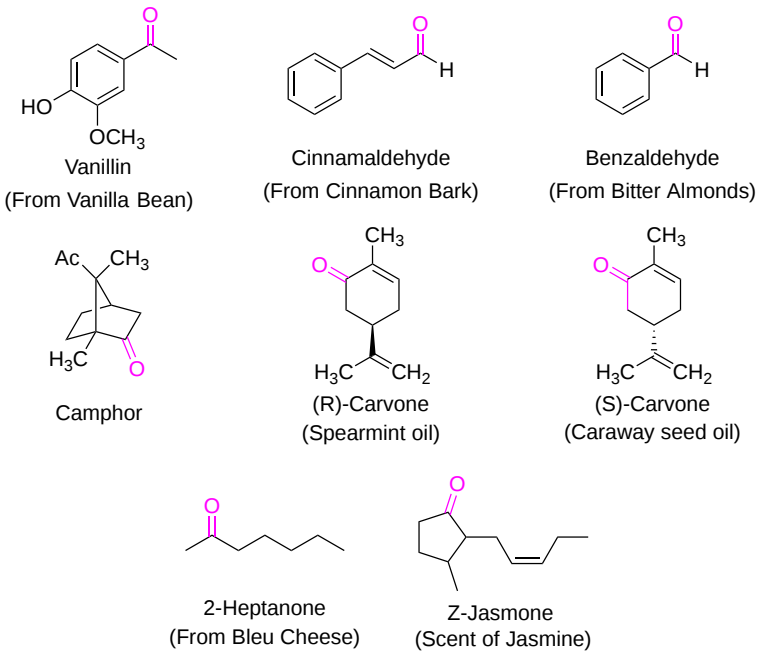


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

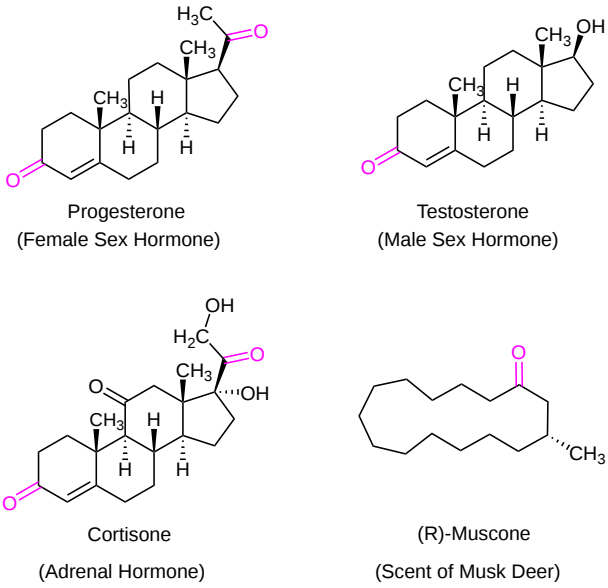


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

Contributors and Attributions

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-
- Layne Morsch (University of Illinois Springfield)

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5.1: Naming Aldehydes and Ketones

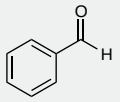
Objectives

After completing this section, you should be able to

- provide the IUPAC name of an aldehyde or ketone, given its Kekulé, condensed, or skeletal structure.
- draw the structure of an aldehyde or ketone, given its IUPAC name.
- draw the structure of the following aldehydes and ketones, given their common names: formaldehyde, acetaldehyde, benzaldehyde, acetone, acetophenone, benzophenone.

Study Notes

We will only use those common names listed under Objective 3, above. We will use systematic names in all other cases. For example, the systematic name of the compound shown below is benzenecarbaldehyde, but it has the common name of benzaldehyde.



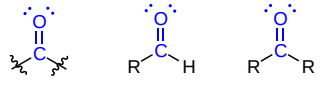
benenecarbaldehyde
(benzaldehyde)

When naming unsaturated aldehydes and ketones, you must give the carbonyl group "priority" over the double bond when you are deciding which end of the carbon chain to begin numbering The carbonyl-carbon of an aldehyde will always be at the end of the carbon chain in an acyclic compound; and therefore numbering always starts at this carbon. It is for this reason, too, that the number "1" is not required when naming a compound such as 2-ethyl-4-methylpentanal.

The most potent and varied odors are aldehydes. Ketones are widely used as industrial solvents. Aldehydes and ketones contain the carbonyl group. Aldehydes are considered the most important functional group. They are often called the formyl or methanoyl group. Aldehydes derive their name from the *dehyd*ration of *al*cohols. Aldehydes contain the carbonyl group bonded to at least one hydrogen atom. Ketones contain the carbonyl group bonded to two carbon atoms.

Introduction to Naming Carbonyls

Aldehydes and ketones are organic compounds which incorporate a **carbonyl functional group**, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an **aldehyde**. If neither is hydrogen, the compound is a **ketone**.

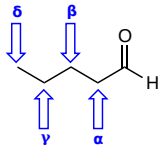


carbonyl group | aldehyde | ketone

Naming Aldehydes

The IUPAC system of nomenclature assigns a characteristic suffix ***-al*** to aldehydes. For example, $H_2C{=}O$ is methan**al**, more commonly called formaldehyde. Since an aldehyde carbonyl group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name. There are several simple carbonyl containing compounds which have common names which are retained by IUPAC.

Also, there is a common method for naming aldehydes and ketones. For aldehydes common parent chain names, similar to those used for carboxylic acids, are used and the suffix ***–aldehyde*** is added to the end. In common names of aldehydes, carbon atoms near the carbonyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



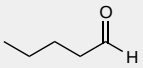
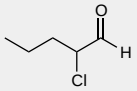
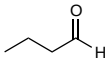
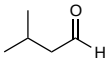
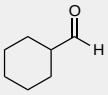
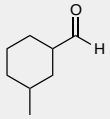
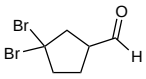
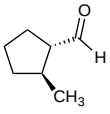
If the aldehyde group (-CHO) is attached to a ring the suffix ***–carbaldehyde*** is added to the name of the ring. The carbon attached to this group will get the #1 location number in naming the ring.

Summary of Aldehyde Nomenclature rules

1. Aldehydes take their name from their parent alkane chains. The ***-e*** is removed from the end and is replaced with ***-al***.
2. The aldehyde funtional group is given the #1 numbering location and this number is not included in the name.
3. For the common name of aldehydes start with the common parent chain name and add the suffix ***-aldehyde***. Substituent positions are shown with Greek letters.
4. When the -CHO functional group is attached to a ring the suffix ***-carbaldehyde*** is added, and the carbon attached to that group is C1.

Example 5.1.1

The IUPAC system names are given on top while the common name is given on the bottom in parentheses.

 methanal (formaldehyde)	 ethanal (acetaldehyde)
 pentanal (valeraldehyde)	 2-chloropentanal (α-chlorovaleraldehyde)
 butanal (butyraldehyde)	 3-methylbutanal (isovaleraldehyde)
 cyclohexanecarbaldehyde	 3-methylcyclohexanecarbaldehyde
 3,3-dibromocyclopentanecarbaldehyde	 *trans*-2-methylcyclopentanecarbaldehyde

Naming Ketones

The IUPAC system of nomenclature assigns a characteristic suffix of ***-one*** to ketones. A ketone carbonyl function may be located anywhere within a chain or ring, and its position is usually given by a location number. Chain numbering normally starts from the end nearest the carbonyl group. Very simple ketones, such as propanone and phenylethanone do not require a locator number, since there is only one possible site for a ketone carbonyl function

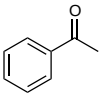
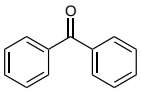
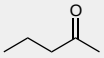
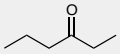
The common names for ketones are formed by naming both alkyl groups attached to the carbonyl then adding the suffix **-ketone**. The attached alkyl groups are arranged in the name alphabetically.

Summary of Ketone Nomenclature rules

1. Ketones take their name from their parent alkane chains. The ending ***-e*** is removed and replaced with ***-one***.
2. The common name for ketones are simply the **substituent groups listed alphabetically + *ketone*.**
3. Some simple ketones are known by their common names. Such as *propanone* which is commonly referred to as *acetone*.

Example 5.1.2

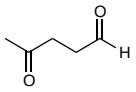
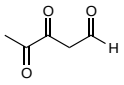
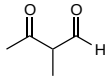
The IUPAC system names are given on top while the common name is given on the bottom in parentheses.

 propanone (acetone)	 acetophenone (methyl phenyl ketone)	 benzophenone (diphenyl ketone)
 2-pentanone (methyl propyl ketone)	 3-methyl-2-butanone (methyl isopropyl ketone)	 3-hexanone (ethyl propyl ketone)

Naming Aldehydes and Ketones in the Same Molecule

As with many molecules with two or more functional groups, one is given priority while the other is named as a substituent. Because aldehydes have a higher priority than ketones, molecules which contain both functional groups are named as aldehydes and the ketone is named as an **"oxo"** substituent. It is not necessary to give the aldehyde functional group a location number, however, it is usually necessary to give a location number to the ketone.

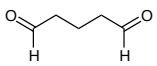
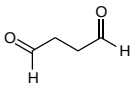
Example 5.1.3

 4-oxopentanal	 3,4-dioxopentanal	 2-methyl-3-oxobutanal

Naming Dialdehydes and Diketones

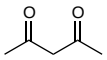
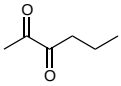
For dialdehydes the location numbers for both carbonyls are omitted because the aldehyde functional groups are expected to occupy the ends of the parent chain. The ending **–dial** is added to the end of the parent chain name.

Example 5.1.4

 pentanedial	 butanedial

For diketones both carbonyls require a location number. The ending **-dione** is added to the end of the parent chain.

Example 5.1.5

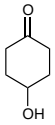
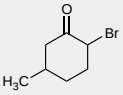
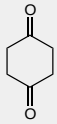
 2,4-pentanedione	 2,3-hexanedione

Naming Cyclic Ketones and Diketones

In cyclic ketones the carbonyl group is assigned location position #1, and this number is not included in the name, unless more than one carbonyl group is present. The rest of the ring is numbered to give substituents the lowest possible location numbers. Remember the prefix **cyclo** is included before the parent chain name to indicate that it is in a ring. As with other ketones the **–e** ending is replaced with the **–one** to indicate the presence of a ketone.

With cycloalkanes which contain two ketones both carbonyls need to be given a location numbers. Also, an **–e** is not removed from the end but the suffix **–dione** is added.

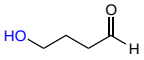
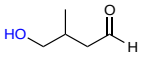
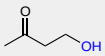
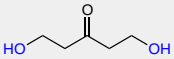
Example 5.1.6

 cyclopentanone	 2-bromocyclopentanone	 4-hydroxycyclohexanone
 2-bromo-5-methylcyclohexanone	 1,4-cyclohexanedione	 1,2-cyclopentanedione

Naming Carbonyls and Hydroxyls in the Same Molecule

When an aldehyde or ketone is present in a molecule which also contains an alcohol functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of alcohols the **OH** is named as a **hydroxyl** substituent. However, the **l** in hydroxyl is generally removed.

Example 5.1.7

 4-hydroxybutanal	 4-hydroxy-3-methylbutanal
 4-hydroxy-2-butanone	 1,5-dihydroxy-3-pentanone

Naming Carbonyls and Alkenes in the Same Molecule

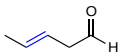
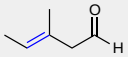
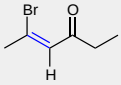
When an aldehyde or ketone is present in a molecule which also contains an alkene functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included.

When carbonyls are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the **-ane** ending)-(an **-en** ending to indicate the presence of an alkene)-(the location number of the carbonyl if a ketone is present)-(either an **–one** or and **-anal** ending).

Remember that the carbonyl has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.

Example 5.1.8

 4-penten-2-one	 *trans*-3-pentenal
 (*E*)-3-methyl-3-pentenal	 (*Z*)-5-bromo-4-hexen-3-one

Aldehydes and Ketones as Fragments

- **Alkanoyl** is the common name of the R-C=O fragment, though the older naming, *acyl*, is still widely used.
- **Formyl** is the common name of the H-C=O fragment.
- **Acetyl** is the common name of the CH_3-C=O- fragment.

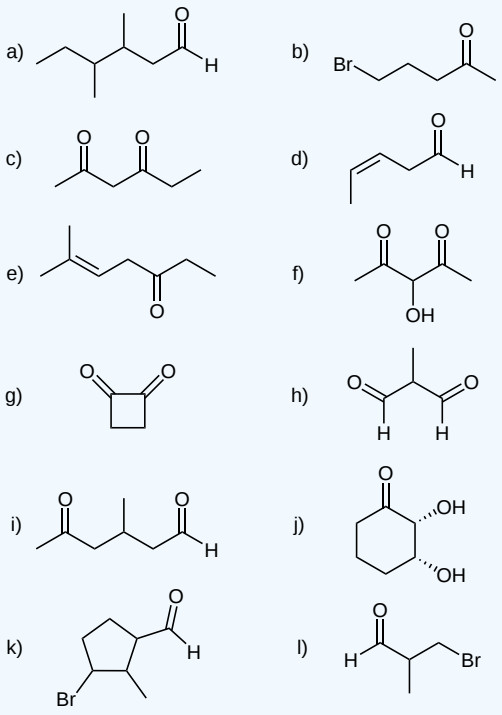
Example 5.1.9

 acetyl chloride	 acetylaldehyde	 formyl fluoride

Exercises

Exercise 5.1.1

Give the IUPAC name for each compound:



Answer

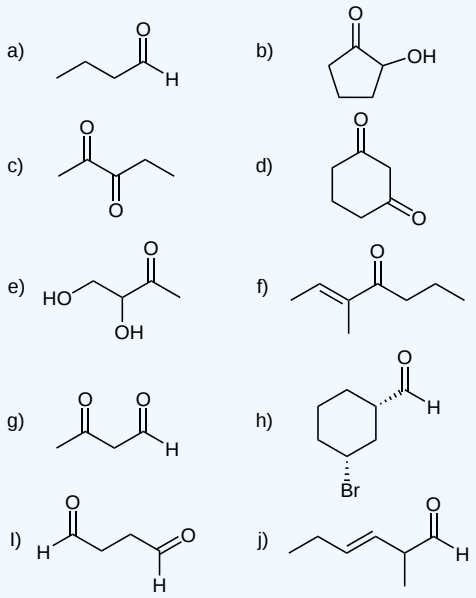
a. 3,4-dimethylhexanal
b. 5-bromo-2-pentanone
c. 2,4-hexanedione
d. *cis*-3-pentenal
e. 6-methyl-5-hepten-3-one
f. 3-hydroxy-2,4-pentanedione
g. 1,2-cyclobutanedione
h. 2-methyl-propanedial
i. 3-methyl-5-oxo-hexanal
j. *cis*-2,3-dihydroxycyclohexanone
k. 3-bromo-2-methylcyclopentanecarboaldehyde
l. 3-bromo-2-methylpropanal

? Exercise 5.1.2

Give the structure corresponding to each IUPAC name:

a. butanal
b. 2-hydroxycyclopentanone
c. 2,3-pentanedione
d. 1,3-cyclohexanedione
e. 3,4-dihydoxy-2-butanone
f. 3-methyl-2-hepten-4-one
g. 3-oxobutanal
h. *cis*-3-bromocyclohexanecarboaldehyde
i. butanedial
j. *trans*-2-methyl-3-hexenal

Answer



References

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry. 5th ed. New York: W.H. Freeman, 2007.
2. Zumdahl, Steven S., and Susan A. Zumdahl. Chemistry. 6th ed. Boston: Houghton Mifflin College Division, 2002.

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5.2: Preparing Aldehydes and Ketones

Objectives

After completing this section, you should be able to

1. describe in detail the methods for preparing aldehydes discussed in earlier units (i.e., the oxidation of primary alcohols and the cleavage of alkenes).
2. write an equation to describe the reduction of an ester to an aldehyde.
   a. identify the product formed when a given ester is reduced with diisobutylaluminum hydride.
   b. identify the reagents and conditions used in the reduction of an ester to an aldehyde.
   c. identify the disadvantages of using diisobutylaluminum hydride to reduce an ester to an aldehyde.
3. describe in detail the methods for preparing ketones discussed in earlier units (i.e., the oxidation of secondary alcohols, the ozonolysis of alkenes, Friedel-Crafts acylation, and the hydration of terminal alkynes).
   a. write an equation to illustrate the formation of a ketone through the reaction of an acid chloride with a dialkylcopper lithium reagent.
   b. identify the ketone produced from the reaction of a given acid chloride with a specified dialkylcopper lithium reagent.
   c. identify the acid chloride, the dialkylcopper lithium reagent, or both, needed to prepare a specific ketone.

Study Notes

You may wish to review the sections in which we discuss the oxidation of alcohols (17.7) and the cleavage of alkenes (8.8). A third method of preparing aldehydes is to reduce a carboxylic acid derivative; for example, to reduce an ester with diisobutylaluminum hydride (DIBAL-H).

There are essentially five methods of preparing ketones in the laboratory. Four of them have been discussed in earlier sections:

1. the oxidation of a secondary alcohol—Section 17.7.
2. the ozonolysis of an alkene—Section 8.8.
3. Friedel-Crafts acylation—Section 16.3.
4. the hydration of a terminal alkyne—Section 9.5.

The "new" method we introduce in this section involves the reaction of an acid chloride with a diorganocopper reagent. The latter substances were discussed in Section 10.9, which you might now wish to review.

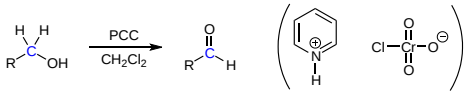
Aldehydes and ketones can be prepared using a wide variety of reactions. Although these reactions are discussed in greater detail in other sections, they are listed here as a summary and to help with planning multistep synthetic pathways. Please use the appropriate links to see more details about the reactions.

Formation of Aldehydes

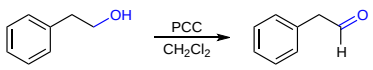
Oxidation of 1º Alcohols to form Aldehydes (Section 17.7)

PCC

Pyridinium chlorochromate (PCC) is a milder version of chromic acid. PCC oxidizes alcohols one rung up the oxidation ladder, from primary alcohols to aldehydes and from secondary alcohols to ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids.

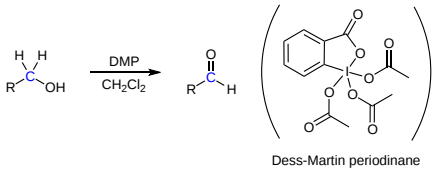


Example oxidation of a primary alcohol to an aldehyde

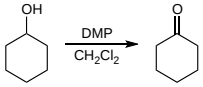


Dess-Martin Periodinane (DMP)

PCC is being replaced in laboratories by Dess-Martin periodinane (DMP), which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983. Similar to PCC, it oxidizes primary alcohols to aldehydes without continuing the oxidation to a carboxylic acid. It can also be used to oxidize secondary alcohols to ketones.

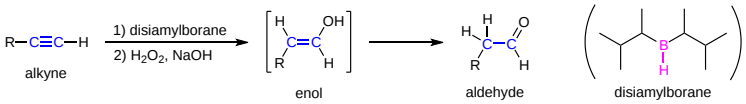


Example oxidation of an alcohol to a ketone using DMP

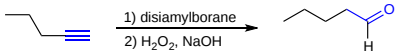


Hydration of an Alkynes to form Aldehydes (Section 9.5)

Anti-Markovnikov addition of a hydroxyl group to an alkyne forms an aldehyde. The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. This can be accomplished by hydroboration-oxidation reactions.

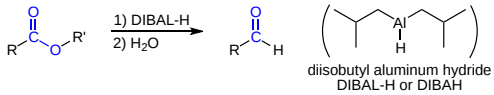


Example reaction of a terminal alkyne with disiamylborane followed by oxidation with hydrogen peroxide and hydroxide converting 1-pentyne to pentanal.



Hydride Reduction of Esters to form Aldehydes (Section 21.8)

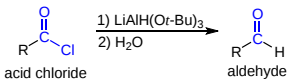
Various hydride sources allow for the partial reduction of some carboxylic acid derivatives to form aldehydes. These reactions are usually carried out at low temperatures (-78 ^oC) to prevent over reaction with the aldehyde product.



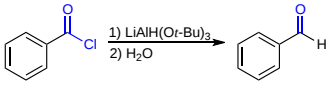
DIBAL-H reduction of methyl benzoate to benzaldehyde

Hydride Reduction of Acid Chlorides to form Aldehydes (Sections 21.6)

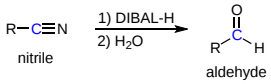
Reduction of acid chlorides to aldehydes requires hydride reagents with reduced reactivity as lithium aluminum hydride will continue reducing to the primary alcohol.



Example reduction of an acid halide to form an aldehyde



Hydride Reduction of a Nitrile to form Aldehydes

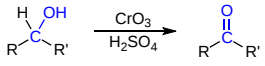


nitrile aldehyde

Formation of Ketones

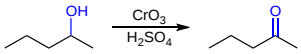
Oxidation of 2° Alcohols to form Ketones (Section 17.7)

Oxidation of 2° alcohols to form ketones typically uses Jones reagent (CrO_3 in H_2SO_4) but many other oxidizing agents can be used.



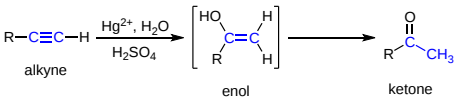
2° alcohol ketone

Example oxidation of a secondary alcohol to a ketone



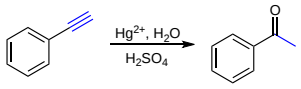
Hydration of Alkynes to form Ketones (Section 9.4)

The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. Markovnikov addition of a hydroxyl group to an alkyne forms a ketone.



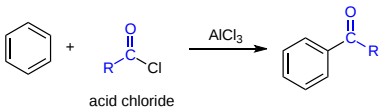
alkyne enol ketone

Example reaction of an alkyne with Hg^{2+}, H_2O, and H_2SO_4 to give a ketone



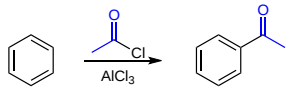
Friedel-Crafts Acylation to form a Ketone (Section 16.3)

Aromatic ketones can synthesized through Friedel–Crafts acylation of an aromatic ring with an acid chloride. Aluminum chloride ($AlCl_3$) is used as a Lewis acid catalyst.



acid chloride

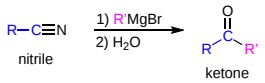
Example of Friedel-Crafts acylation to form a ketone from benzene.



benzene methyl phenyl ketone

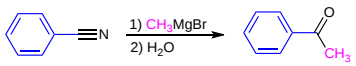
Reaction of Grignard reagents with nitriles to form ketones (Section 20.7)

Grignard reagents can attack the electophillic carbon in a nitrile to form an imine salt. This salt can then be hydrolyzed to become a ketone.



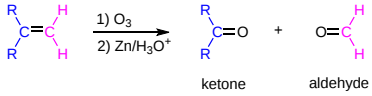
nitrile ketone

Example of Grignard addition to a nitrile to give a ketone.

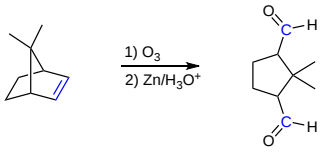


Alkenes can be Cleaved using Ozone (O_3) to form Aldehydes and/or Ketones (Section 8.8)

Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (O_3), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen.

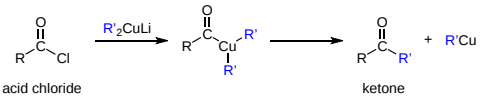


Example ozonolysis of an alkene to form aldehydes.

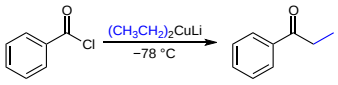


Organocuprate Reagents Convert Acid Chlorides to Ketones (Section 21.4)

An important reaction exhibited by lithium alkylcopper reagents (Gilman Reagents), is the nucleophilic addition to acid chlorides. Gilman reagents are a source of carbanion like nucleophiles similar to Grignard and Organolithium reagents. However, the reactivity of organocuprate reagents is slightly different and this difference is exploited to allow for a single nucleophilic addition to form a ketone.



Example of organocuprate addition to an acid chloride to generate a ketone.



? Exercise 5.2.1

What reagents would be required to prepare hexanal from the following starting materials?

a. $CH_3CH_2CH_2CH_2CH_2CH_2OH$
b. $CH_3CH_2CH_2CH_2CH_2CH{=}CH_2$
c. $CH_3CH_2CH_2CH_2CO_2CH_3$
d. $CH_3CH_2CH_2CH{=}CH_2$

Answer

a. Dess–Martin periodinane or PCC in CH_2Cl_2
b. 1. O_3, 2. Zn/H_3O^+
c. 1. DIBAH 2. H_2O
d. 1. BH_3 2. $H_2O_2/NaOH$; 2. Dess–Martin periodinane or PCC

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5.3: Oxidation of Aldehydes and Ketones

Objectives

After completing this section, you should be able to

- write an equation for the oxidation of an aldehyde using
  - CrO_3/sulphuric acid.
  - Tollens reagent.
- explain the difference in structure which makes aldehydes susceptible to oxidation and ketones difficult to oxidize.
- identify the carboxylic acid produced when a given aldehyde is oxidized.
- identify the aldehyde, the oxidizing agent, or both, needed to prepare a given carboxylic acid.

Key Terms

Make certain that you can define, and use in context, the key term below.

- Tollens reagent

Study Notes

An important difference between aldehydes and ketones is the ease with which the latter can be oxidized. Tollen's reagent is a classical organic laboratory technique to test for the presence of an aldehyde. The reagent consists of silver(I) ions dissolved in dilute ammonia. When the aldehyde is oxidized, the silver(I) ions are reduced to silver metal. When the reaction is carried out in a test-tube, the metallic silver is deposited on the walls of the tube, giving it a mirrorlike appearance. This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

Why do aldehydes and ketones behave differently?

Aldehydes have a proton attached to the carbonyl carbon which can be abstracted, allowing them to be easily oxidized to form carboxylic acids. The lack of this hydrogen, makes ketones generally inert to these oxidation conditions. Nevertheless, ketones can be oxidized but only under extreme conditions.

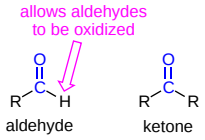
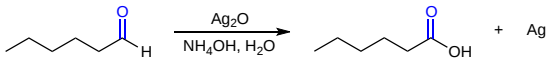


Figure **5.3.1**: This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

A significant distinction between aldehydes and ketones lies in their susceptibility to oxidation, with aldehydes being more easily oxidized than ketones. One of the classic methods for identifying aldehydes in the laboratory is through the use of **Tollen's reagent** which consists of silver(I) ions dissolved in dilute ammonia. When an aldehyde is present, it undergoes oxidation, causing the silver(I) ions to be reduced to metallic silver. This reduction results in the deposition of silver on the surface of the test tube, forming a reflective, mirror-like coating. This reaction is commonly referred to as the "silver mirror test," and it serves as a reliable way to distinguish aldehydes from ketones. Ketones, in contrast, do not react with Tollen's reagent, making this test specific for aldehydes.



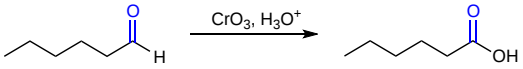
Figure 5.3.2: Tollens test for Aldehyde. The left side is positive (silver mirror) and the right side is negative.



Oxidation of hexanal to form hexanoic acid using Tollens Reagent

Oxidation of Aldehydes

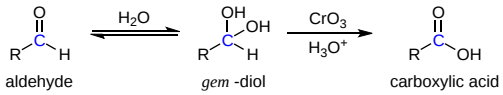
There are a wide variety of reagents which can cause the oxidation of aldehydes to carboxylic acids. The most common reagent for this conversion is CrO_3 in aqueous acid also called **Jones Reagent**. This reaction generally gives good yields at room temperature.



Example of the oxidation of hexanal to form hexanoic acid using Jones Reagent

Mechanism

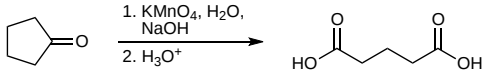
The oxidation of aldehydes occur through the reversible nucleophilic addition of water to the carbonyl to form a gem-diol functional group. This addition reaction is discussed in greater detail in Section 19.5. One of the OH groups of the *gem*-diol is oxidized to create a carbonyl (C=O) thereby forming a carboxylic acid.



aldehyde *gem* -diol carboxylic acid

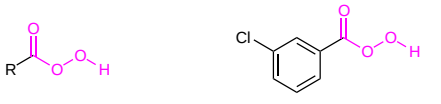
Oxidation of Ketones and Baeyer-Villiger Oxidation

Because ketones do not have hydrogen atom attached to their carbonyl, they are resistant to oxidation. Only very strong oxidizing agents such as potassium manganate(VII) (potassium permanganate) solution oxidize ketones. However, this type of powerful oxidation occurs with cleavage, breaking carbon-carbon bonds and forming two carboxylic acids. Because of this destructive nature this reaction is rarely used.

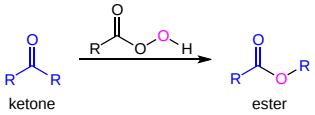


Oxidation of cyclopentanone to form pentanedioic acid

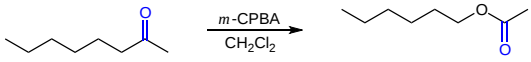
Peroxycarboxylic acids, such as **meta-chloroperoxybenzoic acid (mCPBA)**, are capable of oxidizing ketones to esters in a reaction known as the **Baeyer-Villiger oxidation**. Baeyer-Villiger oxidation has considerable synthetic utility because ketones normally are difficult to oxidize without degrading the structure to smaller fragments.



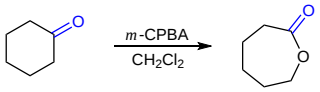
peroxycarboxylic acid *meta* -chloroperoxybenzoic acid



Baeyer-Villiger oxidations can be used with both straight chain ketones and cyclic ketones as shown in the following examples.



Baeyer-Villiger Oxidation of 2-octanone to form hexyl ethanoate

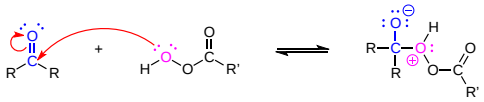


Baeyer-Villiger Oxidation of cyclohexanone to 6-hexanolactone

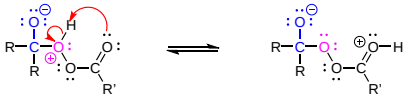
Mechanism

The mechanism of the Baeyer-Villiger oxidation has been studied extensively and is of interest because it involves a rearrangement step in which a substituent group (R) moves from a carbon to an oxygen. In the first step, one oxygen from the peroxy carboxylic acid adds to the carbonyl group of the ketone. The adduct has multiple oxygen atoms on which protons can reside. An intramolecular proton transfer followed by protonation allows for generation of the Criegee intermediate. Migration of an alkyl group and elimination of a carboxylic acid, R^1CO_2H, then occur in the fourth step. This generates a protonated form of the ester product, which is deprotonated in the final step of the mechanism.

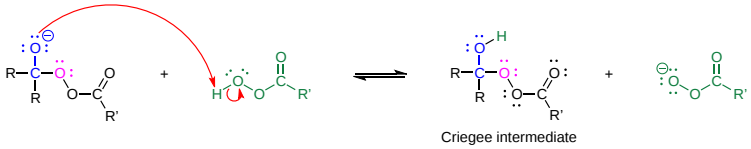
Step 1: Nucleophilic attack on the carbonyl



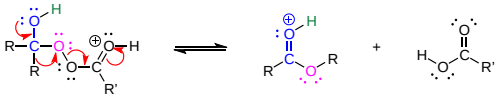
Step 2: Intramolecular Proton Transfer



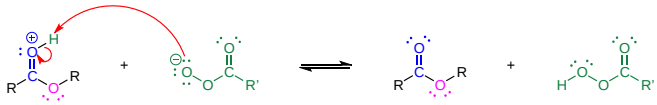
Step 3: Protonation of the alkoxide



Step 4: Migration of an Alkyl Group



Step 5: Deprotonation



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5.4: Nucleophilic Addition Reactions of Aldehydes and Ketones

Objectives

After completing this section, you should be able to

- give a general description of the nucleophilic addition reactions of aldehydes and ketones, identifying the two possible courses (or variations) that such reactions can take after the initial attack by the nucleophile.
- explain why, in general, aldehydes undergo nucleophilic addition reactions more readily than do ketones, and determine which of two given aldehydes or ketones will react most readily in such reactions.

Key Terms

Make certain that you can define, and use in context, the key term below.

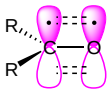
- nucleophilic addition reaction

Study Notes

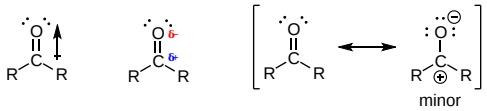
We have already discussed electrophilic addition reactions at some length; in this section nucleophilic addition reactions will be presented. Nucleophilic addition reactions involve the initial attack of a nucleophile on the slightly positive carbon center of the carbonyl group.

Introduction

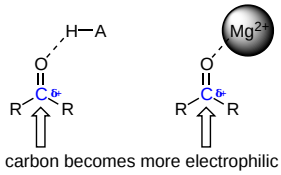
Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming three sigma bonds by overlapping with orbitals from the R groups (carbons or hydrogens) and an sp^2 hybrid orbital from oxygen. Due to the sp^2 orbitals, these three bonds adopt trigonal planar geometry seen in carbonyls. The carbonyl carbon's remaining unhybridized 2p orbital is perpendicular to this plane, and forms a ‘side-by-side’ pi bond by overlapping with a 2p orbital from the carbonyl oxygen.



The carbon-oxygen double bond is polar since oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow (pointing toward the more electronegative atom), or by showing the oxygen as holding a partial negative charge and the carbonyl carbon with a partial positive charge. A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pi bond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty 2p orbital and a full positive charge.



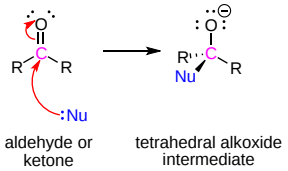
The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond’s polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen. The same effect can also be achieved if a Lewis acid, such as a magnesium ion (Mg^{2+}), is located near the carbonyl oxygen.



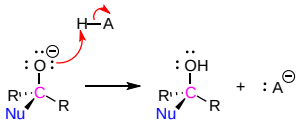
Nucleophilic Addition to a Carbonyl

Most important reactions involving carbonyl groups characteristically have a nucleophilic addition as part of their mechanism. The generic mechanism for the nucleophilic addition of a negatively charged nucleophile to a carbonyl is shown below.

In the first step of the nucleophilc addition mechanism, the nucleophile forms a bond with the the electrophilic C=O carbon atom. This causes the rehybridization of the carbonyl carbon from sp^2 to sp^3. These reactions differ from nucleophilic substitution reactions since neither aldehydes nor ketones have a leaving group. Instead electrons in the pi bond are pushed up to the electronegative oxygen atom forming a tetrahedral alkoxide intermediate.

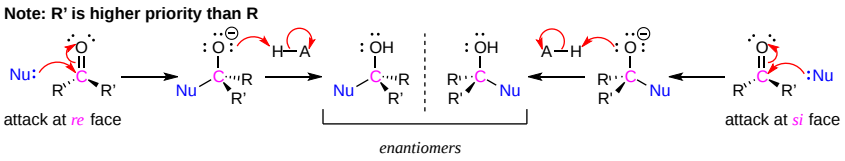


In the second step of the mechanism, the alkoxide is protonated by the addition of an acid to form an alcohol.



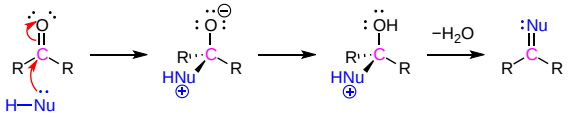
Stereochemistry of Nucleophilic Addition to a Carbonyl

When the two groups adjacent to a carbonyl are not the same, we can distinguish between the **re** and **si** 'faces' of the planar structure. The concept of a trigonal planar group having two distinct faces comes into play when we consider the stereochemical outcome of a nucleophilic addition reaction. Notice that in the course of a carbonyl addition reaction, the hybridization of the carbonyl carbon changes from sp^2 to sp^3, meaning that the bond geometry changes from trigonal planar to tetrahedral. If the two R groups are not equivalent, then a chiral center is created upon addition of the nucleophile. The configuration of the new chiral center depends upon which side of the carbonyl plane the nucleophile attacks from. Reactions of this type often result in a 50:50 racemic mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant, depending on the structure of the reactants and the conditions under which the reaction takes place.



Nucleophilic Addition of a Neutral Nucleophile

Neutral nucleophiles can also undergo nucleophilic addition to carbonyls. The mechanism is slightly different than with a negatively charged nucleophile. The presence of an additional hydrogen atom in the nucleophile allows for the the carbonyl oxygen to be completely removed as water and a C=Nu bond to be formed.



Relative Reactivity of Aldehydes and Ketones to Nucleophilic Addition

In general, aldehydes are more reactive than ketones because they have a greater polarization of the carbonyl bond. The primary carbocation formed in the polarizing resonance structure of an aldehyde (shown below) is less stable and therefore more reactive than the secondary carbocation formed in a similar resonance structure formed by a ketone. The stability difference in these resonance structures is due to the extra alkyl group present in the ketone. Alky groups stabilize carbocations through induction as discussed in Section 7.11.

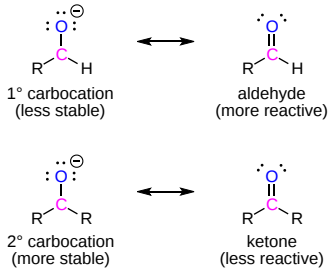


Figure 5.4.1). The carbonyl carbon of formaldehyde is more positive (more blue) and therefore more reactive towards nucleophlic addition than the carbonyl carbon in acetone which is less positive (more green). As discussed above, electron-attracting groups can further increase its positive character of a carbonyl carbon and thereby facilitate nucleophilic addition.

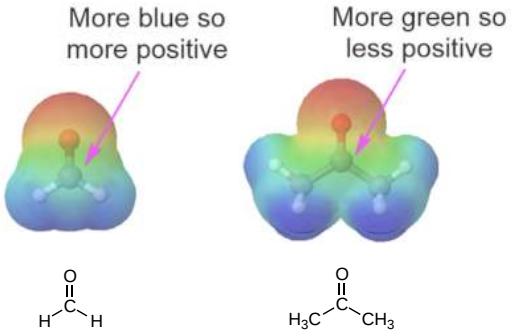


Figure 5.4.1: The Electrostatic Potential Map of Formaldehyde (Left) and Acetone (Right)

Another reason aldehydes tend to me more reactive to nucleophilic addition than ketones is steric hindrance. Ketones have two alkyl groups attached to their carbonyl carbon while aldehydes only have one. This means nucleophiles have a less sterically hindered path when attacking the carbonyl carbon of an aldehyde. Also, the transition state of the rate determining step for formation of the tetrahedral intermediate is less sterically crowded, lower in energy, and more kinetically favorable for an aldehyde than a ketone. The difference in sterics in the carbonyl carbon of an aldehyde and a ketone is easily seen when comparing the space filling models of acetaldehyde and acetone (Figure 5.4.2).

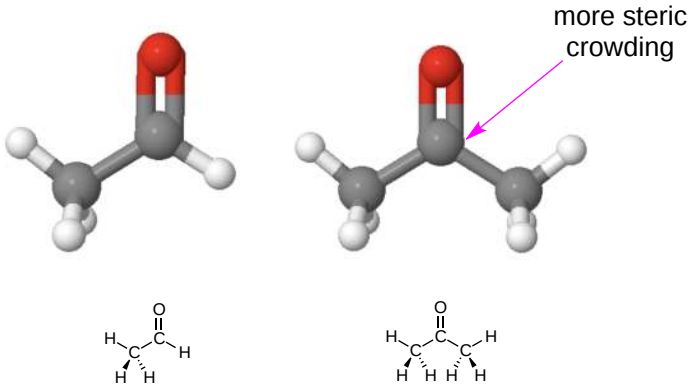
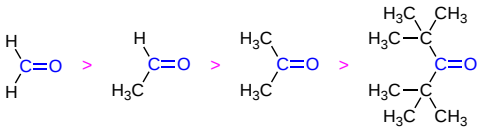


Figure 5.4.2: The Relative Steric Crowding of Acetaldehyde (Left) and Acetone (Right)

In fact, reactivity of a carbonyl toward nucleophilic addition decreases with increasing bulkiness of carbonyl substituents, as seen in the following series.

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Exercise 5.4.1

Benzaldehyde is less reactive to nucleophilic addition reactions than aliphatic aldehydes. Explain.

Answer

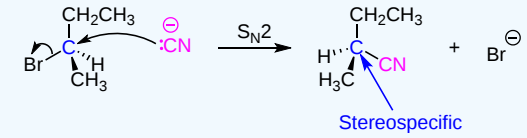
Aromatic rings act as an electron-donating group due to resonance effect. Electron donating groups make the carbonyl group in benzaldehyde less electrophilic.

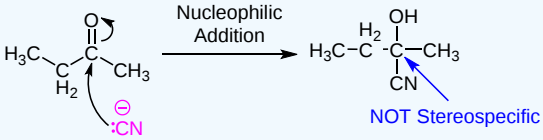
Exercise 5.4.2

Compare the mechanisms of an S_N2 reaction between 2-bromobutane and cyanide and the tetrahedral complex formation between 2-butanone and cyanide.

Answer

In the S_N2 reaction the cyanide nucleophilic must undergo back side attack. This causes an inversion of stereochemistry and creates a product which is stereospecific. The carbonyl used in the nucleophilic addition is trigonal planar. This means the cyanide nucleophile can attack from either plane. This tends to create a racemic mixture of enantiomers.





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5.5: Nucleophilic Addition of Hydride - Alcohol Formation

Objectives

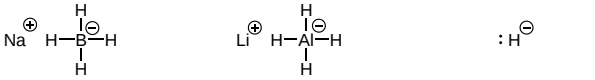
After completing this section, you should be able to

1. write the general mechanism of nucleophilic addition of the “hydride ion” in the reduction of a carbonyl group.

Reduction of Carbonyls to Alcohols Using Metal Hydrides

We saw in Alcohol's Chapter that the most common method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of carbonyl compounds. Like carbon, hydrogen can be used as a nucleophile if it is bonded to a metal in such a way that the electron density balance favors the hydrogen side. A hydrogen atom that carries a net negative charge and bears a pair of unshared electrons is called a **hydride ion.** How much negative charge density resides on hydrogen depends on the difference in electronegativity between hydrogen and the metal it’s bonded to.

The most common sources of the hydride anion ($^{-}$:H) are **lithium aluminum hydride ($LiAlH_4$)** and **sodium borohydride ($NaBH_4$)**. Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Also, each are capable of delivering up to 4 hydride equivalents. The reaction equation of hydride reductions are not typically balanced (*i.e.* it does not specify the stoichiometry of the reagent). Because aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making $LiAlH_4$ a stronger reducing agent.



sodium borohydride | lithium aluminum hydride | hydride nucleophile

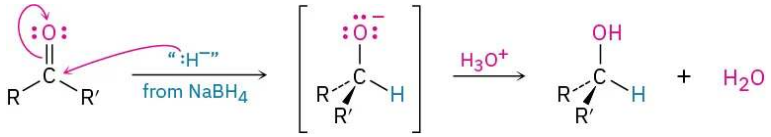
Aldehydes are reduced with sodium borohydride ($NaBH_4$) to give primary alcohols, and ketones are reduced similarly to give secondary alcohols.



Aldehyde **1° Alcohol** **Ketone** **2° Alcohol**

Carbonyl reduction occurs by a typical nucleophilic addition mechanism under basic conditions. Although the details of carbonyl-group reductions are complex, $LiAlH_4$ and $NaBH_4$ act as if they were donors of hydride ion nucleophile, **:**H^{-}, and the initially formed alkoxide ion intermediate is then protonated by addition of aqueous acid. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction.

The reaction is effectively irreversible because the reverse process would require the expulsion of a very poor leaving group.

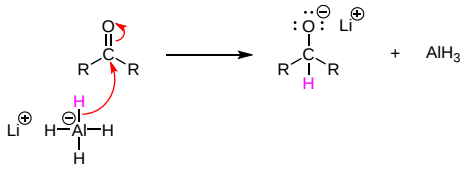


Mechanism for the Reduction of Carbonyls using $LiAlH_4$

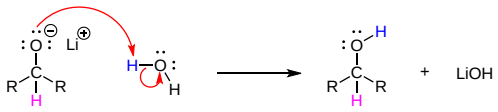
Both $NaBH_4$ and $LiAlH_4$ act as if they were a source of hydride. The hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and forming a tetrahedral alkoxide ion intermediate. The alkoxide ion is subsequently converted to an alcohol by reaction with a proton source (such as water). In the $LiAlH_4$ reduction, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the borohydride reduction the hydroxylic solvent system achieves this hydrolysis automatically. The lithium, sodium, boron and aluminum end up as soluble inorganic salts.

Note! The reaction and the corresponding mechanism of hydride reductions of carbonyls is fairly complicated. The following mechanism has been simplified for easier understanding.

Step 1: Nucleophilic attack to form a tetrahedral alkoxide intermediate



Step 2: Protonation to form an alcohol



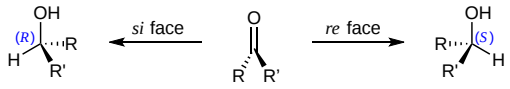
Properties of Hydride Sources

Two practical sources of hydride-like reactivity are the complex metal hydrides lithium aluminum hydride (LiAlH4) and sodium borohydride (NaBH4). These are both white (or near white) solids, which are prepared from lithium or sodium hydrides by reaction with aluminum or boron halides and esters. Lithium aluminum hydride is by far the most reactive of the two compounds, reacting violently with water, alcohols and other acidic groups with the evolution of hydrogen gas. The following table summarizes some important characteristics of these useful reagents.

Reagent	Preferred Solvents	Functions Reduced	Reaction Work-up
Sodium Borohydride $NaBH_4$	ethanol; aqueous ethanol 15% NaOH; diglyme avoid strong acids	aldehydes to 1°-alcohols ketones to 2°-alcohols inert to most other functional groups	**1)** simple neutralization **2)** extraction of product
Lithium Aluminum Hydride $LiAlH_4$	ether; THF avoid alcohols and amines avoid halogenated compounds avoid strong acids	aldehydes to 1°-alcohols ketones to 2°-alcohols carboxylic acids to 1°-alcohols esters to alcohols epoxides to alcohols nitriles & amides to amines halides & tosylates to alkanes most functional groups react	**1)** careful addition of water **2)** remove aluminum salts **3)** extraction of product

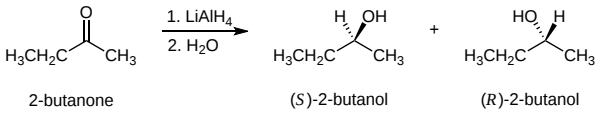
Limitations of Hydride Reductions

A hydride addition to an asymmetric ketone has the possibility of forming a chiral carbon that is not stereospecific. Attack by the hydride can occur from either the *re* or the *si* face of an asymmetrical carbonyl, leading to a mixture of the (*S*) and (*R*) alcohols. These reactions can be made to have stereochemical control by using several different methods including stereospecific reagents, sterics, and by the affect of an enzyme during a biological reduction.



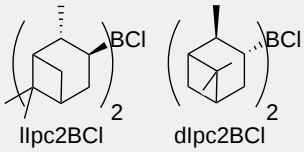
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Example



Something Extra

As previously mentioned, a hydride reduction using $LiAlH_4$ or $NaBH_4$ has the possibility of forming R or S stereoisomers of a chiral carbon in the product. An important area of organic synthesis is developing stereoselective methods that yield only one of the possible R and S stereocenters. Stereoselective hydride reductions can be accomplished by using the reagent **Diisopinocampheylchloroborane (Ipc_2BCl).** The two versions of this reagent, (+)-Ipc_2BCl & (−)-Ipc_2BCl, allow for either an R or S stereocenter to be created during the hydride reduction. Ipc_2BCl was first reported in 1961 by Zweifel and Brown and is considered a pioneering work in stereoselective synthesis using boranes. Herbert Charles Brown (1912-2004) was an American chemist who received the Nobel Prize in Chemistry in 1979 for his work with organoboranes.

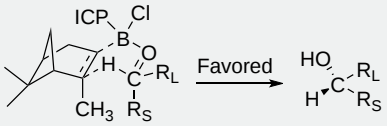


Ipc_2BCl allows for stereoselectivity by changing the mechanism of the hydride reduction and introducing sterics to the reaction. Asymmertric carbonyls which have a sterically large substituent (R_L) and a sterically small substituent (R_S) will have a preferred orientation during this reaction causing a particular stereoisomer to be formed.

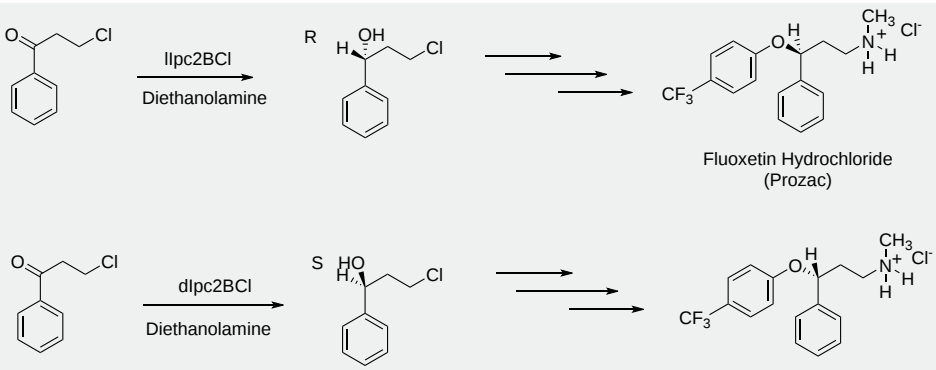
Asymmetric Carbonyl



RL = Sterically Large Substituent
RS = Sterically Small Substituent



Stereochemical control during a synthesis is important because a particular stereoisomer is usually the target molecular. This is particularly true in the synthesis of pharmaceuticals, where one stereoisomer often has different biological properties and another. An example of this is the drug Fluoxetine (Prozac), which was shown to have superior biological properties when the R isomer of its single chiral carbon was tested. Fluoxetine is an antidepressant given FDA approval in 1987. in 2010, over 24.4 million prescriptions for fluoxetine were filled in the United States alone. Currently, there are many different synthesis pathways to Fluoxetine. A fragment of one pathway is shown below which uses the two Ipc_2BCl versions to synthesis both the R and S enantiomers of Fluoxetine.

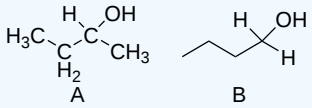


Exercise 5.5.1

Please draw the products of the reaction of the following substrates with LAH:

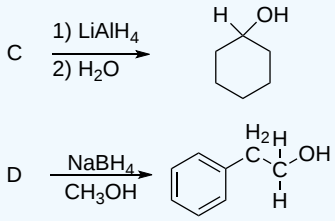
a- 2-butanone b-butanal

Answer

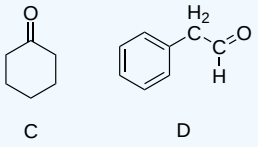


Exercise 5.5.2

Draw the structure of the molecule which must be reacted to produce the product.

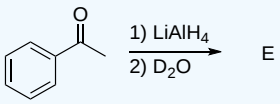


Answer

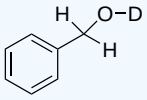


Exercise 5.5.1

Deuterium oxide (D_2O) is a form of water where the hydrogens have been replaced by deuteriums. For the following $LiAlH_4$ reduction the water typically used has been replaced by deuterium oxide. Please draw the product of the reaction and place the deuterium in the proper location. Hint! Look at the mechanism of the reaction.



Answer



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5.6: Nucleophilic Addition via Organometallic Reactions - Alcohol Formation

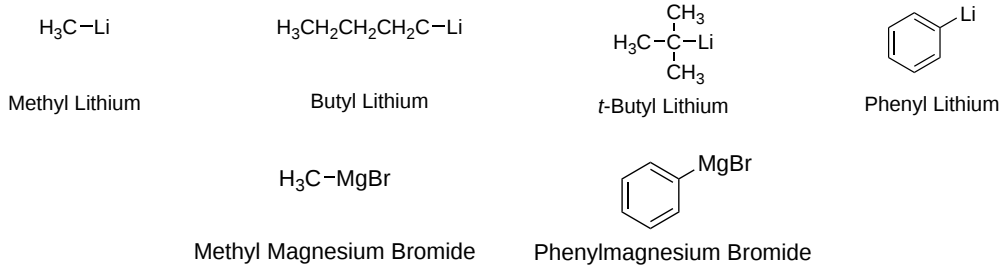
Objectives

After completing this section, you should be able to

1. write the equation to describe the nucleophilic addition reaction between a Grignard reagent and a carbonyl group.

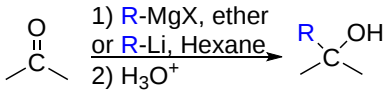
Organometallic Reactions

Just as aldehydes and ketones undergo nucleophilic addition with hydride ion to give alcohols, they undergo a similar addition with Grignard reagent nucleophiles, $R:^{-}\ ^{+}MgX$. Lithium and magnesium metals reduce the carbon-halogen bonds of alkyl halides to form **organolithium reagents** and **Grignard reagents** respectively. In both cases, the carbon bonds to the metal and has characteristics similar to a carbanion ($R:^{-}$) nucleophile. Some common organometallic reagents are shown below:



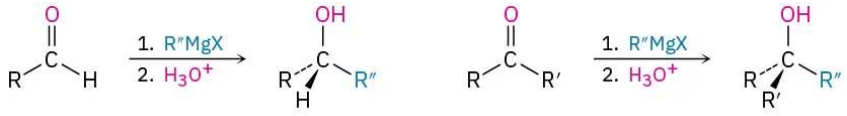
Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. Aldehydes and ketones will undergo nucleophilic addition with organolithium and Grignard reagent nucleophiles.

General Reaction



Addition of Grignard Reagents, RMgX

The nucleophilic carbon in the organometallic reagents forms a C-C single bond with the electrophilic carbonyl carbon. An alkoxide ion intermediate is formed which becomes an alcohol with subsequent protonation with an acid. Both Grignard and organolithium reagents will perform these reactions. Aldehydes give secondary alcohols when reacting with Grignard reagents in an ether solution, and ketones give tertiary alcohols.



Aldehyde **2° Alcohol** **Ketone** **3° Alcohol**

Mechanism for the Addition of Grignard Reagents to Carbonyls

As shown in Figure 5.6.1, 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. Like reduction, Grignard additions are effectively irreversible because a carbanion is too poor a leaving group to be expelled in a reversal step.

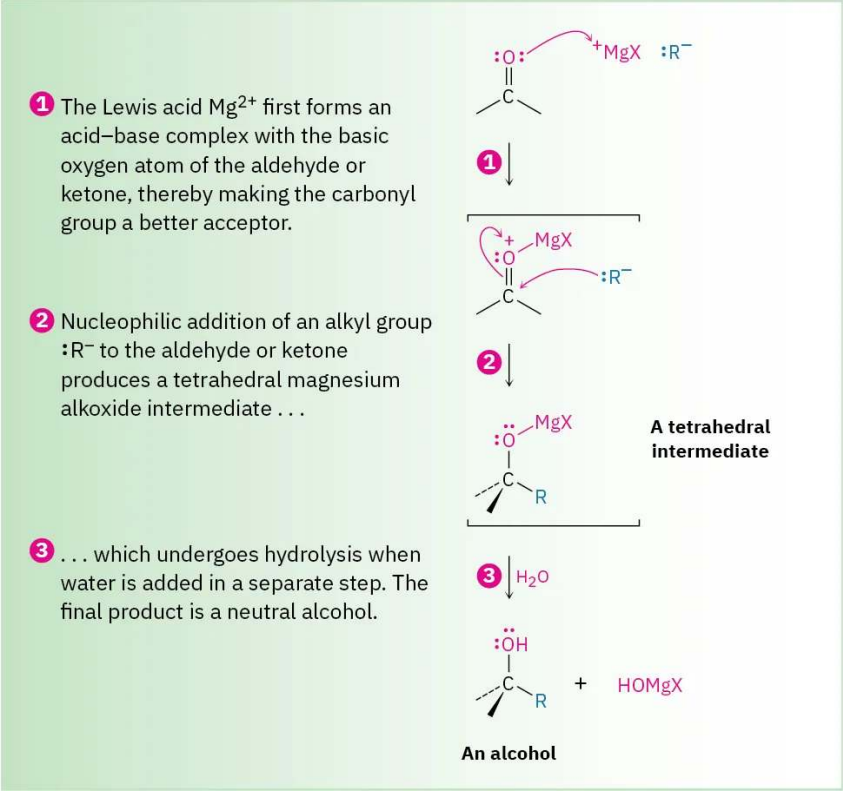
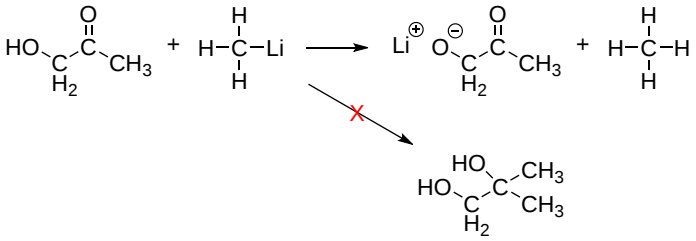


Figure 5.6.1: Mechanism of the Grignard reaction. Complexation of the carbonyl oxygen with the Lewis acid Mg^{2+} and subsequent nucleophilic addition of a carbanion to an aldehyde or ketone is followed by protonation of the alkoxide intermediate to yield an alcohol.

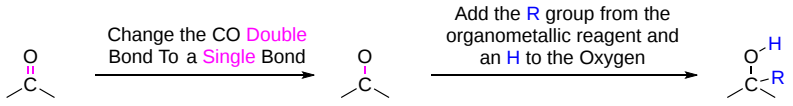
Limitation of Organometallic Reagents

Grignard and organolithium reagents are powerful bases. Because of this, they cannot be used as nucleophiles on compounds that contain acidic hydrogens. If they are used they will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used with organometallic reagents includes: alcohols, amides, 1º amines, 2º amines, carboxylic acids, and terminal alkynes.

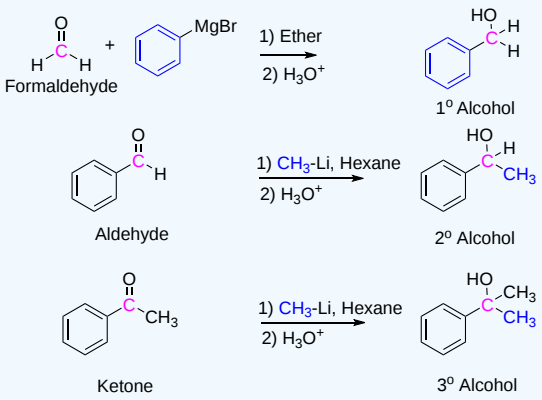


Predicting the Product of Addition of Organometallic Reagents to Aldehydes and Ketones

During the reaction, the C=O double bond in the reactant forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which was originally in the carbonyl. The carbon will gain whatever R group was part of the organometallic reagent and the oxygen will gain a "H".



Example 5.6.2

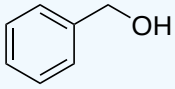


Planning an Alcohol Synthesis Using a Grignard Reaction

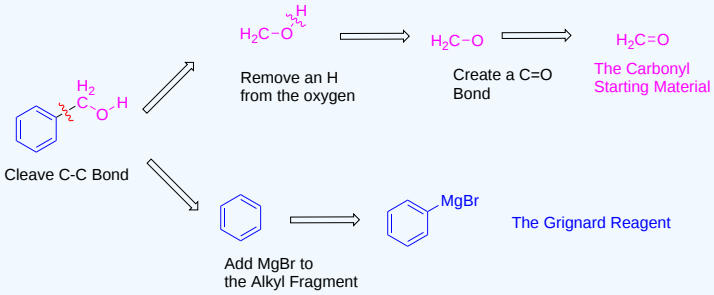
The nucleophilic addition of a Grignard reagent to a carbonyl is a powerful tool in organic synthesis because if forms a C-C bond. Also, there is often more than one way to make a given target molecule. Primary alcohols have one C-C bond which can be retrosynthetically cleaved. Secondary alcohols have two and tertiary alcohols have three.

Example 5.6.2

What reagents are required to make the following molecule using a Grignard Reaction?

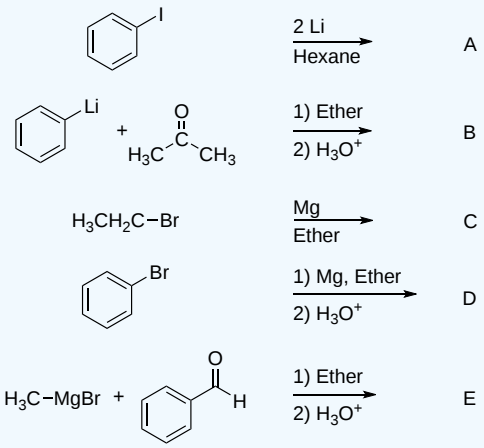


Solution

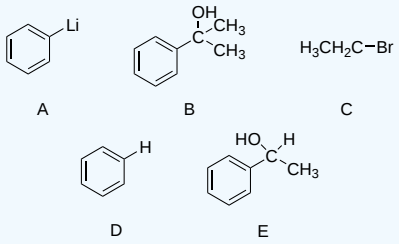


\Exercise 5.6.1

Please write the product of the following reactions.

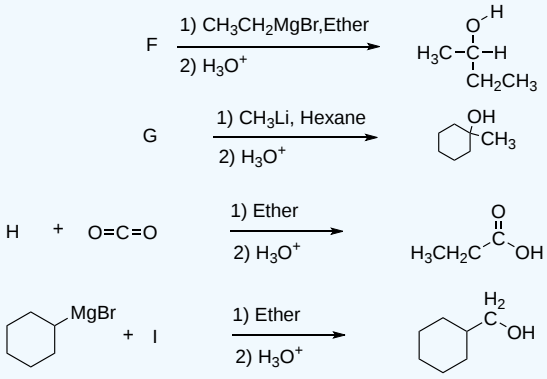


Answer

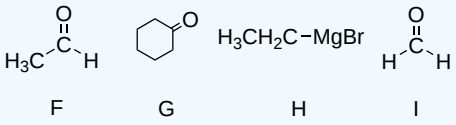


Exercise 5.6.2

Please indicate the starting material required to produce the product.



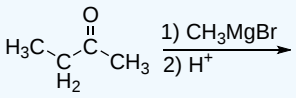
Answer



Exercise 5.6.3

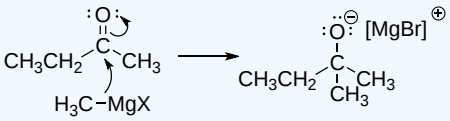
Give a detailed mechanism and the final product of this reaction

https://chem.libretexts.org/@go/page/515155

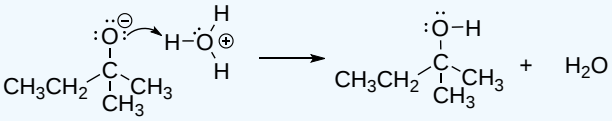


Answer

Step 1: Nucleophilic attack

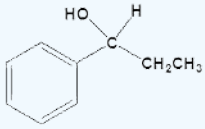


Step 2: Protonation

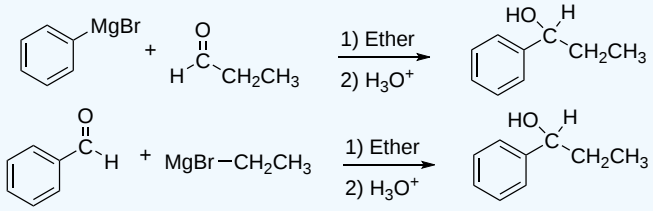


? Exercise 5.6.4

How two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.



Answer



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5.7: Nucleophilic Addition of HCN - Cyanohydrin Formation

Objectives

After completing this section, you should be able to

1. write an equation to describe the formation of a cyanohydrin from an aldehyde or ketone.
2. identify the cyanohydrin formed from the reaction of a given aldehyde or ketone with hydrogen cyanide.
3. identify the aldehyde or ketone, the reagents, or both, needed to prepare a given cyanohydrin.
4. write the detailed mechanism for the addition of hydrogen cyanide to an aldehyde or ketone.

Key Terms

Make certain that you can define, and use in context, the key term below.

- cyanohydrin

Study Notes

For successful cyanohydrin formation it is important to have free cyanide ions available to react with the ketone or aldehyde. This can be achieved by using a salt (e.g. KCN or NaCN) or a silylated (e.g. Me_3SiCN) form of cyanide under acidic conditions or by using HCN with some base added to produce the needed CN^- nucleophile.

Hydrogen cyanide (HC≡N), adds reversibly to aldehydes and many ketones forming hydroxyalkanenitrile adducts commonly known and as **cyanohydrins**. Cyanohydrins have the structural formula of $R_2C(OH)CN$. The "R" on the formula represents an alkyl group, aryl group, or hydrogen.

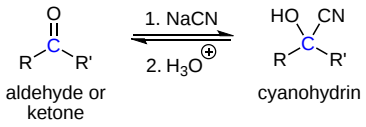
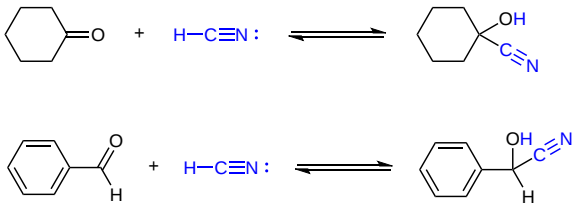


Figure 5.7.1: General Reaction of Cyanohydrin Formation

An important feature of cyanohydrin formation is that it requires a basic catalyst. Since hydrogen cyanide itself is a weak acid (pK_a = 9.25), the best results occur when a small amount of a strong base activates hydrogen cyanide by converting it to **cyanide ion ($^-$C≡N)**, which can function as a carbon nucleophile. In the absence of base, the reaction does not proceed, or is at best very slow. Cyanohydrin formation is weakly exothermic, and is favored for aldehydes, and unhindered cyclic and methyl ketones.



Examples of Cyanohydrin Formation

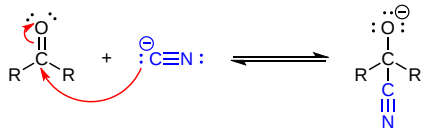
Hydrogen cyanide (HCN) is hazardous to handle because it is highly toxic. Therefore in many syntheses of cyanohydrins, HCN is created *in situ* by adding a strong acid to a mixture of sodium cyanide and the carbonyl compound, so that hydrogen cyanide is generated *in situ*. The amount of acid added should be insufficient to consume all the cyanide ion, therefore sufficiently alkaline conditions are maintained for rapid addition.

Mechanism of Cyanohydrin Formation

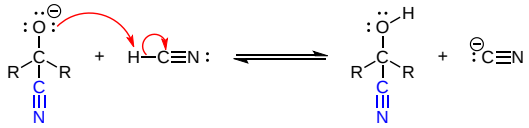
In the first step of the mechanism, the cyanide ion acts as a nucleophile and forms a C-C bond with the electrophillic carbonyl carbon. The two electrons in the carbonyl pi bond are pushed on to the electronegative oxygen forming a tetrahedral alkoxide ion

intermediate. In the second step, the alkoxide ion is protonated by HCN which regenerates the cyanide ion.

Step 1: Nucleophilic attack

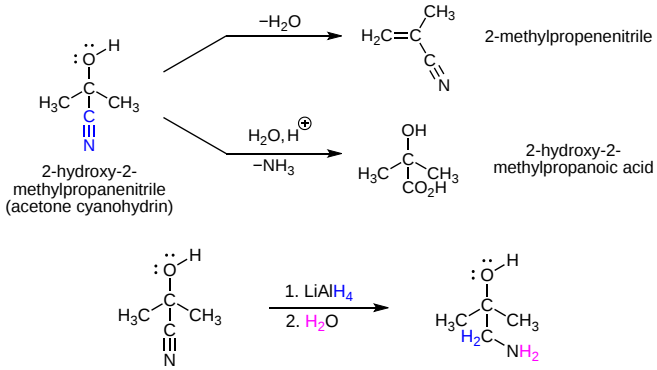


Step 2: Protonation



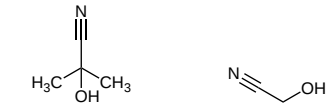
Further Chemistry of Cyanohydrins

Cyanohydrin functional groups often prove useful because of the further chemistry that can be carried out due to the presence of a hydroxyl and a nitrile functionality. In particular, dehydration can convert the hydroxyl group into an alkene (Section 17.6). The nitrile can be converted into a carboxylic acid function group through reaction with a hot acidic aqueous solution (Section 20.7). Also, the nitrile can be reduced by the addition of $LiAlH_4$ to form a primary amine.



Other Cyanohydrins

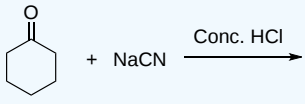
Other interesting cyanohydrins are: **acetone cyanohydrin**, and **glycolonitrile**.



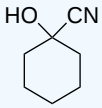
Acetone cyanohydrin has the structure, $(CH_3)_2C(OH)CN$, and is used in the production of methyl methacrylate (also known as acrylic). Glycolonitrile is an organic compound with the structural formula of $HOCH_2CN$, which is the simplest cyanohydrin that is derived by formaldehydes.

? Exercise 5.7.1

Complete the following reaction for cyanohydrins.

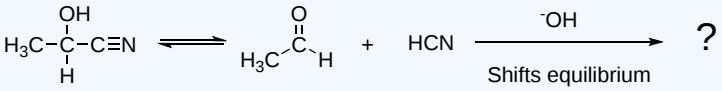


Answer

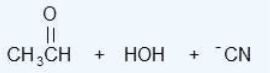


Exercise 5.7.2

Complete the following reaction for cyanohydrins.



Answer



Exercise 5.7.3

True or False: For a cyanohydrin to form, a *fast addition* of strong acid to cyanide salt is carried out to convert the salt into HCN.

Answer

False, slow addition

Exercise 5.7.4

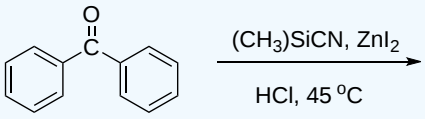
True or False: Cyanohydrin reactions are *irreversible*.

Answer

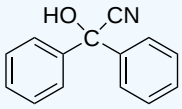
False, reversible

Exercise 5.7.5

What is the product for the overall reaction?



Answer



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5.8: Nucleophilic Addition of Phosphorus Ylides - The Wittig Reaction

Objectives

After completing this section, you should be able to

- write an equation to illustrate the formation of an ylide (phosphorane).
- write an equation to illustrate the reaction that takes place between an ylide and an aldehyde or ketone.
- identify the alkene which results from the reaction of a given ylide with a given aldehyde or ketone.
- identify the aldehyde or ketone, the ylide, or both, needed to prepare a given alkene by a Wittig reaction.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- betaine
- Wittig reaction
- ylide (phosphorane)

Study Notes

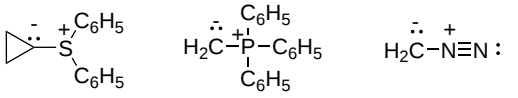
The name triphenylphosphine is derived as follows: the compound PH_3 is called phosphine; replacing the three hydrogen atoms with phenyl groups therefore gives us triphenylphosphine.

Note the following series of IUPAC-accepted trivial names:

- NH_3—ammonia
- PH_3—phosphine
- AsH_3—arsine

Phosphorus Ylides

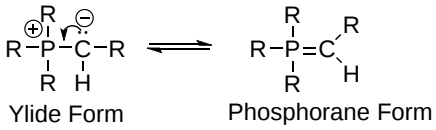
An **ylide,** is defined as a compound with positive and negative charges on adjacent atoms and an overall neutral charge. There are multiple types of ylides but for the Wittig reaction an **organophosphorus ylide**, also called a **Wittig Reagent**, will be used.



Sulfur Ylide Phosphorus Ylide Nitrogen Ylide

Although many Wittig reagents are commercially available, it is often necessary to create them synthetically. Wittig reagents can be synthesized from an **alkylphosphonium salt** created using an S_N2 reaction between an alkyl halide and a nucleophilic trialkyl phosphine. Because trialkyl phosphines typically make good nucleophiles, the S_N2 reactions usually occur with high yields. The subsequent alkylphosphonium salt has an increased acidity (pKa ~22) and can be deprotonated using strong bases, such as *n*-butyllithium, sodium amide, sodium hydride, and alkoxides to create the neutral Wittig reagent. The increased acidity of the alkylphosphonium salt is due to the stabilizing inductive and resonance effects provided by the phosphorus adjacent to the carbanion conjugate base.

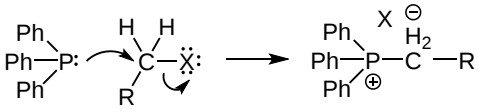
The ability of phosphorus to hold more than eight valence electrons allows for a resonance structure to be drawn forming a double bonded structure call a **phosphorane**. Although Wittig reagents are commonly drawn in the phosphorane form, the ylide form is often used because it shows the nucleophilic carbanion.



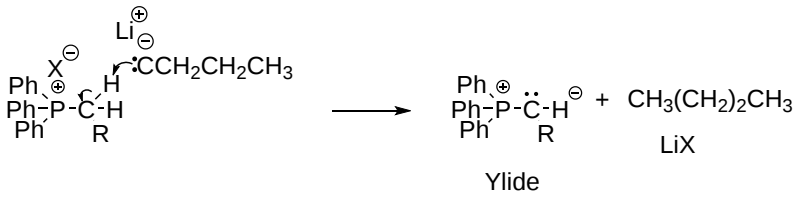
Mechanism of Ylide Formation

The lone pair electrons on the phosphine attack the electrophilic carbon of an alkyl halide as part of a S_N2 reaction. This forms a P-C bond while ejecting the halogen leaving group to create an alkylphosphonium salt. A strong base, such as *n*-butyllithium, deprotonates the acidic hydrogen of the alkylphosphonium salt to create an ylide Wittig reagent.

Step 1: S_N2 Reaction

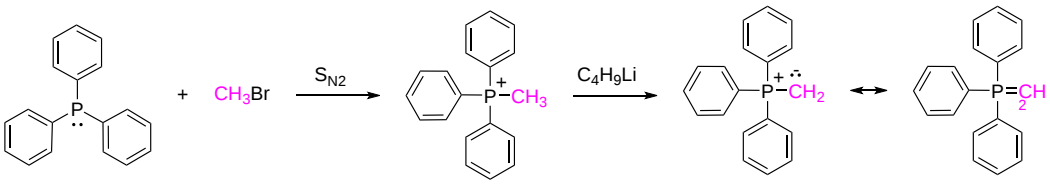


Step 2: Deprotonation



Example

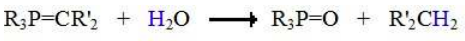
A common Wittig reagent is **methylenetriphenylphosphorane** ($Ph_3P{=}CH_2$) which is synthesized by reacting **Triphenyl phosphine** with methylbromide followed by deprotonation with *n*-butyllithium.



Ylides in Synthesis

Because an S_N2 reaction is used in the synthesis of ylides, methyl and primary halides perform the best. Secondary halides can also be used but the yields are generally lower. This should be considered when planning out a synthetic pathway which involves a synthesized Wittig reagent.

The ylides are typically strong bases and are protonated by water, alcohols, and other acidic hydrogens. Contact with water causes phosphorous ylides to decompose in to hydrocarbons and phosphine oxides, as shown below.

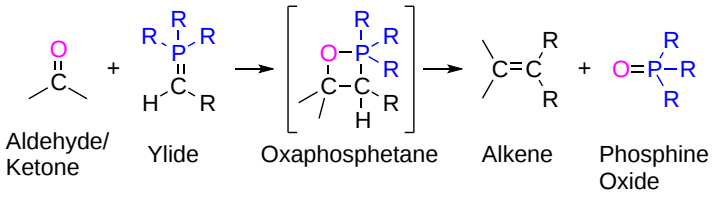


The Wittig Reaction

Alkylidenephosphorane ylides (Wittig Reagents) react with aldehydes or ketones through nucleophilic addition, to give substituted alkenes in a reaction called the **Wittig reaction**. This reaction was developed in 1954 by George Wittig who was awarded the Nobel Prize for this work in 1979. Because of its reliability and wide applicability, the Wittig reaction has become a standard tool used in organic synthesis for the preparation of alkenes.

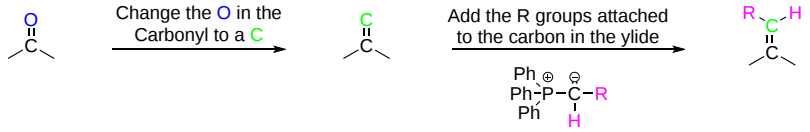
In the Wittig reaction, an **ylide** (typically triphenylphosphorus ylide), adds to an aldehyde or ketone to yield a four-membered heterocyclic intermediate called an **oxaphosphetane**. The oxaphosphetane intermediate spontaneously decomposes to produce an

alkene plus a **phosphine oxide**. Cleavage of the oxaphosphetane to alkene and phosphine oxide products is exothermic and irreversible.

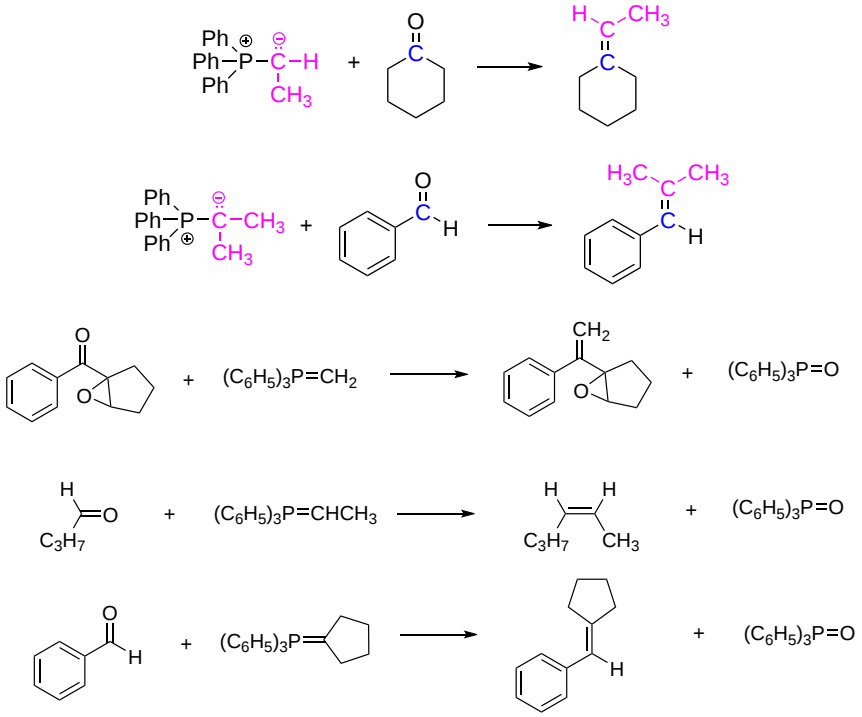


Predicting the Product of a Wittig Reaction

Overall the carbonyl oxygen of an aldehyde or ketone is replaced by the nucleophilic, carbanion present in the ylide while still maintaining the double bond. First, convert the oxygen in the starting material into a carbon while maintaining the double bond. This carbon represents the nucleophilic carbon in the ylide. Then look at the ylide reactant and observe the two groups attached to the nucleophilic carbon. Then transfer these to the bare carbon in the double bond. There may be some possibility of creating E/Z isomers and this will be discussed later.



Examples of the Wittig Reaction



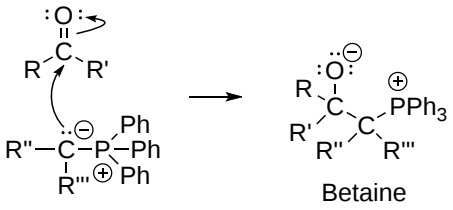
Mechanism of the Wittig Reaction

The initial mechanistic step to form the oxaphosphetane intermediate appears to take place by different pathways which is dependent on the structure of the reactants and the exact experimental conditions. One pathway involves a [2+2] cycloaddition between the ylide and carbonyl to directly form the oxaphosphetane. Cyloadditions, such as this, will be discussed in more detail in section 30.5.

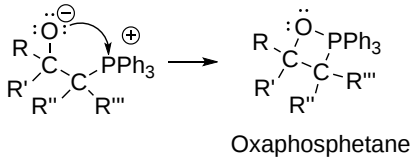
In another postulated mechanism, the ylide undergoes nucleophilic addition to the carbonyl group, forming the initial carbon-carbon bond and creating a dipolar charge-separated intermediate species called a **betaine**. The betaine subsequently undergoes

ring closure to form the four-membered oxaphosphetane structure. In the final step of the mechanism, the oxaphosphetane undergoes intramolecular elimination to give an alkene and a triphenylphosphine oxide.

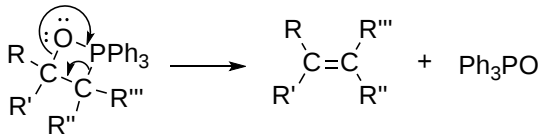
Step 1: Nucleophillic attack on the carbonyl double bond.



Step 2: Formation of the 4-membered oxaphosphetane ring.

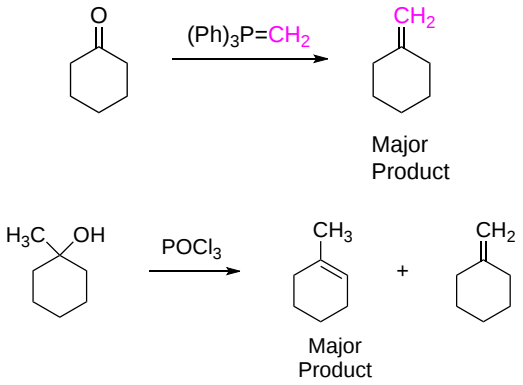


Step 3: Intramolecular elimination



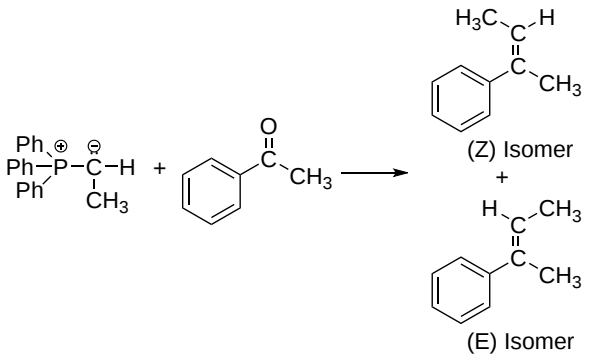
Benefits of the Wittig Reaction

A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration or other elimination reactions.



Limitations of the Wittig Reaction

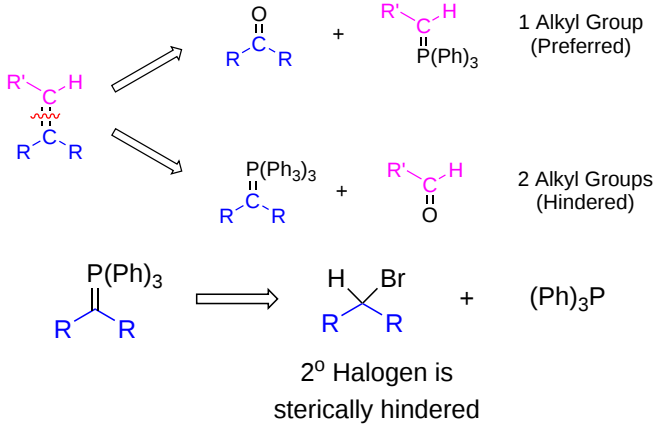
One limitation of the Wittig reaction is possibility of E and Z isomers of the alkene forming. With simple ylides, the product formed is usually primarily the Z-isomer, although a lesser amount of the E-isomer is often also formed. If the E-isomer is the desired product, variations of the Wittig reaction, such as the **Schlosser modification** which uses a stabilized ylide, may be used. It is common to avoid the possibility of forming E/Z isomer by either using symmetrical ketones or symmetrical ylides.



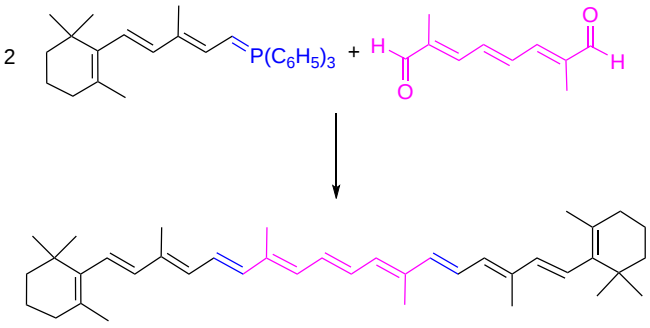
As mentioned above, the Wittig reagent itself is usually derived from an S_N2 reaction with an alkyl halide. Ylide formation with most secondary halides is inefficient. For this reason, Wittig reagents are rarely used to prepare tetrasubstituted alkenes. However, the Wittig reaction is robust and can tolerate the presence of many other functional groups including alkenes, aromatic rings, ethers, alcohols, and ester groups. Bis-ylides (containing two P=C bonds) have also been made and used successfully.

Retrosynthetic analysis Using the Wittig Reaction

When using retrosynthetic analysis to determine the preferred route to synthesize an alkene, it is important to remember that Wittig reagents are commonly prepared by using an S_N2 reaction. To find the possible reactants of a Wittig reaction, cleave the C=C bond in the target molecule to create two pieces. Place an oxygen on one piece to create a carbonyl and place a $(Ph_3)P$ on the other piece to create the Wittig reagent. There are two possible combinations of this separation. The one whose Wittig reagent has the fewest number of alkyl groups will be easier to prepare by the required S_N2 reaction and will represent the preferred route.



The Wittig reaction is commonly used in the preparations of pharmaceuticals and other commercial chemicals. The dietary source of **vitamin A (β-Carotene)** can be synthesized by a Wittig reaction using two equivalents of the ylide, **β-ionylideneacetaldehyde**.

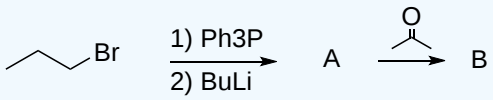


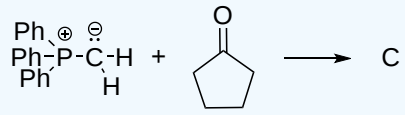
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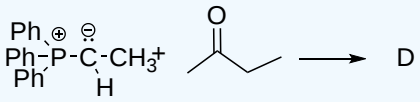
Exercises

Exercise 5.8.1

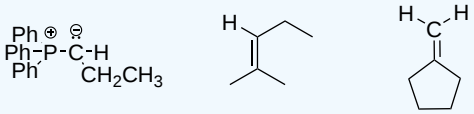
Draw the product of the following reactions.

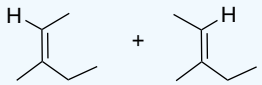






Answer



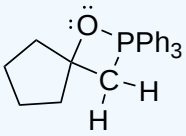


D

Exercise 5.8.2

Draw the structure of the oxaphosphetane which is made during the mechanism of the reaction given that produces product **C**.

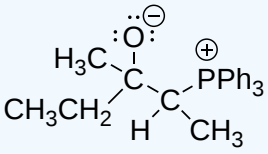
Answer



Exercise 5.8.3

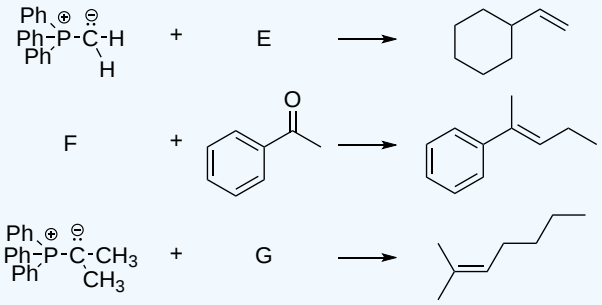
Draw the structure of the betaine which is made during the mechanism of the reaction given that produces product **D**.

Answer

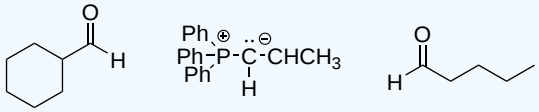


Exercise 5.8.4

Indicate the starting material required to produce the product in each reaction.



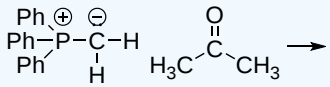
Answer



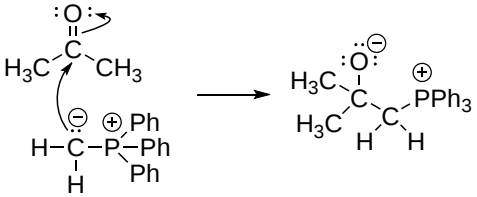
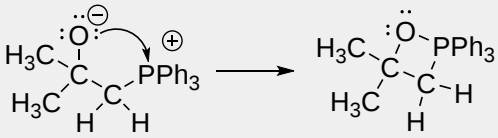
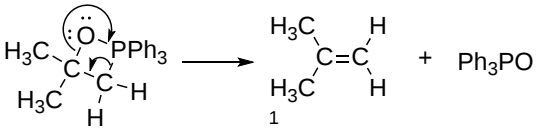
E F G

Exercise 5.8.5

Give a detailed mechanism and the final product of this reaction



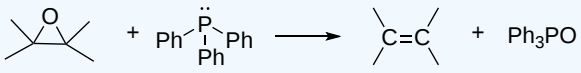
Answer

1- Nucleophilic attack on the carbonyl	
2- Formation of a 4 membered ring	
3- Formation of the alkene	

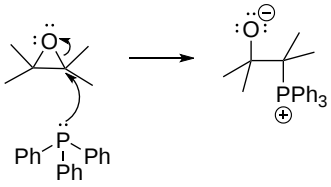
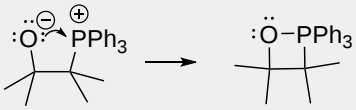
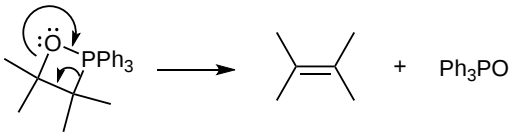
1

Exercise 5.8.6

It has been shown that reacting and epoxide with triphenylphosphine forms an alkene. Please propose a mechanism for this reaction. Review the section on epoxide reactions if you need help.



Answer

1- Nucleophilic attack on the epoxide	
2- Formation of a 4 membered ring	
3- Formation of the alkene	

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5.9: Nucleophilic Addition of Water- Hydration

Objectives

After completing this section, you should be able to

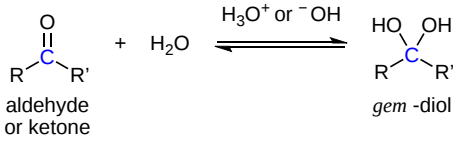
- write the step-wise mechanism for the base-catalyzed hydration of an aldehyde or ketone.
- write the step-wise mechanism for the acid-catalyzed hydration of an aldehyde or ketone.

Key Terms

Make certain that you can define, and use in context, the key term below.

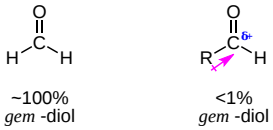
- geminal (gem) diol

It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl group of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (geminal-diol, *gem*-diol, or 1,1-diol). The term hydrate implies the addition of water. The word germinal or abbreviation gem comes from the Latin word for twin, *geminus*.



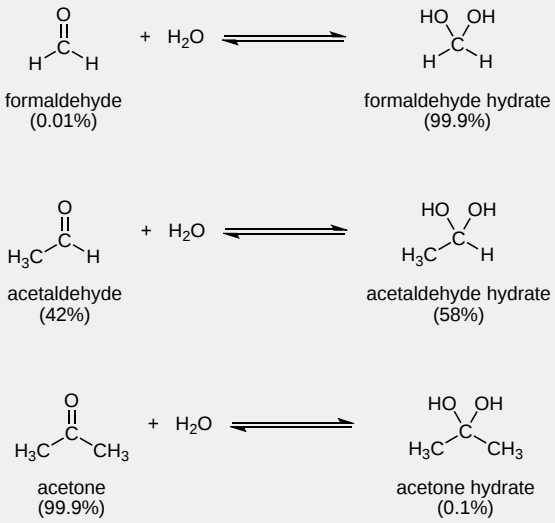
Factors Affecting the Hydrate Equilibrium

The equilibrium for hydrate formation depends both on steric and electrical factors of the carbonyl as discussed in the previous section. In most cases the resulting *gem*-diol is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde where the small size of the hydrogen substituents relative to aldehydes and ketones favor hydrate formation. Thus, a solution of formaldehyde in water (formalin) is almost exclusively the hydrate, or polymers of the hydrate. The addition of electron donating alkyl groups stabilized the partial positive charge on the carbonyl carbon and decreases the amount of *gem*-diol product at equilibrium. Because of this ketones tend to form less than 1% of the hydrate at equilibrium.

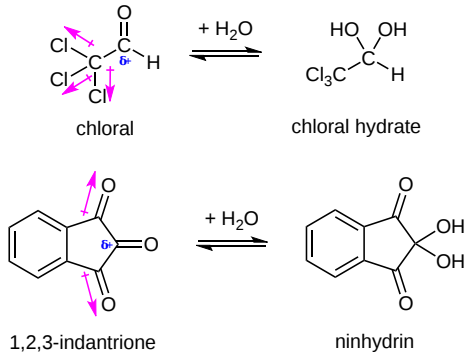


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Equilibrium Distribution of Common Aldehydes and Ketones with their Hydrate Forms

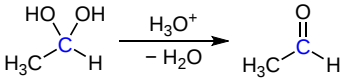


Likewise, the addition of strong electron-withdrawing groups destabilizes the carbonyl and tends to form stable hydrates. Two examples of this are chloral, and 1,2,3-indantrione. It should be noted that chloral hydrate is a sedative and has been added to alcoholic beverages to make a “knock-out” drink also called a Mickey Finn. Also, ninhydrin is commonly used by forensic investigators to reveal fingerprints.



Reversibility of Hydrate Formation

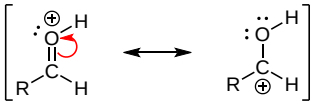
Isolation of hydrates is difficult because the reaction is reversible. Removal of water from the hydrate can cause the conversion of a gem-diol back to the corresponding carbonyl.



Acid or Base Catalyzed Hydrate Formation

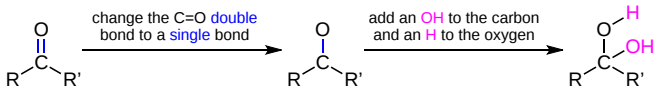
The nucleophilic addition of water to a carbonyl to form a hydrate is usually slow under neutral condition (pH = 7). The rate can be significantly increased through the addition of an acid or base as a catalyst.

The addition of an acid or base changes the mechanism and promote the nucleophilic addition of water to a carbonyl to form a hydrate. Basic conditions speed up the reaction because hydroxide is a better nucleophile than water. Acidic conditions speed up the reaction because the carbonyl becomes protonated. Protonation increases the polarity of the carbonyl bond which increase the partial positive charge on the carbon making it more electrophilic.

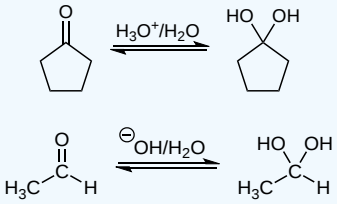


Predicting the Product of a Hydration

Overall, the C=O of the carbonyl in the starting material is removed and replaced by two single bonds both of which are attached to the original carbonyl carbon. Both of these single bonds are attached to OH groups in the product.



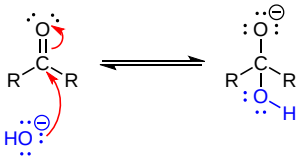
Example 5.9.1



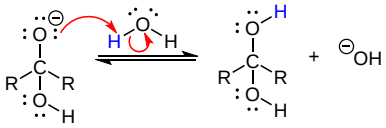
Mechanism of Acid or Base Catalyzed Hydrate Formation

Hydrate Formation under Basic conditions

Step 1: Basic conditions means there is a significant amount of hydroxide present. Hydroxide is a better nucleophile than water which speeds up the reaction. The negatively charged hydroxide forms a single bond with the electrophilic carbonyl carbon. This pushes the two electrons of the pi bond onto the electronegative oxygen forming an alkoxide ion intermediate.

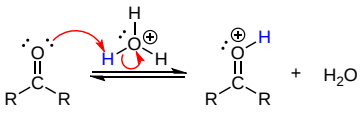


Step 2: Water acts as an acid and protonates the alkoxide ion to form a neutral hydrate while also regenerating hydroxide. The fact that hydroxide is not being used during the reaction is consistent with it acting as a catalyst.



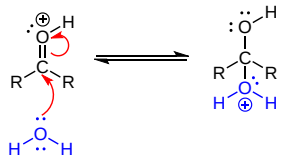
Hydrate Formation under Acidic conditions

Step 1: Acidic conditions means there is a significant amount of hydronium present. Hydronium protonates the carbonyl oxygen thereby making the carbonyl carbon more electrophilic. After protonation the oxygen becomes positively charged.

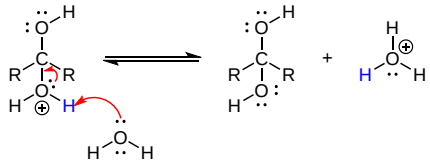


Step 2: Under acidic conditions the most nucleophilic species is water. Water forms a single bond with the electrophilic carbon. This pushes the two electrons in the carbonyl pi bond onto the electronegative oxygen. The oxygen from the carbonyl becomes

neutral while the oxygen from the water nucleophile become positively charged.

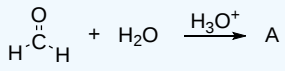


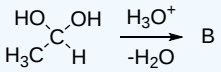
Step 3: Water acts as a base and deprotonates the intermediate to produce the neutrally charged hydrate while regenerating hydronium. The fact that hydronium is not being used during the reaction is consistent with it acting as a catalyst.

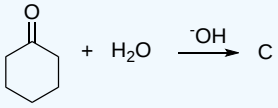


Exercise 5.9.1

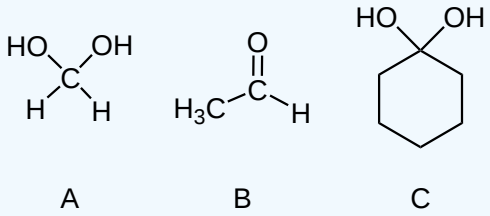
Draw the expected products of the following reactions.







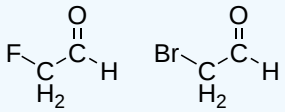
Answer



A B C

Exercise 5.9.2

Of the following pairs of molecules which would you expect to form a larger percentage of *gem*-diol at equilibrium? Please explain your answer.

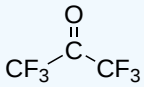


Answer

The compound on the left would. Fluorine is more electronegative than bromine and would remove more electron density from the carbonyl carbon. This would destabilize the carbonyl allowing for more gem-diol to form.

Exercise 5.9.3

Would you expect the following molecule to form appreciable amount of *gem*-diol in water? Please explain your answer.



Answer

Although ketones tend to not form gem-diols, this compound exists almost entirely in the gem-diol form when placed in water. Ketones tend to not form gem-diols because of the stabilizing effect of the electron donating alkyl group. However, in this case the electron donating effects of the alkyl group is dominated by the presence of six highly electronegative fluorines turning these into electron withdrawing groups.

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5.10: Nucleophilic Addition of Alcohols - Acetal Formation

Objectives

After completing this section, you should be able to

- write an equation to illustrate the formation of acetals.
- identify the acetal formed from the reaction of a given aldehyde or ketone with a given alcohol.
- identify the carbonyl compound, the alcohol, or both, needed to form a given acetal.
- write a detailed mechanism for the reaction which occurs between an aldehyde or a ketone and an alcohol.
- explain how an acid catalyst makes aldehydes and ketones more susceptible to attack by alcohols.
- illustrate how the reversibility of the reaction between an aldehyde or a ketone and an alcohol can be used to protect a carbonyl group during an organic synthesis.

Key Terms

Make certain that you can define, and use in context, the key terms below.

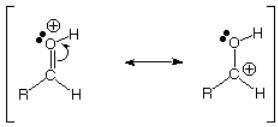
- acetal
- hemiacetal

Study Notes

This section presents a second example of the use of a protecting group. [The first was in the discussion of alcohols, Section 17.8.] Because of the reactivity of hydroxy groups and carbonyl groups, we often need to protect such groups during organic syntheses. When you are designing multi-step syntheses as part of an assignment or examination question, you must always keep in mind the possibility that you may need to protect such groups to carry out the desired sequence of reactions successfully.

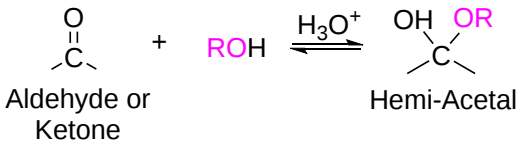
It has been demonstrated in Section 19.5 that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diols. In a similar reaction, one equivalent of an alcohol, in the presence of an acid catalyst, adds reversibly to aldehydes and ketones to form a hydroxy ether called a **hemiacetal** (R_2COHOR') (h*emi*, Greek, half). This reaction can continue by adding another equivalent of an alcohol to form a diether called an **acetal** $R_2C(OR')_2$. Hemiacetals and acetals are important functional groups because they appear in the structures of many sugars.

An acid catalyst must be used during this reaction because alcohols are weak nucleophiles and would add very slowly under neutral conditions. Under acidic conditions, the oxygen of the carbonyl becomes protonated, increasing the electrophilicity of the carbonyl carbon, speeding up the reaction.

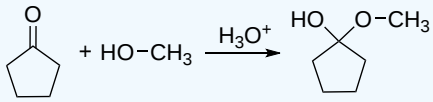


Also, it is common to actively remove the water created with the formation of an acetal by using molecular sieves or a **Dean-Stark trap**. This step is important, since acetal formation is reversible, and the removal of water pushes the equilibrium to the right by Le Chatelier's principal. Indeed, once pure hemiacetals or acetals are obtained, they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.

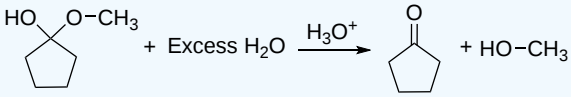
Formation of Hemiacetals



Example 5.10.1: Formation of a Hemiacetal

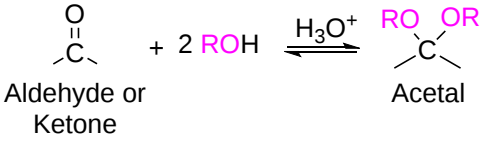


Example 5.10.2: Hemiacetal Hydrolysis Reverting to the Ketone



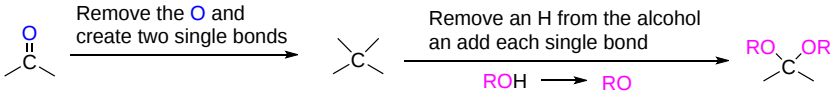
Formation of Acetals

Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents (or an excess amount) of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. It is important to note that a hemiacetal is formed as an intermediate during the formation of an acetal.

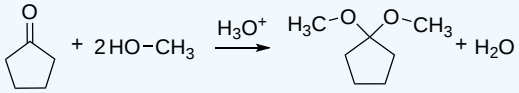


Predicting the Product of a Acetal Formation

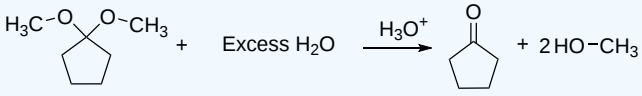
Overall, the carbonyl in the reactant is removed and replaced by two single bonds between oxygen and the original carbonyl carbon. Both of these single bonds are attached O-R groups produced after the reagent alcohol has lost a hydrogen.



Example 5.10.3: Formation of Acetals



Example 5.10.4: Acetal Hydrolysis Reverting to the Ketone



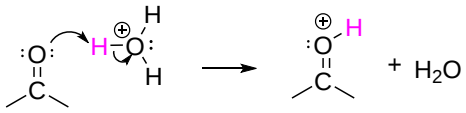
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Mechanism for Hemiacetal and Acetal Formation

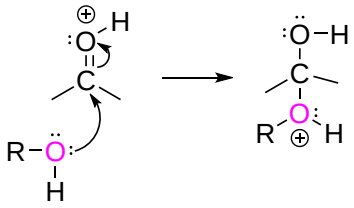
After protonation, an alcohol undergoes nucleophilic addition to the carbonyl group initially forming a hemiacetal upon deprotonation. Further protonation of the OH group in the hemiacetal allows for the elimination of water to form an oxonium ion. A second alcohol nucleophile adds to the oxonium ion to produce a protonated acetal. After deprotonation, the product acetal is formed.

The mechanism shown here applies to both acetal and hemiacetal formation.

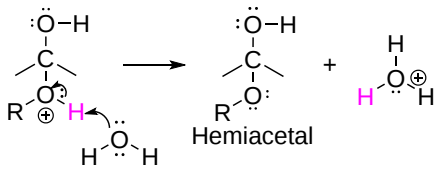
Step 1: The acid catalyst protonates the carbonyl oxygen, making the carbonyl carbon more electrophilic.



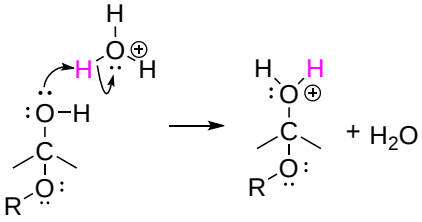
Step 2: An alcohol undergoes nucleophilic addition to the carbonyl producing a protonated hemiacetal.



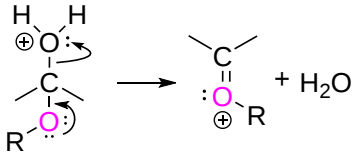
Step 3: Water acts as base to cause a deprotonation creating a hemiacetal and hydronium.



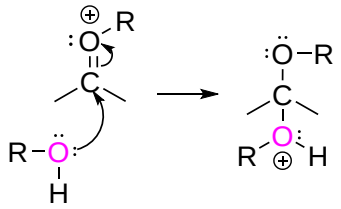
Step 4: The OH group of the hemiacetal is protonated making it into a good leaving group.



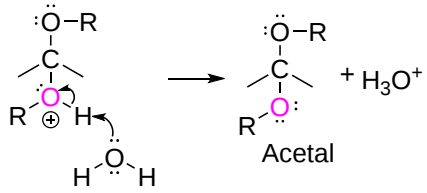
Step 5: Lone pair electrons on the ether oxygen reforms the C=O bond causing the elimination of water and producing an oxonium ion.



Step 6: A second alcohol undergoes nucleophilic addition to oxonium ion producing a protonated acetal.

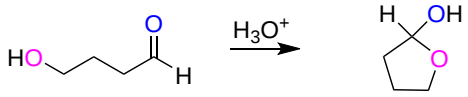


Step 7: Water acts as a base and causes a deprotonation, creating the product acetal and hydronium.



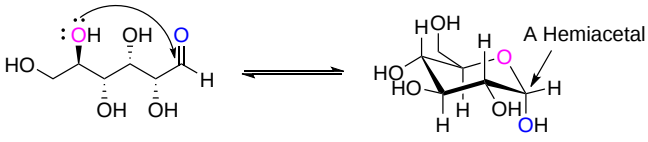
Biological Acetal and Hemiacetal Formation

Molecules which have both an alcohol and a carbonyl can undergo an intramolecular reaction to form a cyclic hemiacetal.



Cyclic Hemiacetal

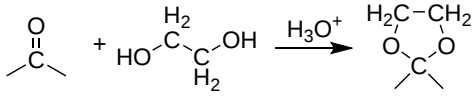
Because sugars often contain alcohol and carbonyl functional groups, intramolecular hemiacetal formation is common in carbohydrate chemistry as we will see in Section 25.7. For example, the common sugar glucose exists in the cylcic manner more than 99% of the time in a mixture of aqueous solution.



Conversion of D-Glucose to Beta-D-Glucopyranose (Cyclic Hemiacetal)

Acetals as Protecting Groups

The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride reagents ($LiAlH_4$ & $NaBH_4$), and organometallic reagents (RMgX & RLi). If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented. To accomplish this, it is common to use a diol such as ethylene glycol(rather than two equivalents of a simple alcohol) to form a cyclic acetal ring commonly called a dioxolane.

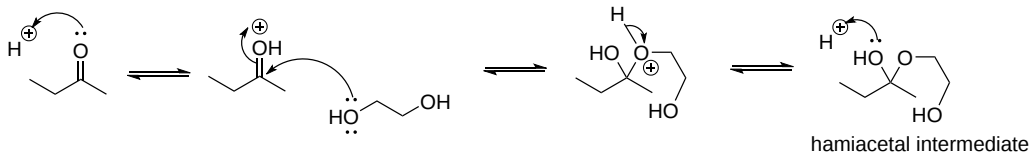


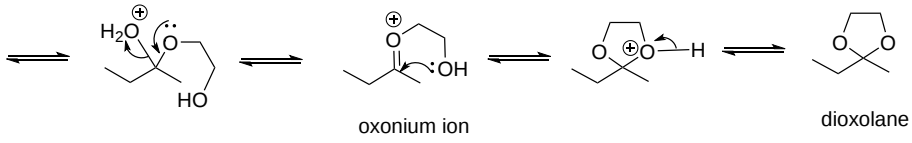
Ethylene Glycol

Cyclic Acetal

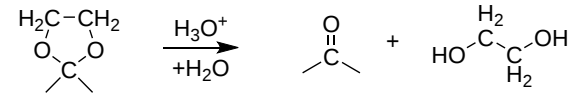
Because both OH groups are part of the same molecule, the second nucleophilic addtion in the formation of the acetal is intramolecular and forms a ring. Cyclic acetals are more stable towards hydrolysis than acyclic ones and are also kinetically

favored because the intramolecular ring-closing reaction is fast.

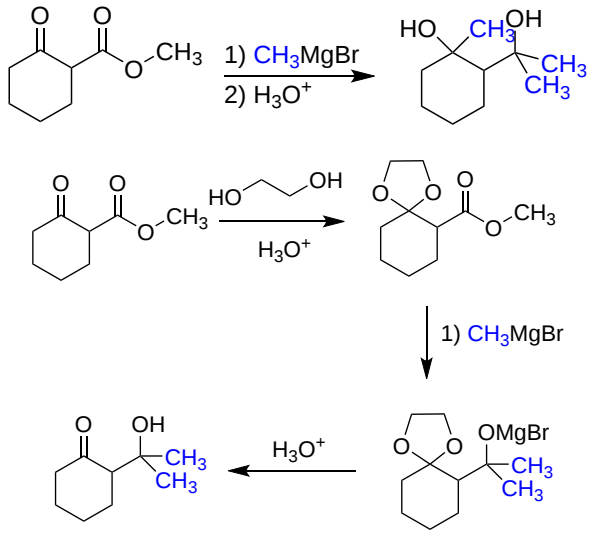




Once the addition reaction is accomplished (or whatever reaction required protecting the carbonyl), the reversibility of acetal formation can be used to reform the original carbonyl.

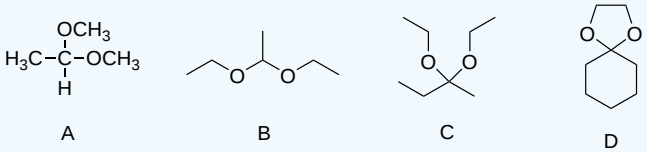


In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with both esters and ketones with the ketone typically more reactive than the ester. This reaction sequence uses ethylene glycol to form the cyclic acetal protecting group for the ketone followed by reaction of the ester with a Grignard reagent. Once this reaction is complete, the acetal is hydrolyzed back to the ketone in the same step that reprotonates the alcohol (while eliminating the MgBr).

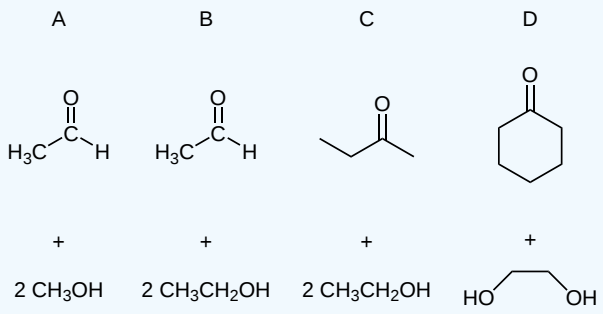


? Exercise 5.10.1

For each acetal/ketal A-D in the figure below, specify the required aldehyde/ketone and alcohol starting materials.

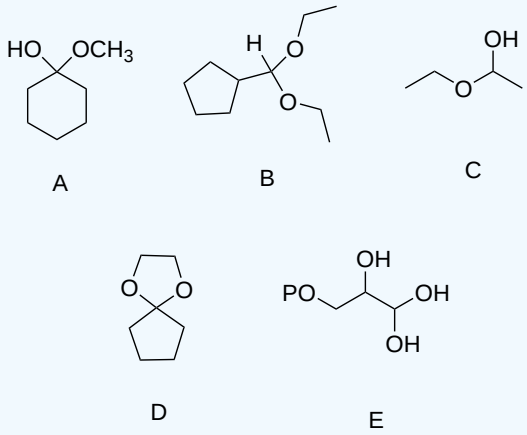


Answer



Exercise 5.10.2

Categorize each of the following molecules as a hemiacetal, acetal, hydrate of an aldehyde, or hydrate of a ketone.



Answer

A - hemiacetal, B - acetal, C - hemiacetal, D - acetal, E - hydrate of an aldehyde

Exercise 5.10.3

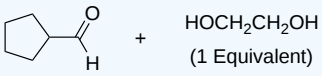
Specify the acetal that would form from a reaction between the given starting compounds.

a.



(2 Equivalents)

b.

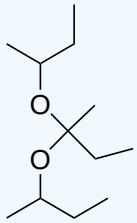


(1 Equivalent)

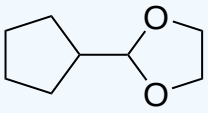
Answer

a.

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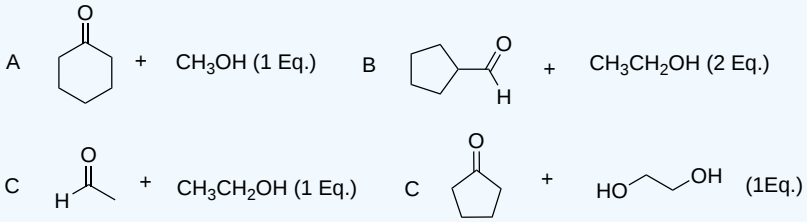
b.



Exercise 5.10.4

Specify the aldehyde/ketone and alcohol combination that would be required to form the compounds in exercise 2.

Answer



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5.11: Nucleophilic Addition of Amines - Imine and Enamine Formation

Objectives

After completing this section, you should be able to

- write equations to describe the reactions that occur between aldehydes or ketones and primary or secondary amines.
- identify the product formed from the reaction of a given aldehyde or ketone with a given primary or secondary amine.
- identify the aldehyde or ketone, the amine, or both, required in the synthesis of a given imine or enamine.
- write the detailed mechanism for the reaction of an aldehyde or ketone with a primary amine.
- write the detailed mechanism for the reaction of an aldehyde or ketone with a secondary amine.
- explain why the rate of a reaction between an aldehyde or ketone and a primary or secondary amine is dependent on pH.

Key Terms

Make certain that you can define, and use in context, the key terms below.

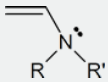
- 2,4-dinitrophenylhydrozone
- enamine
- imine

Study Notes

An imine is a compound that contains the structural unit



An enamine is a compound that contains the structural unit



Both of these types of compound can be prepared through the reaction of an aldehyde or ketone with an amine.

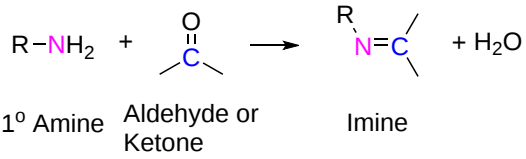
You may have the opportunity to observe the reaction of an aldehyde and ketone with 2,4-dinitrophenylhydrazine (Brady's reagent) to form a 2,4-dinitrophenylhydrozone in the laboratory. This is a classical organic chemistry test to confirm the presence of a carbonyl group. The reaction produces very colorful and bright precipitates of yellow, orange and red.

If you can understand why the two reactions of imine and enamine formation are essentially identical, and can write a detailed mechanism for each one, you are well on the way to mastering organic chemistry. If you understand how and why these reactions occur, you can keep the amount of material that you need to memorize to a minimum.

The nucleophilic addition of amines involves reacting primary or secondary amines with carbonyl compounds like aldehydes or ketones. This forms imines (with primary amines) or enamines (with secondary amines) along with water as a byproduct. These reactions are crucial in organic synthesis for building carbon-nitrogen bonds and creating various functional groups.

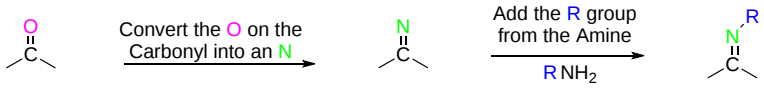
Reaction with Primary Amines to form Imines

The reaction of aldehydes and ketones with ammonia or 1º-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction.

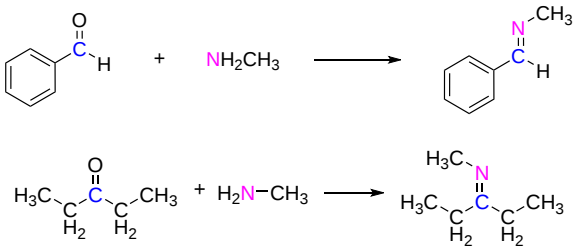


Predicting the Products of an Imine Forming Reaction

During imine formation, the carbonyl oxygen is completely removed. The nitrogen of the 1° amine reactant replaces the carbonyl oxygen to form the imine C=N bond. During the process the nitrogen of the 1° amine loses both of its hydrogens.



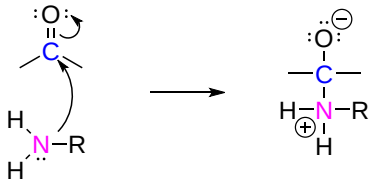
Examples of Imine Forming Reactions



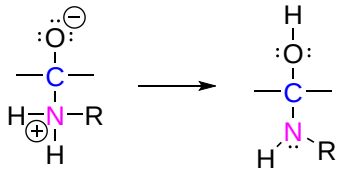
Mechanism of Imine Formation

Imine formation is a reversible process that starts with the nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or ketone. Next, a proton transfer forms a neutral amino alcohol called a carbinolamine. Acid protonation of the carbinolamine oxygen converts it into a better leaving group which is subsequently eliminated as water producing an iminium ion. Deprotonation of nitrogen gives the final imine product.

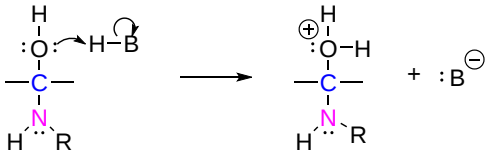
Step 1: Nucleophilic addition



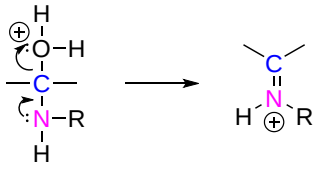
Step 2: Proton transfer



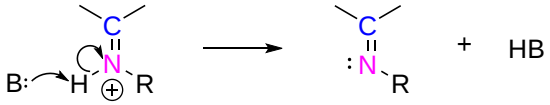
Step 3: Protonation



Step 4: Water is eliminated to form an iminium ion

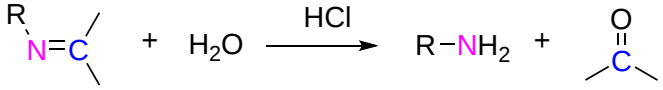


Step 5: Deprotonation



Reversibility of Imine Forming Reactions

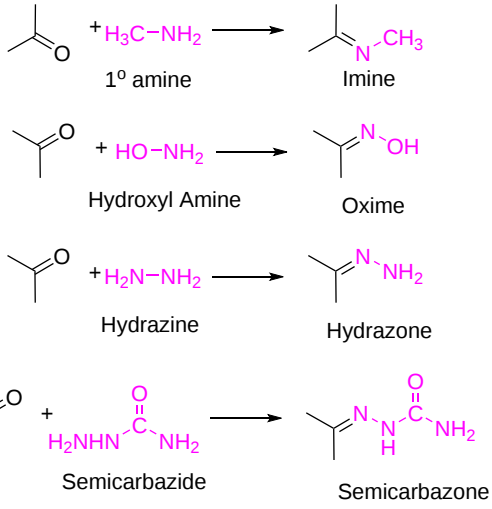
Imines can be hydrolyzed back to the corresponding 1° amine under acidic conditions.



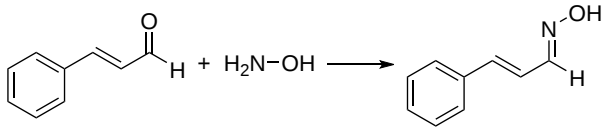
Reactions Involving other Reagents of the type Y-NH_2

A wide variety of substances with $-NH_2$ groups can react with aldehydes and ketones by an addition-elimination sequence to yield compounds with a carbon-nitrogen double bond. Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type $Y–NH_2$ have been studied, and found to give stable products ($R_2C=N–Y$) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed below, together with the structures and names of their carbonyl reaction products. Hydrazones are used as part of the Wolff-Kishner reduction and will be discussed in more detail in Section 19.9.

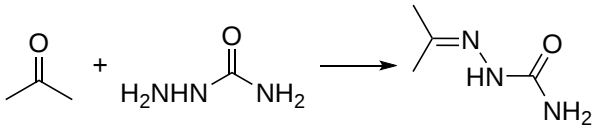
With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. It should be noted that although semicarbazide has three nitrogen groups ($–NH_2$) only one of them is a reactive amine. The other two are similar to amides and are deactivated by resonance with the adjacent carbonyl group.



Example



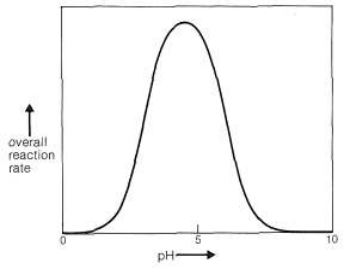
Cinnamaldehyde reacting with hydroxylamine to form cinnamaldehyde oxime



Acetone reacting with semicarbazide to form acetone semicarbazide

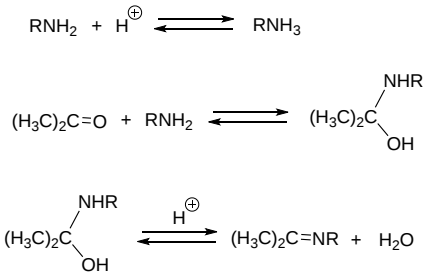
The pH Dependence of Imine Forming Reactions

The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H_2O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.



Schematic variation of the rate of condensation of RNH_2 with a carbonyl compound as a function of pH.

Clearly, if the unshared electron pair on the nitrogen of RNH_2 is combined with a proton it cannot attack the carbonyl carbon to give the aminoalkanol produced during the mechanism. So at high acid concentration (low pH) we expect the rate and the equilibrium for the overall reaction to be unfavorable.

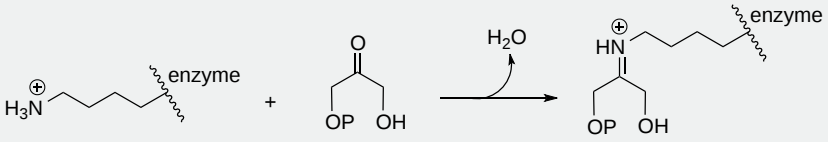


Dehydration of the aminoalkanol is acid catalyzed; this reaction normally is fast at pH values smaller than 3-4. As the pH is increased above 4, the dehydration step in the mechanism decreases in rate because it requires an acid catalyst. At pH 6 dehydration is the slow step of the mechanism, and at higher pH values it finally becomes too slow to give a useful overall rate of reaction.

Biological Imine Forming Reactions

Imine intermediates are common in biological pathways. Carbon-carbon bond forming enzymes called aldolases often form a protonated iminium link between a carbonyl carbon on a substrate and the $-NH_3^+$ from a lysine amino acid found in the active site of the enzyme. The reaction below shows an aldolase reaction from the Calvin Cycle where the carbonyl containing

substrate is dihydroxyacetone. The Calvin Cycle is involved in the biochemical processes of carbon fixation and the production of sugars in plants.

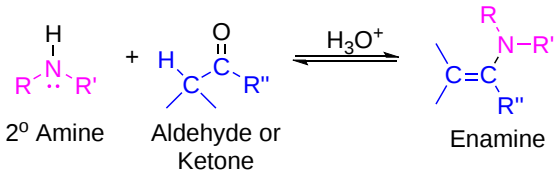


Protonated Amine From Lysine | **Dihydroxyacetone** | **A Protonated Iminium Linkage**

After the carbon-carbon bond forming part of an aldolase reaction is completed, the iminium linkage is hydrolyzed, freeing the product so that it can diffuse out of the active site and allow another catalytic cycle to begin.

Reaction with Secondary Amines to form Enamines

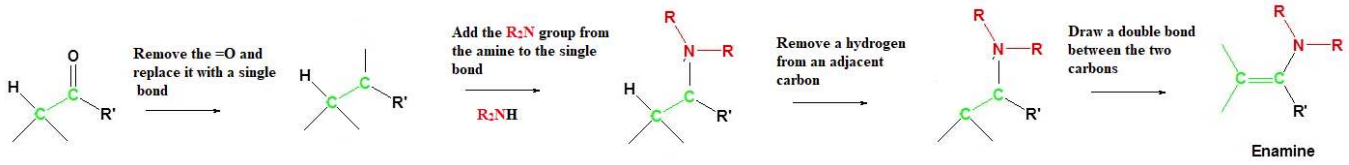
Most aldehydes and ketones react with 2°-amines to give products known as **enamines** (alkene + amine). It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Secondary amines form a distinctly different functional group after nucleophilic addition because they lack the second hydrogen on nitrogen required for imine formation. During this reaction a hydrogen is removed from an adjacent carbon forming a C=C bond.



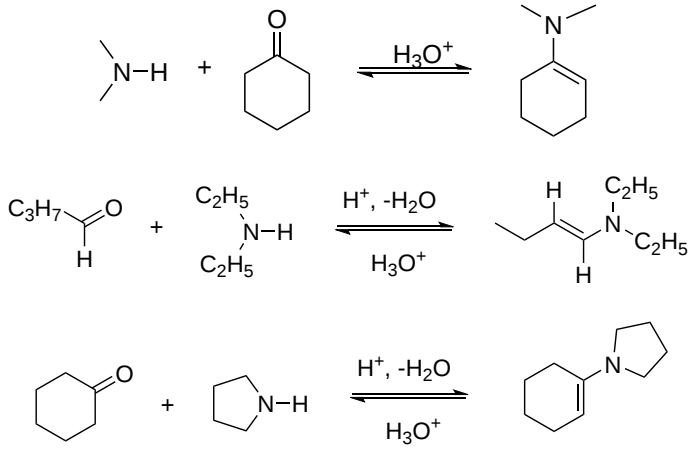
2° Amine | Aldehyde or Ketone | Enamine

Predicting the Products of an Enamine Forming Reaction

During enamine formation the carbonyl oxygen is completely removed. The nitrogen of the amine reactant replaces the oxygen to form a N-C bond. During the process the amine loses its lone hydrogen. A hydrogen is removed from a carbon adjacent to the original carbonyl carbon forming a C=C between them.

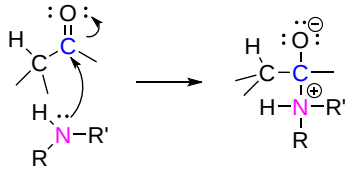


Example

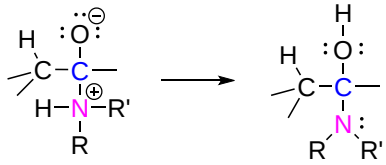


Mechanism

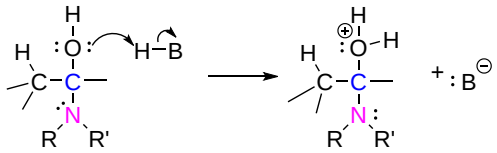
Step 1: The secondary amine undergoes nucleophilic addition to form a neutral tetrahedral intermediate



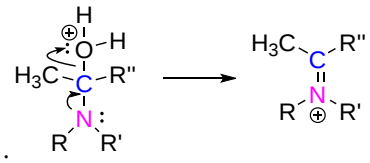
Step 2: A proton is transferred from the ammonium ion moiety of the tetrahedral intermediate to the alkoxide ion moiety. This forms a neutral functional group called a carbinolamine



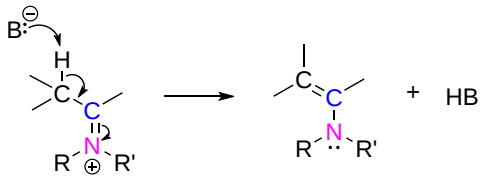
Step 3: The OH group on the carbinolamine is protonated by hydronium turning it into a good leaving group



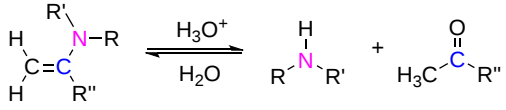
Step 4: The lone pair electrons on the nitrogen form the C=N double bond causing water to be eliminated. This forms an iminium ion



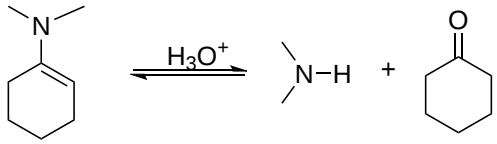
Step 5: Water (or a base) removes a hydrogen from an adjacent carbon to form an alkene bond. This pushes two electrons from the C=N double bond onto the positively charged nitrogen creating the neutral enamine product and hydronium (or BH).



Reversibility of Enamines



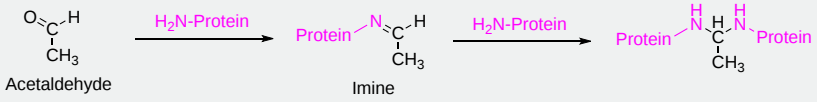
Example



https://chem.libretexts.org/@go/page/500411

Something Extra: How does Alcohol Cause Cirrhosis and Liver Cancer?

One of the most insidious aspects of alcohol abuse is the fact that it will allow a user to continue, sometimes for decades, while it slowly destroys their body. Our bodies are actually designed to handle limited amounts of alcohol. Human metabolism includes enzymes that can convert alcohol into harmless metabolites in three steps. In the first step, an enzyme called alcohol dehydrogenase (ADH) acts as a catalyst for the conversion of alcohol to the toxic intermediate acetaldehyde.

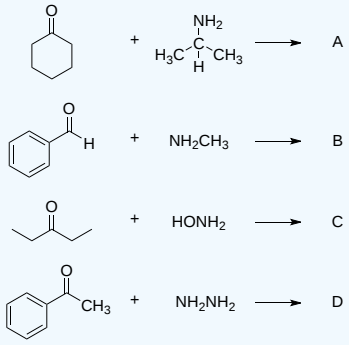


How acetaldehyde forms a protein adduct

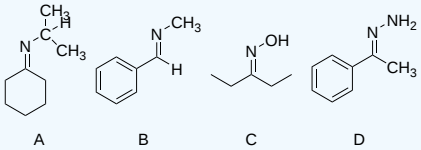
Forming adducts with DNA changes its structure and increases the chances of irregular replication, which is the starting point of cancer. Our bodies have processes that can repair or replace damaged proteins and DNA, but if enough build up they can lead to cirrhosis, liver cancer, liver failure, and death. Alcohol accounts for 28% of all liver-disease-related deaths in the U.S., and is also responsible for a little over 3% of all cancer deaths that occur globally. Hepatocellular carcinoma (liver cancer) is the fifth most common type of cancer, with an estimated 500,000 new cases being diagnosed every year worldwide. Because this type of cancer is usually discovered late, the prognosis is poor, with a median survival time of 1-2 months.

Example 5.11.1

Please draw the products of the following reactions.



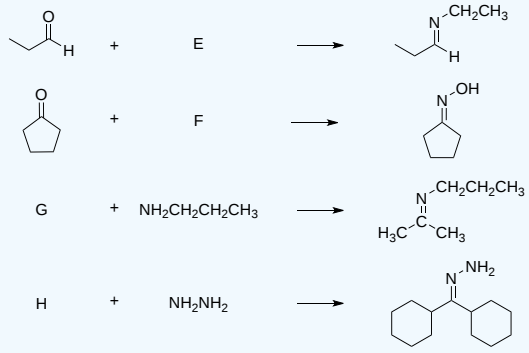
Solution



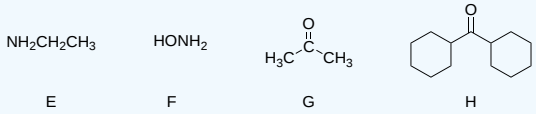
Example 5.11.2

Please draw the structure of the reactant needed to produce the indicated product.

https://chem.libretexts.org/@go/page/500411



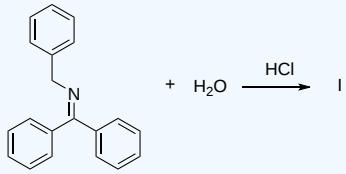
Solution



E F G H

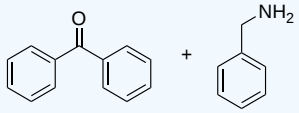
Example 5.11.3

Please draw the products of the following reactions.



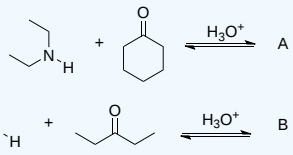
Solution

I

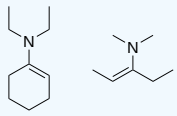


Example 5.11.4

Please draw the products for the following reactions.



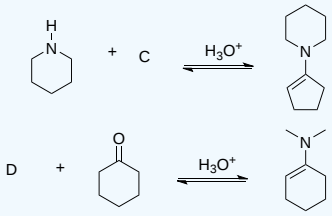
Solution



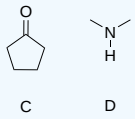
A B

Example 5.11.5

Please give the structure of the reactant needed to product the following product



Solution



C D

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5.12: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction

Objectives

After completing this section, you should be able to

- write an equation to illustrate the Wolff-Kishner reduction of an aldehyde or ketone.
- identify the product formed from the Wolff-Kishner reduction of a given aldehyde or ketone.

Key Terms

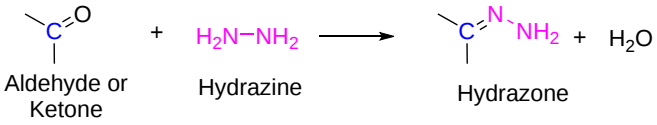
Make certain that you can define, and use in context, the key term below.

- Wolff-Kishner reduction

Study Notes

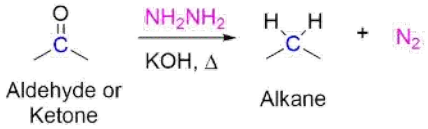
After studying this section, you can add yet another method of reducing organic compounds to your growing list of reduction reactions.

Aldehydes and ketones can be converted to a hydrazone derivative by reaction with hydrazine (H_2NNH_2). Hydrazone formation is a variation of the imine forming reaction discussed in the previous section.



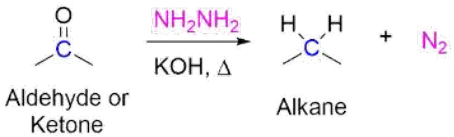
Reaction with a Base and Heat Converts a Hydrazone to an Alkane

Hydrazones can be further converted to the corresponding alkane by reaction with a base, usually KOH, and heat. Typically a high boiling point solvent, such as ethylene glycol, is used to provide the high temperatures needed for this reaction to occur. In the examples below the symbol "Δ" represents the addition of heat to a reaction. During this reaction nitrogen gas, which contains a very stable N-N triple bond, is produced.

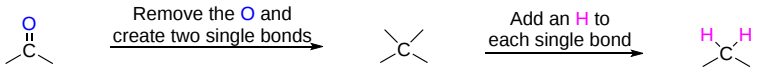


Both Reactions Together Produce the Wolff-Kishner Reduction

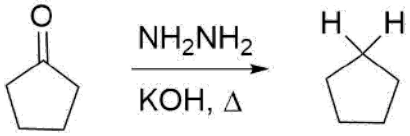
These two steps previously discussed can be combined to provide a general reaction for the conversion of aldehydes and ketones to alkanes called the Wolff-Kishner Reduction. Overall, the Wolff-Kishner reduction removes the carbonyl oxygen in the form of water by forming an intermediate hydrazone. The hydrazone then undergoes loss of N_2 gas along with protonation to give the alkane reaction product. Note that the Clemmensen reduction accomplishes the same transformation of a carbonyl to an alkane under acidic conditions.



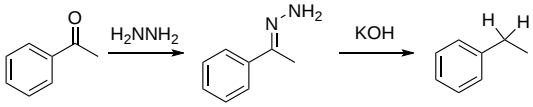
Predicting the Products of a Wolff-Kishner Reduction



Examples



Conversion of Cyclopentanone to cyclopentane

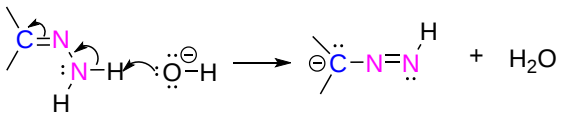


Conversation of Acetophenone to Ethylbenzne

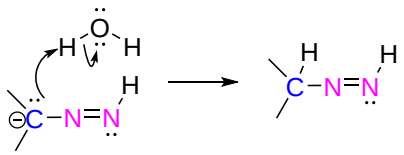
Mechanism of the Wolff-Kishner Reduction

Hydrazine reacts with a carbonyl to form a hydrazone using a mechanism similar to that of an imine formation discussed in the previous section. The weakly acidic N-H bond is deprotonated to form the hydrazone anion. The hydrazone anion has a resonance structure that places a double bond between the nitrogens and a negative charge on carbon. The hydrazone anion is then protonated to form a neutral intermediate. A second weakly acidic N-H bond is deprotonated which causes the formation of N_2 gas and a carbanion. In the final step the carbanion is protonated to form an alkane product.

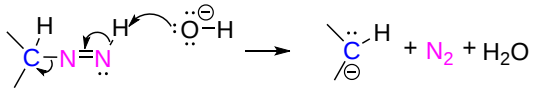
Step 1: Deprotonation



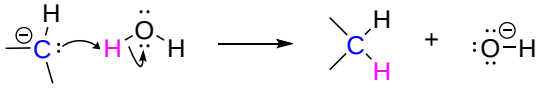
Step 2: Protonation



Step 3: Second deprotonation

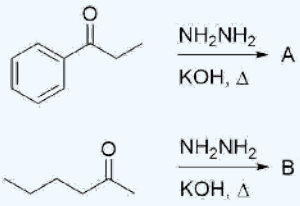


Step 4: The carbanion is protonated to form the alkane product.

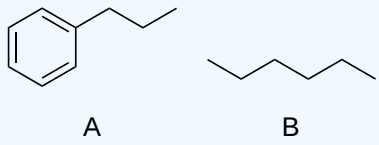


? Exercise 5.12.1

Please draw the products of the following reactions.



Answer



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5.13: Biological Reductions

Objectives

After completing this section, you should be able to

- determine whether or not a given aldehyde will undergo the Cannizzaro reaction.
- write an equation to illustrate the Cannizzaro reaction.
- identify the products formed when a given aldehyde undergoes a Cannizzaro reaction.
- write the detailed mechanism of the Cannizzaro reaction.

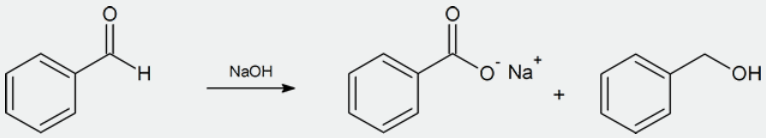
Key Terms

Make certain that you can define, and use in context, the key term below.

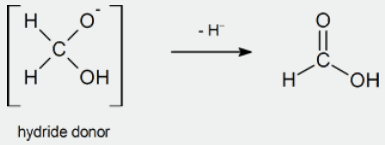
- Cannizzaro reaction

Study Notes

In 1853 Stanislao Cannizzaro discovered that the base-induced disproportionation of an aldehyde resulted in a carboxylic acid (oxidation product) and an alcohol (reduction product).



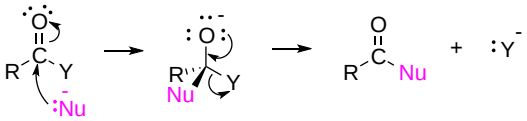
Note that in the mechanism shown in the reading has an intermediate generated from methanal (formaldehyde) that effectively becomes a hydride (H^-) donor, which reduces a second molecule of methanal to methanol.



hydride donor

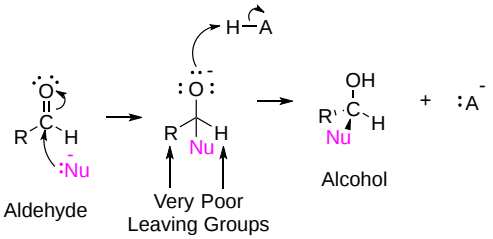
Carbonyl reductions are a part of important biological pathways in living organisms. Recall in Section 17.4 that NADH can donate H^- to reduce aldehydes and ketones. You may wish to review this section.

As seen in Section 18.11, nucleophilic addition reactions usually do not occur in many carboxylic acid derivatives due to the presence of a leaving group. Following nucleophilic addition, the tetrahedral alkoxide intermediate can reform the carbonyl by eliminating the leaving group as part of a reaction called **nucleophilic acyl substitution**. The nucleophilic acyl substitution reaction will be discussed in greater detail in Chapter 21.



Y = -Br, -Cl, -OR, -NR_2, -O_2R

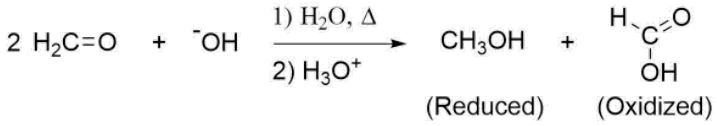
This reaction does not occur in aldehydes or ketones because alkyl or hydrogen substituents make very poor leaving groups. After nucleophilic addition, the negative charge on the tetrahedral alkoxide intermediate remains on the oxygen and is subsequently protonated to form a hydroxyl group (OH). This represents the 1,2 nucleophilc addition reaction discussed in most of this chapter.



The Cannizzaro Reaction

An important exception to the idea of hydrogen making a poor leaving group is seen in the **Cannizzaro reaction**, discovered in 1853 by Stanislao Cannizzaro. A characteristic reaction of aldehydes without α hydrogens is the self oxidation-reduction they undergo in the presence of strong base. If the aldehyde has α hydrogens, other reactions usually occur more rapidly. The Cannizzaro reaction, combines many features of other reactions studied in this chapter. During this reaction, nucleophilic addition of a hydroxide ($^{-}$OH) to an aldehyde gives a tetrahedral alkoxide intermediate. The alkoxide subsequently reforms the carbonyl, eliminating a hydride ion ($^{-}$:H) as a leaving group, and creating an oxidized carboxylic acid product. The eliminated hydride ion reduces a second aldehyde molecule, in a similar fashion as hydride containing reagents $LiAlH_4$ and $NaBH_4$, to create a reduced alcohol product. For example, methanal creates methanol (reduced) and methanoic acid (oxidized) when heated with aqueous NaOH.

Example

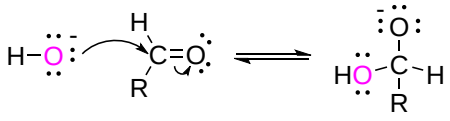


Methanal Undergoing a Cannizzaro Reaction to form Methanol and Methanoic Acid

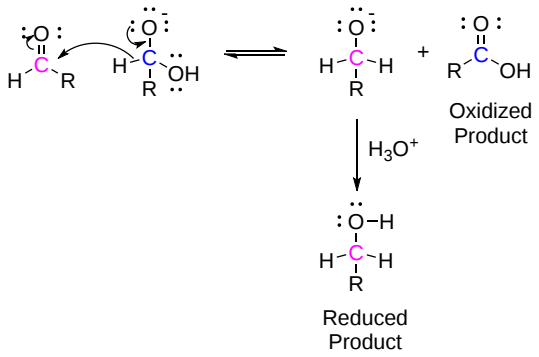
Mechanism of the Cannizzaro Reaction

The first step of the mechanism is the reversible nucleophilic addition of a hydroxide ion to the carbonyl group of an aldehyde. This is analogous to the first mechanistic step in the formation of a hydrate under basic conditions. The hydroxide nucleophile attacks the electrophilic carbonyl carbon forming a C-O single bond. The two electrons from the carbonyl pi bond are pushed onto the electronegative oxygen to form a tetrahedral alkoxide intermediate. In the second step of the mechanism, the alkoxide intermediate reforms the carbonyl, eliminating a hydride ion as the leaving group, and forms a carboxylic acid functional group as an oxidized product. The hydride ion acts as a nucleophile and attacks the carbonyl carbon of a second aldehyde forming a C-H bond. The two electrons from the second pi bond are pushed onto the electronegative oxygen to form a different alkoxide intermediate. This alkoxide intermediate is quickly protonated to form an alcohol functional group as a reduced product.

Step 1: Nucleophilic attack



Step 2: Hydride transfer

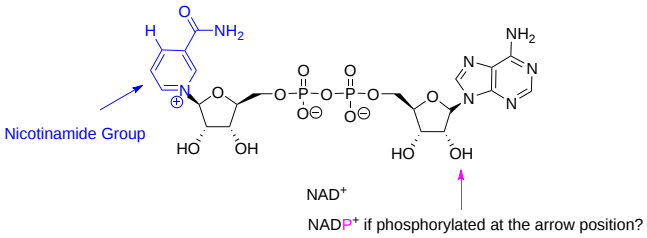


Biological Reductions Using Hydride Transfer to a Carbonyls

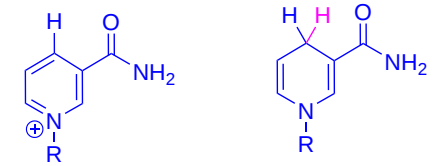
The Cannizzaro reaction is interesting because its mechanism is analogous to the hydride reductions of carbonyls which occur in the biological pathway of many living organisms. One of the most important biological reducing agents is NADH (the reduced form of nicotinamide adenine dinucleotide) which can act as a source of the hydride ion. NADH donates a hydride to carbonyls in an analogous fashion to the alkoxide ion intermediate of the Cannizzaro reaction. A set of lone pair electrons on a NADH nitrogen atom pushes the hydride off as a leaving group forming NAD+ (the oxidized form of nicotinamide adenine dinucleotide). The ejected hydride adds as a nucleophile to a wide variety of carbonyl containing biological molecules. Some examples of this addition are described below.

Nicotinamide Adenine Dinucleotide - a Hydride Transfer Coenzyme

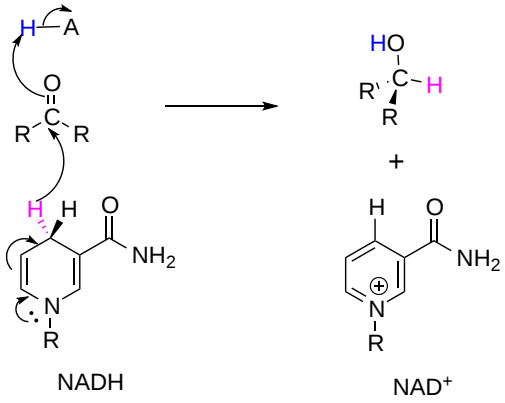
Although we are talking about hydrides acting as nucleophiles and leaving groups in this section, you already know that discreet hydride ions are far too unstable to exist as actual intermediates in the organic reactions of living cells. Biochemical redox reactions involving hydride transfer require the participation of a hydride transfer coenzyme. In reactions involving carbonyl compounds, a molecule called nicotinamide adenine dinucleotide generally plays this role. The full structure of the oxidized form of this coenzyme, abbreviated NAD+, is shown below, with the active nicotinamide group colored blue.



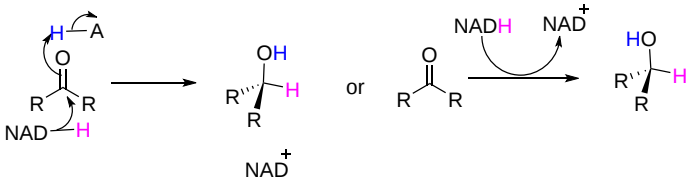
Because the redox chemistry occurs specifically at the nicotinamide part of the molecule, typically the rest of the molecule is simply designated as an 'R' group. NAD^+ and $NADP^+$ both function in biochemical redox reactions as hydride acceptors: that is, as oxidizing agents. The other forms of the coenzyme, NADH and NADPH, serve as hydride donors: that is, as reducing agents.



The phosphate on the nucleotide pentose group of NADP+ and NADPH is located far from the nicotinamide ring, and does not participate directly in the hydride transfer function of the cofactor.

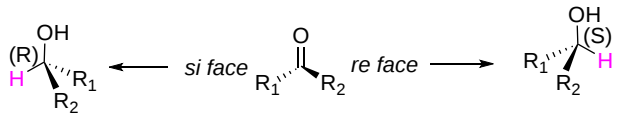


This reaction can be simplified in the following way:

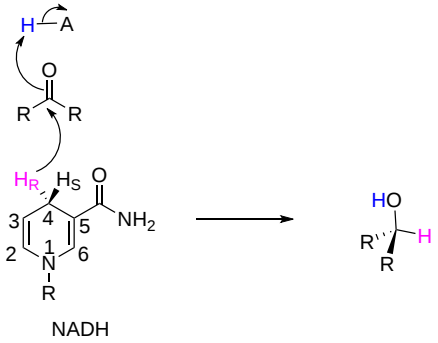


Stereochemistry of Hydride Transfer Reactions

Ketone/aldehyde hydrogenase reactions are stereospecific in two distinct ways. In the hydrogenase direction, attack by the hydride can occur from either the *re* or the *si* face of an asymmetrical carbonyl, leading to the *S* or *R* alcohol depending on the priorities of R_1 and R_2 (in the example R_1 has higher priority than R_2).

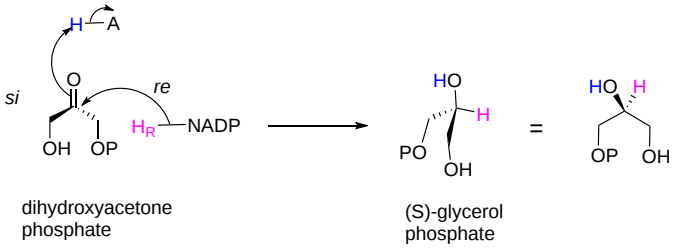


The specificity is determined by which side of the ketone or aldehyde substrate the NAD(P)H cofactor is bound to in the active site. In addition, hydrogenases specifically catalyze the transfer of either the *pro-R* or the *pro-S* hydrogen at C_4 of the nicotinamide ring. In the example below, the *pro-R* hydrogen of NADH is transferred to reduce the ketone.



Examples of Biological Hydride Transfer Reactions

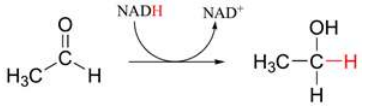
1. In 1997, an enzyme was discovered in a class of microbes known as ‘archaea’ that catalyzes the same reaction with the opposite substrate stereochemistry (J. Biochem 1997, 122, 572). The primary metabolic role of the enzyme is apparently to catalyze the reduction of dihydroxyacetone phosphate to (S)-glycerol phosphate, with transfer of the pro-R hydrogen atom from NADPH to the *re* face of dihydroxyacetone phosphate.



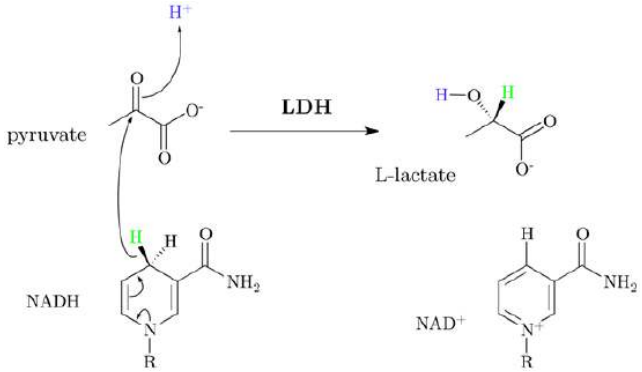
dihydroxyacetone phosphate

(S)-glycerol phosphate

2. In a reaction that is very important to people in the wine and beer-making industry, an NADH-dependent enzyme in yeast produces ethanol by reducing acetaldehyde. The acetaldehyde is derived from the thiamine diphosphate-dependent decarboxylation of pyruvate.

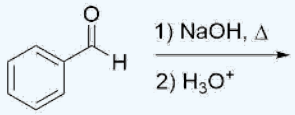


3. Lactic acid fermentation occurs by converting pyruvate into lactate through hydride addition using the enzyme lactate dehydrogenase and producing NAD+ in the process. This process takes place in oxygen depleted muscle and some bacteria. It is responsible for the sour taste of sauerkraut and yogurt.

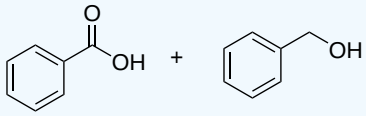


Exercise 5.13.1

Please draw the expected products of the following reaction:



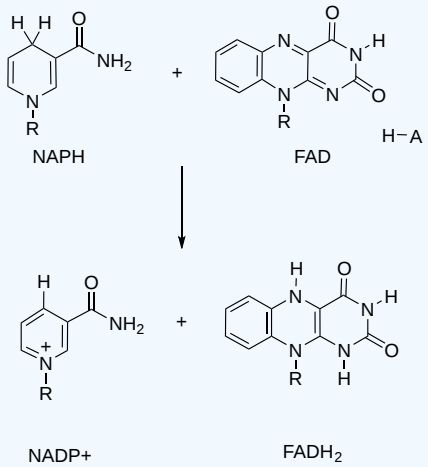
Answer



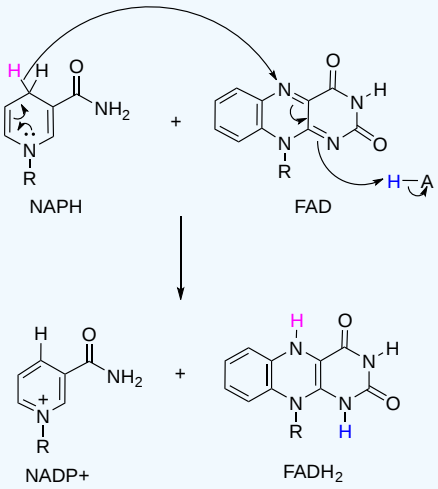
Exercise 5.13.2

Please draw the mechanism for the following hydride transfer reaction:

https://chem.libretexts.org/@go/page/500415



Answer



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5.14: Conjugate Nucleophilic Addition to α, β-unsaturated Aldehydes and Ketones

Objectives

After completing this section, you should be able to

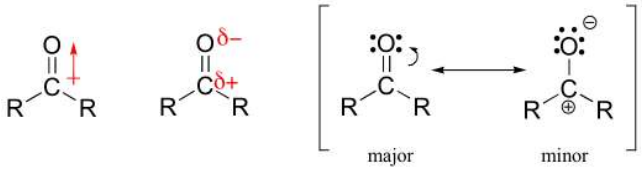
- explain how the carbonyl group which is present in *α*, *β*-unsaturated aldehydes and ketones activates the carbon-carbon double bond so that it is susceptible to attack by nucleophiles.
- write equations to illustrate the addition of amines, water and lithium diorganocopper reagents to *α*, *β*-unsaturated aldehydes and ketones.
- identify the product formed from the reaction of a given primary or secondary amine with a given *α*, *β*-unsaturated aldehyde or ketone.
- identify the aldehyde or ketone, the primary or secondary amine, or both, needed to prepare a given *β*-amino aldehyde or ketone.
- identify the product formed from the reaction of an *α*, *β*-unsaturated aldehyde or ketone with water.
- identify the product formed from the reaction of a given *α*, *β*-unsaturated aldehyde or ketone with a given lithium diorganocopper reagent.
- identify the *α*, *β*-unsaturated aldehyde or ketone, the lithium diorganocopper reagent, or both, needed to prepare a given product through a conjugate addition reaction.

Study Notes

At first this section may appear to contain a considerable amount of information, but you should realize that much of the material presented is really repetition. Essentially we see how three different nucleophilic reagents, primary and secondary amines, water and lithium diorganocoppers can add across a carbon-carbon double bond when the latter is conjugated to the carbonyl group of an aldehyde or ketone. Note that the first reagent can also react directly with the carbonyl group of an aldehyde or ketone when there is no conjugated carbon-carbon double bond present, but that the third reagent, lithium dialkylcopper, cannot do so.

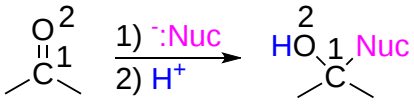
You may be confused about the designation of the product from the conjugate addition to an *α*, *β*-unsaturated aldehyde or ketone as a 1,4 adduct. You can more clearly understand this name if you recognize that the proton added in the second step of the reaction first adds to the oxygen of the enolate ion to produce an enol. The latter then tautomerizes to the more stable keto form.

One of the largest and most diverse classes of reactions involves nucleophilic additions to a carbonyl group. As discussed in Section 19.4, carbonyl carbons are electrophilic due to bond polarity created by resonance.



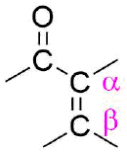
Previously in this chapter, we have discussed a nucleophilic addition to carbonyl carbons called a **1,2 addition**. During 1,2 addition the nucleophile adds to the carbonyl carbon which is defined as the one position. Subsequently, hydrogen adds to the carbonyl oxygen which considered the two position. Overall an atom is added in both the 1 and 2 position justifying the reaction name, 1,2 addition.

Basic Reaction of 1,2 Addition

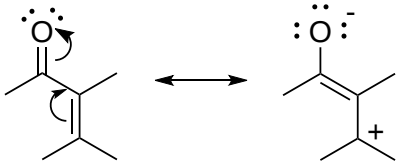


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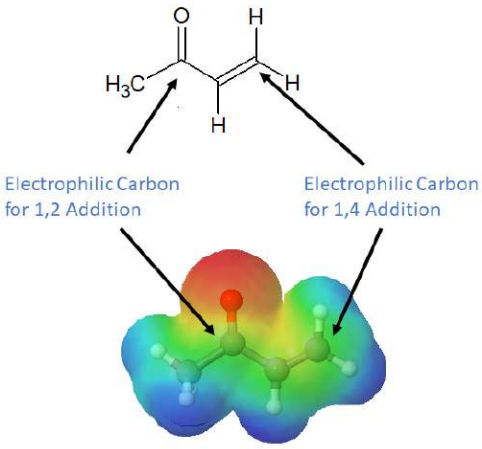
An important functional group is created when an alkene is placed in conjugation with a carbonyl. These conjugated carbonyl are called enones or **α, β-unsaturated carbonyls**. The term α commonly refers to the carbon adjacent to a carbonyl and β referrers to the next carbon in the chain.



Conjugation transmits the electrophilic character of the carbonyl carbon to the β-carbon of the **α, β-unsaturated carbonyl** double bond. The resonance structure shown below shows that the electronegative oxygen atom in α, β-unsaturated carbonyls pulls electrons away from the β carbon making it more electrophilic than a typical alkene carbon.

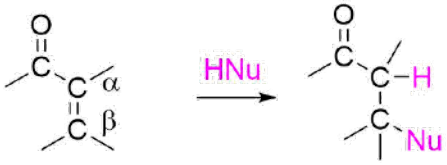


From this resonance form, it should be clear that nucleophiles may attack either at the carbonyl carbon or at the β-alkene carbon. These two modes of reaction are referred to as 1,2-addition and **1,4-addition** respectively. A 1,4-addition is also called a **conjugate addition**.



Basic Reaction of 1,4 Conjugate Addition

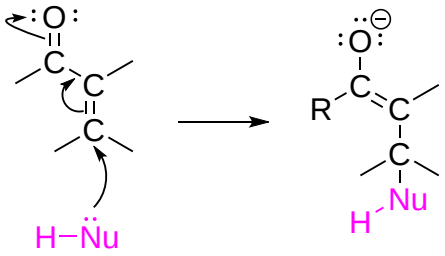
In 1,4 addition, a nucleophile is added to the carbon β to the carbonyl while a hydrogen is added to the carbon α to the carbonyl. Overall, the carbonyl is unaffected by the nucleophilic addition. It is important to note that this reaction only occurs because the alkene is conjugated with a carbonyl. The utility of 1,4 conjugate addition is shown by the wide variety of nucleophiles which can be added to a α, β unsaturated carbonyls.



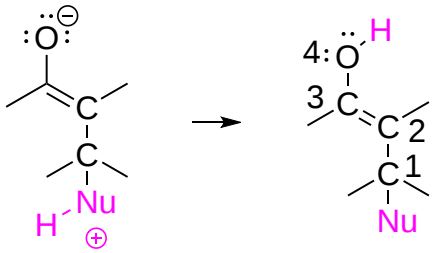
General Mechanism for 1,4 Conjugate Addition

The mechanism starts with the nucleophile attacking the electrophilic β carbon forming a single bond. The two electrons from the alkene pi bond are pushed onto the electronegative carbonyl oxygen creating an enolate. In the next step the the enolate is protonated to form an enol. If the original nucleophile was neutral, this addition will cause it to become positively charge. A proton transfer will occur making the nucleophile neutral and turning the enolate into an enol. If the original nucleophile was negatively charged this protonation is accomplished by the subsequent addition of a proton source. The product of the second step of the mechanism shows why the reaction is called a 1,4 addition. The nucleophile bonds to the β alkene carbon which is considered the one position and the hydrogen adds to the carbonyl oxygen which is in the four position. Overall, addition occurs in the one and four position. In the final step of the mechanism, the enol undergoes a rearranges to form a carbonyl during a process called tautomerization. Tautomerization causes the hydrogen to move from the oxygen to the β-carbon. The tautomerization process will be discussed in greater detail in Section 22.3.

Step 1: Nucleophilic attack



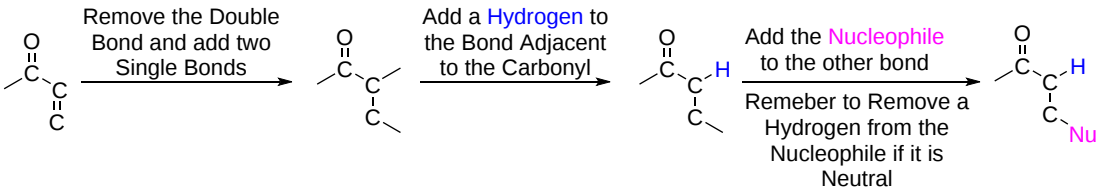
Step 2: Protonation



Step 3: Tautomerization

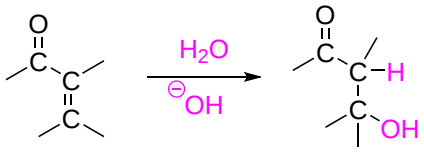
Predicting the Products of a 1,4 Conjugate Addition

In total, 1,4 addition occurs across the alkene bond of the α, β unsaturated carbonyl. The alkene pi bonds is broken to form two single bonds, one on the α-carbon and one on the β-carbon. During 1,4 addition, the α-carbon of the α, β unsaturated carbonyl forms a bond with a hydrogen while the β-carbon forms a bond to the nucleophile. Remember that neutral nucleophiles typically lose a hydrogen during 1,4 addition.

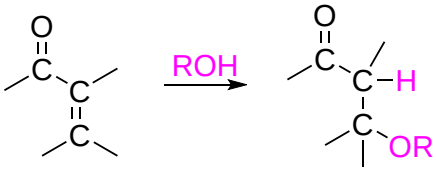


Nucleophiles Which add 1,4 to α, β Unsaturated Carbonyls

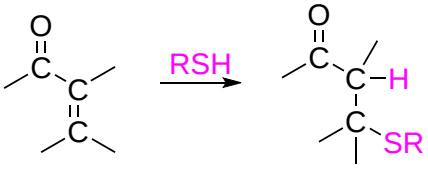
Hydroxide



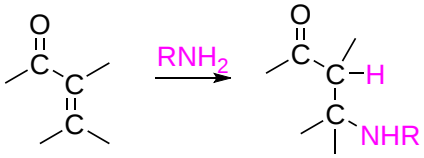
Alcohols



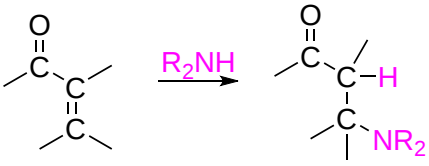
Thiols



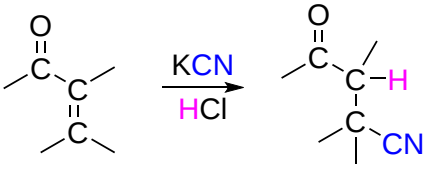
1° Amines



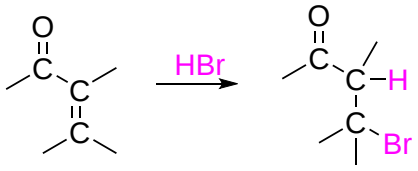
2° Amines



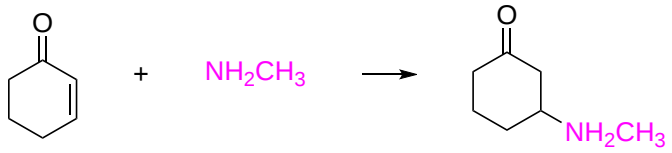
Cyanides



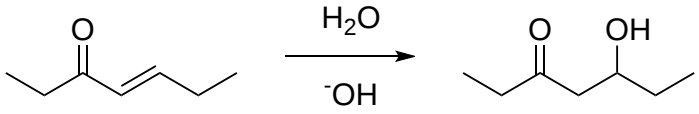
HBr



Examples



The synthesis of 3-(*N*-Methylamino)cyclohexanone



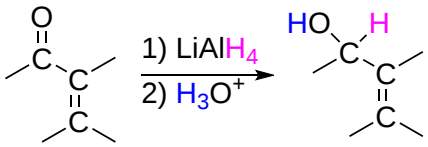
The Synthesis of 5-Hydroxy-3-heptenone

1,2 vs. 1,4 Addition

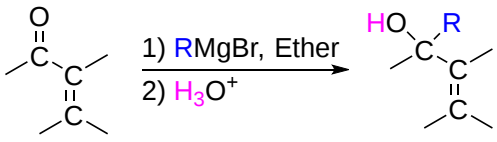
Whether 1,2 or 1,4-addition occurs to a α, β unsaturated carbonyl depends on multiple variables but is mostly determined by the nature of the nucleophile. During the addition of a nucleophile there is a competition between the formation 1,2 and 1,4 addition products. If the nucleophile is a strong base, such as Grignard reagents or metal hydrides, both the 1,2 and 1,4 reactions are irreversible and therefor are under kinetic control. Since 1,2-additions to the carbonyl group are fast, we would expect to find a predominance of 1,2-products from these reactions. If the nucleophile is a weak base, such as, water, alcohols or amines, then the possible 1,2 addition is usually reversible. This means the competition between 1,2 and 1,4 addition is under thermodynamic control. In this most cases, the 1,4-addition product dominates because the stable carbonyl group is retained.

Nucleophiles Which add 1,2 to α, β-Unsaturated Carbonyls

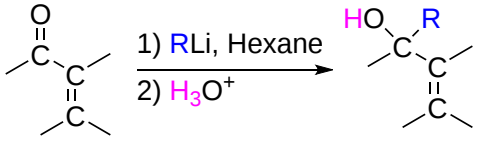
Metal Hydrides ($LiAlH_4$)



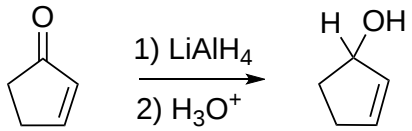
Grignard Reagents



Organolithium Reagents

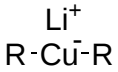


Example



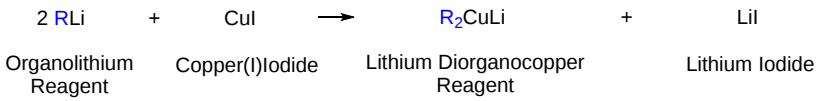
Gilman Reagents

Another important reaction exhibited by organometallic reagents is metal exchange. Organolithium reagents react with cuprous iodide to give a **lithium diorganocopper reagent**, which often is referred to as a **Gilman reagent**. Remember that organolithium reagents are formed by a reaction of lithium metal with an organohalide. Lithium diorganocopper reagents are considered a source of carbanion like nucleophiles similar to Grignard and Organolithium reagents. However, the reactivity of lithium diorganocuprate reagents is slightly different and this difference will be exploited in different situations. Diorganocuprate reagents are made from the reaction of two equivalents of an organolithium reagent and copper (I) iodide (CuI). The created lithium diorganocuprate reagent acts as a source of $R:^-$

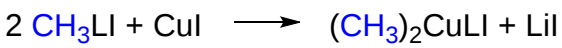


Lithium Diorganocopper (Gilman Reagent)

General Reaction



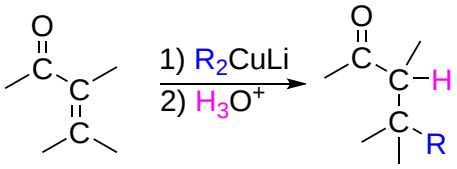
Example



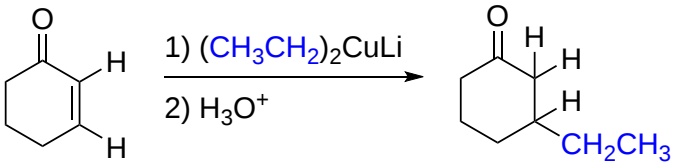
Formation of Lithium Dimethylcopper

Reaction of 1,4 Conjugate Addition of Gilman Reagents to α, β Unsaturated Ketones

Lithium diorganocopper reagents, R_2CuLi, undergo 1,4 conjugate addition when reacted with α, β Unsaturated ketones. Using lithium diorganocopper reagents allows for a wide range of organic groups to undergo this 1,4 conjugate addition including alkyl, aryl, and alkenyl groups. Because a C-C single bond is formed this reaction is an excellent method for adding to the carbon framework of a ketone.

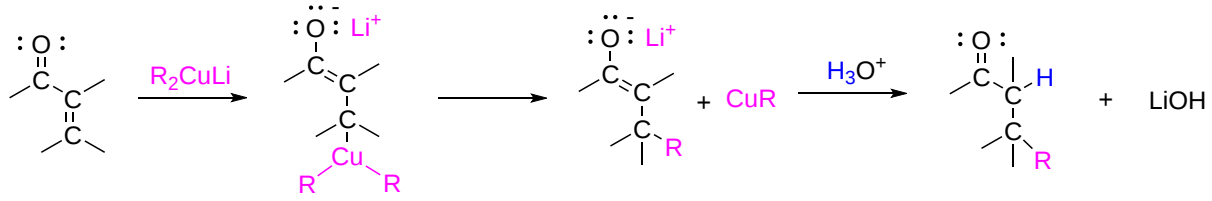


Example



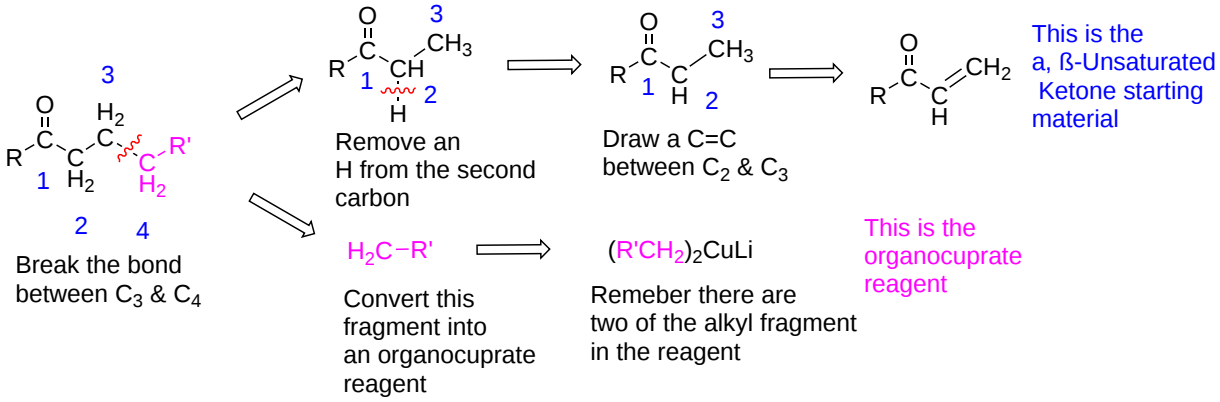
Mechanism for the 1,4 Conjugate Addition of Lithium Diorganocopper Reagents to α, β-Unsaturated Ketone

This mechanism is only slightly different than the general mechanism for 1,4 conjugate addition described above. The mechanism starts with the nucleophilc diorganocopper anion (R_2Cu^-) adding to the electrophilc β alkene carbon forming a Cu-C bond. The R group from the diorganocopper is then transferred to the β alkene carbon with elimination of a neutral organocopper species (RCu). Protonation of the enolate ion followed by tautomerization creates the final 1,4 addition product.



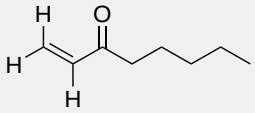
Synthesis of Ketones using 1,4 Conjugate Addition of Lithium Diorganocopper Reagents to α, β Unsaturated Ketones

When using retrosynthetic analysis to plan the synthesis of a ketone, remember this reaction allows for the formation of a C-C bond between third and fourth carbon away from a ketone. The carbonyl group in the target molecule will become a α, β unsaturated carbonyl in the probable reactant. To determine the structure of a possible reactant, start by cleaving the C-C between the third and fourth carbon away from the carbonyl to create two fragments. The take the fragment which retains the carbonyl and remove a hydrogen from the second carbon and connect the second and third carbon with a double bond. The creates the required α, β unsaturated carbonyl reactant. The other fragment will become the lithium diorganocopper reagent. Remember the lithium diorganocopper reagent contains two of the required R group. Note! If the fourth carbon away from the ketone in the target molecule is tertiary or quarternary there may be multiple bonds which could be retrosynthetically cleaved.



Something Extra: Why do Metals Have a Smell When They are Nonvolatile?

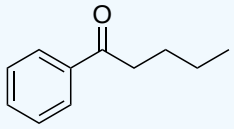
If you have ever encountered a metallic scent when counting coins or handling metals, especially copper, you were probably being fooled. The metallic smell could not have come from the metal because metals are non-volatile and do not evaporate. This means the odor molecules associated with metal scent must come from a different source. The volatile molecules that create the metallic smell are produced by a chemical reaction between skin oils and the metal itself. These volatile molecules, primarily aldehydes and ketones, create a sensory illusion that the metal is producing the smell, even though metals have no natural odor. The main molecule is the α, β Unsaturated Ketone, 1-Octen-3-one, which is described as smelling like mushrooms or metal. This is an illusion because the molecule doesn't smell like metals; metals smells like this molecule. Because we have smelled 1-Octen-3-one coming from metals for so long, we mistake its smell with the metal itself. This kind of chemical reaction also explain why blood produces a metallic smell when it comes into contact with skin. Blood contains iron in hemoglobin, and the same chemical reaction produces odor molecules when blood touches skin.



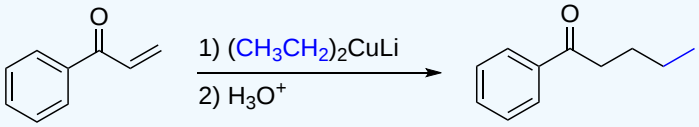
Structure of 1-Octen-3-one

Exercise 5.14.1

How would you make the following molecule using a 1,4 Conjugate Addition of a Gilman Reagent to a α, β Unsaturated Ketone?



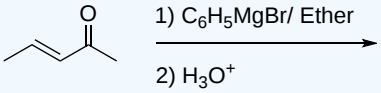
Answer



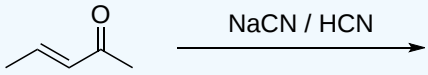
Exercise 5.14.2

Draw the bond-line structures for the products of the reactions below.

a)

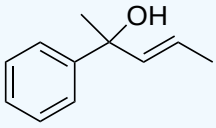


b)

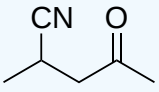


Answer

A



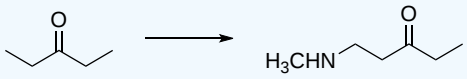
b)



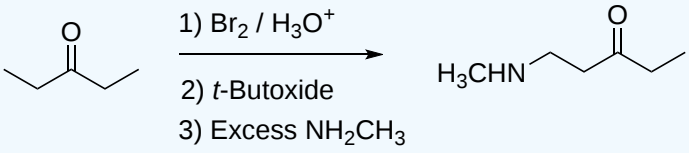
https://chem.libretexts.org/@go/page/500416

Exercise 5.14.3

Specify the reagents needed to perform the following chemical transformation.



Answer



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5.15: Spectroscopy of Aldehydes and Ketones

Objectives

After completing this section, you should be able to

1. identify the region of the infrared spectrum in which the carbonyl absorption of aldehydes and ketones is found.
2. identify the region of the infrared spectrum in which the two characteristic C-H absorptions of aldehydes are found.
3. use a table of characteristic absorption frequencies to assist in the determination of the structure of an unknown aldehyde or ketone, given its infrared spectrum and other spectral or experimental data.
4. identify the region of a proton NMR spectrum in which absorptions caused by the presence of aldehydic protons and protons attached to the α-carbon atoms of aldehydes and ketones occur.
5. identify two important fragmentations that occur when aliphatic aldehydes and ketones are subjected to analysis by mass spectrometry.

Key Terms

Make sure you can define and use the key term below in context.

- McLafferty rearrangement

Study Notes

The appearance of a strong absorption at 1660–1770 cm^{-1} in the infrared spectrum of a compound is a clear indication of the presence of a carbonyl group. Although you need not remember the detailed absorptions it is important that you realize that the precise wavenumber of the infrared absorption can often provide some quite specific information about the environment of the carbonyl group in a compound. Notice how conjugation between a carbonyl group and a double bond (α, β-unsaturated aldehyde or ketone or aromatic ring) lowers the absorption by about 25–30 cm^{-1}.

You may wish to review the McLafferty rearrangement and the alpha cleavage from the CHEM 231 textbook.

IR Spectra

Ketones

The carbonyl (C=O) stretching vibration band of saturated aliphatic ketones appears at:

- Aliphatic ketones 1715 cm^{-1}
- α, β-unsaturated (enone) 1685-1666 cm^{-1}

Figure 1. shows the spectrum of 2-butanone. This is a saturated ketone, and the C=O band appears at 1715.

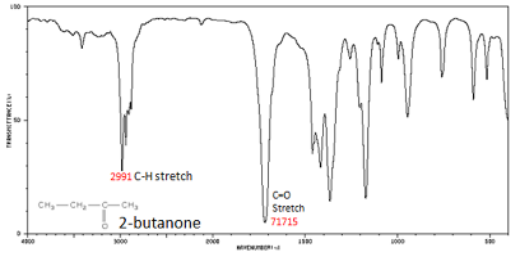


Figure 1. Infrared Spectrum of 2-Butanone

Aldehyde

In the IR spectra of an aldehyde, a peak usually appears around 2720 cm^{-1} and often appears as a shoulder-type peak just to the right of the alkyl C–H stretches.

H–C=O stretch 2830-2695 cm^{-1}

C=O stretch

- Aliphatic aldehydes 1740-1720 cm^{-1}
- α, β-unsaturated aldehydes (enones) 1710-1685 cm^{-1}

Figure 2. shows the spectrum of butyraldehyde.

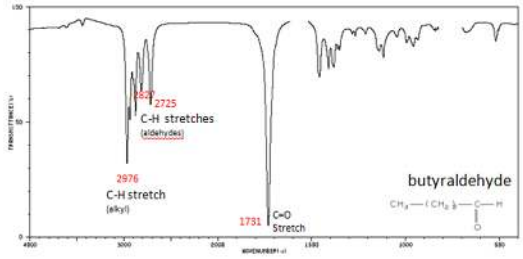
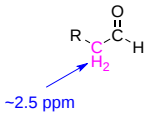


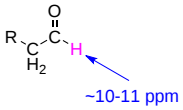
Figure 2. Infrared Spectrum of Butyraldehyde

^{1}H NMR Spectra

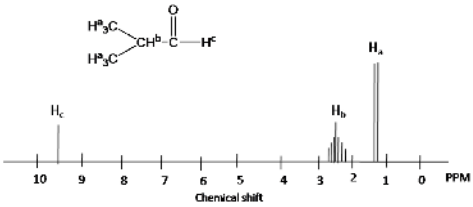
Hydrogens attached to a carbon adjacent to the sp^2 hybridized carbon in aldehydes and ketones are deshielded due to the anisotropy created by the C=O bond and usually show up at 2.0-2.5 ppm.



Aldehyde hydrogens are highly deshielded, appearing far downfield at 9-10 ppm, due to the anisotropy created by the pi electrons of the C=O bond, and induction caused by the highly electronegative oxygen atom.

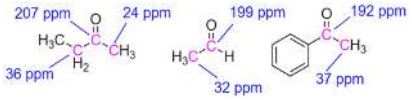


The ^{1}H NMR spectra of 2-methylpropanal is shown below. The methyl groups, (H_b), show up at 1.1 ppm. The -CH- group is moved downfield due to effect an adjacent aldehyde group (2.4 ppm). The chemical shift of aldehyde hydrogen is highly deshielded (9.6 ppm). Splitting pattern is determined by (N+1) rule: H_a is split into two peaks by H_b(#of proton=1). H_b has the septet pattern by H_a (#of proton=6). H_c has one peak. (Note that H_c has doublet pattern by H_b due to vicinal proton-proton coupling.)



^{13}C NMR Spectra

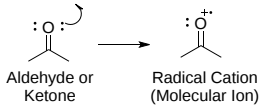
Aldehydes and ketones have distinctive ^{13}C NMR peaks which appear in the range 190 to 215 ppm range. Very few types of carbons absorb in this range so the presence of ^{13}C peak around 200 ppm is considered evidence for a carbonyl group.



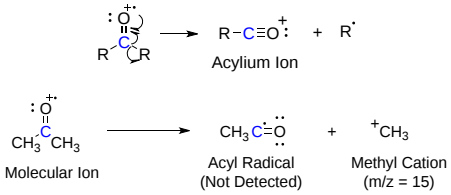
Mass Spectra

Aldehydes and ketones generally give moderately intense signals due to their molecular ions, M^+. Thus the determination of the molecular weight of a ketone by mass spectroscopy usually is not difficult. Furthermore, there are some characteristic fragmentation patterns that aid in structural identification. These are:

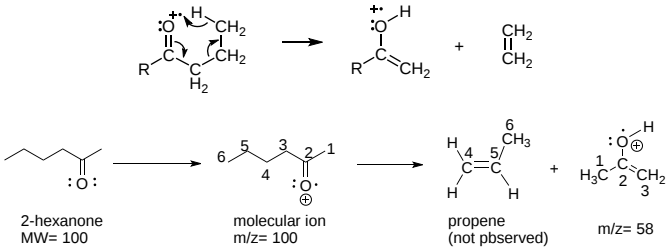
- Formation of the molecular ion:



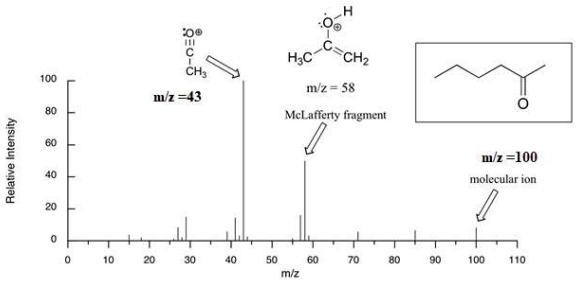
- *α cleavage to form an acylium ion. This is usually the base peak in the mass spectra.*



- *A common fragmentation pattern for larger carbonyl compounds is a transfer of γ hydrogen with β cleavage* called the **Mc-Lafferty rearrangement:**



The mass spectrum of 2-hexanone shows a 'Mc Lafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is an acylium ion formed after alpha cleavage is m/z = 43. The molecular ion peak is at m/z =100.

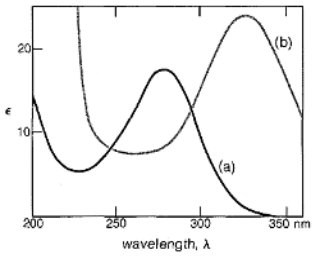


Electronic Absorption Spectra



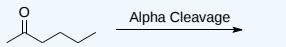
2-Butanone 3-Buten-2-one

The absorption at 277 nm for 2-butanone is an n → pi* transition, and with 3-buten-2-one, this absorption shifts to longer wavelengths (324 nm). There is also an intense absorption band for 3-buten-2-one at 219 nm, which is a pi →pi* transition. With 2-butanone, a corresponding absorption occurs at 185 nm, which is out of the range of the spectrometer used to take the spectra.



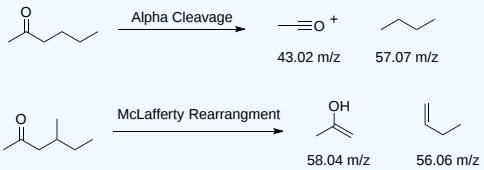
? Exercise 5.15.1

What are the masses of all the components in the following fragmentations?





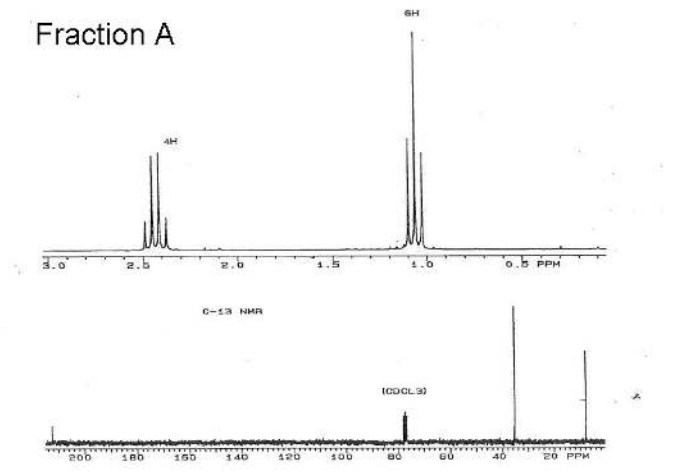
Answer

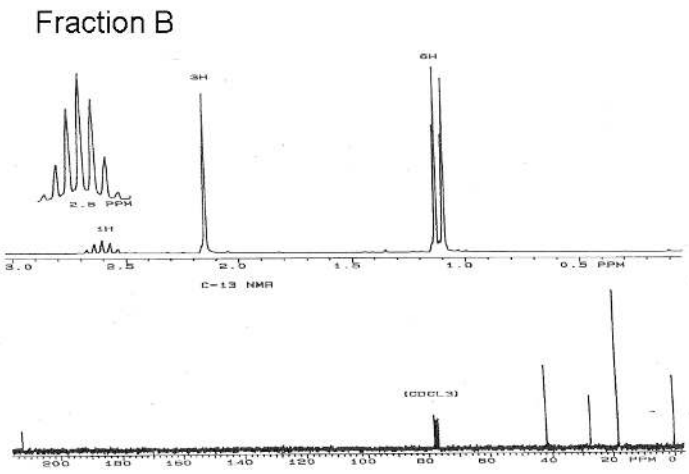


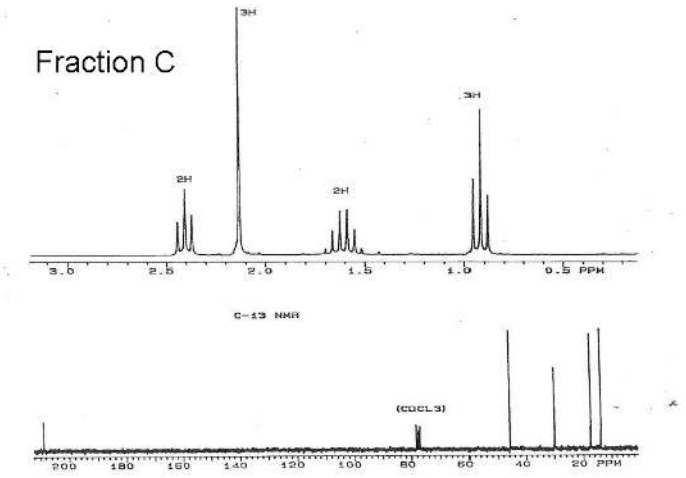
? Exercise 5.15.2

A mixture was separated into three fractions: A, B, and C. Elemental analysis reveals that the fractions are structural isomers with the following composition: 69.72% C, 11.70% H, and 18.58% O. The IR spectra for all fractions show several moderate bands around 2950 cm^{-1}, and a strong band near 1700 cm^{-1}. The proton and ^{13}C NMR spectra for each fraction are shown below. Give the common name and draw the bond-line structure for each fraction and correlate the NMR signals with their respective atoms.

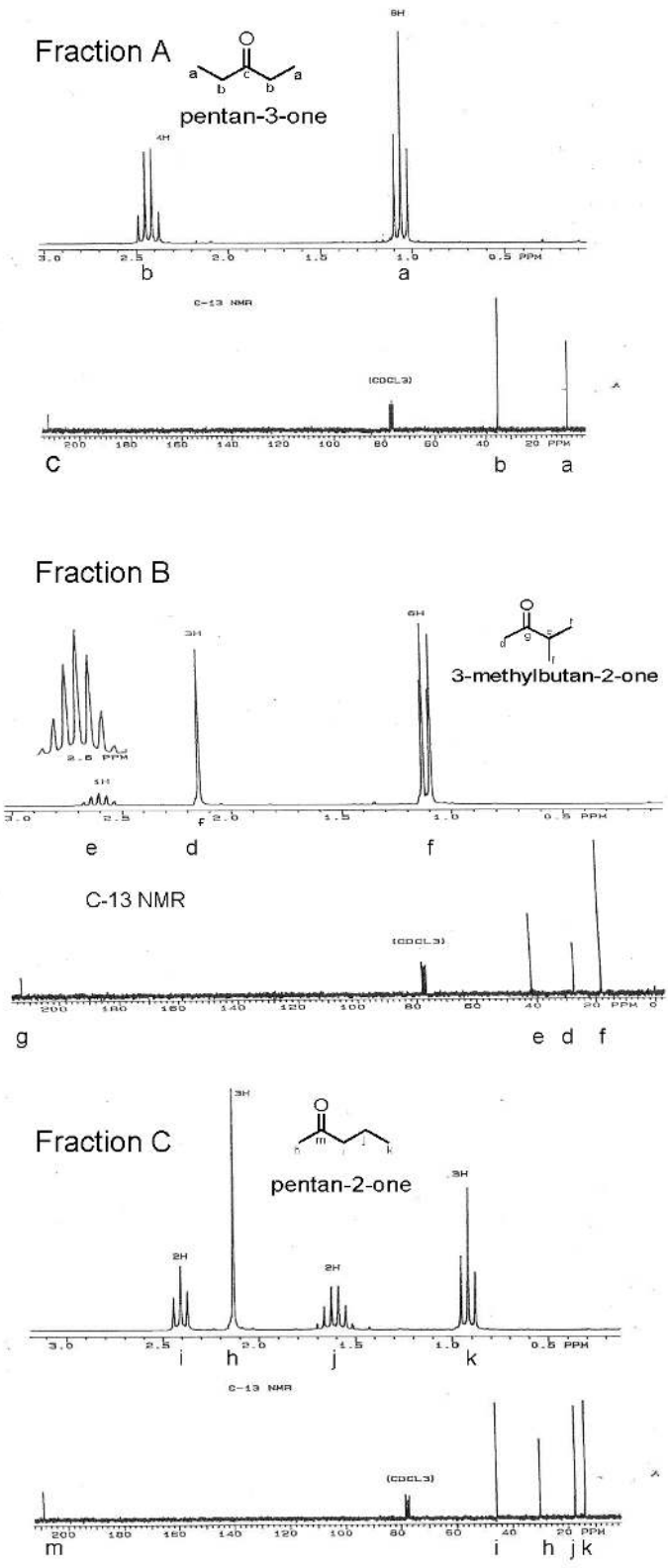
https://chem.libretexts.org/@go/page/500417


Fraction A
6H
4H
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
(CDCL3)
200
180
150
140
120
100
80
60
40
20 PPM


Fraction B
6H
3H
2.8 PPM
1H
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
(CDCL3)
200
180
150
140
120
100
80
60
40
20 PPM


Fraction C
3H
3H
2H
2H
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
(CDCL3)
200
180
150
140
120
100
80
60
40
20 PPM

Answer



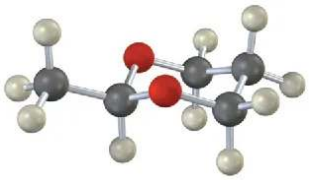
This page titled 5.15: Spectroscopy of Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Sol Parajon Puenzo (Cañada College) .

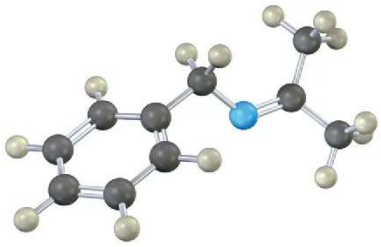
- **19.14: Spectroscopy of Aldehydes and Ketones** by Dietmar Kennepohl, John Roberts, Layne Morsch, Marjorie C. Caserio, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

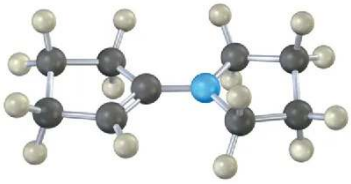
5.16: Additional Problems

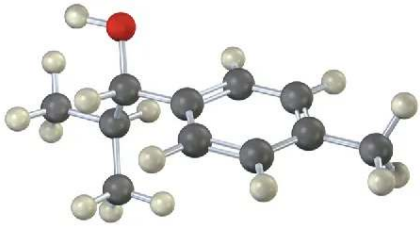
Visualizing Chemistry

PROBLEM 5-27 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.

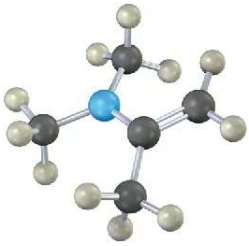
(a) 

(b) 

(c) 

(d) 

PROBLEM 5-28 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.



PROBLEM 5-29 The enamine prepared from acetone and dimethylamine is shown in its lowest-energy form.

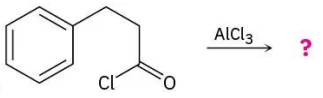
(a) What is the geometry and hybridization of the nitrogen atom?

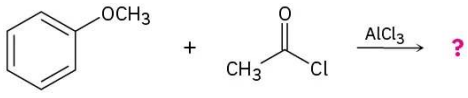
(b) What orbital on nitrogen holds the lone pair of electrons?

(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?

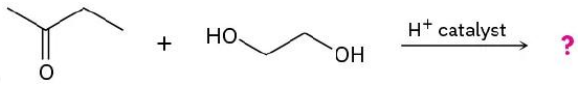
Mechanism Problems

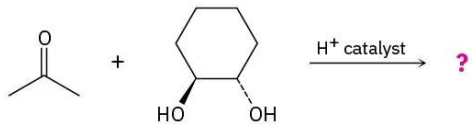
PROBLEM 5-30 Predict the product(s) and propose a mechanism for each of the following reactions:

(a) 

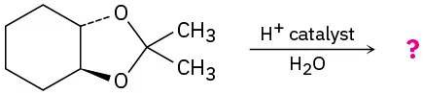
(b) 

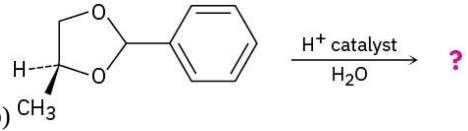
PROBLEM 5-31 Predict the product(s) and propose a mechanism for each of the following reactions:

(a) 

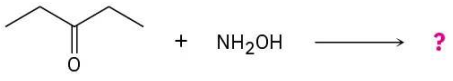
(b) 

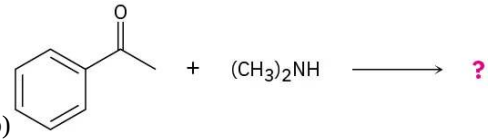
PROBLEM 5-32 Predict the product(s) and propose a mechanism for each of the following reactions:

(a) 

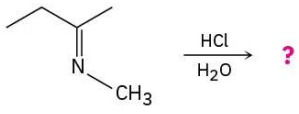
(b) 

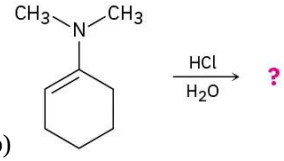
PROBLEM 5-33 Predict the product(s) and propose a mechanism for each of the following reactions:

(a) 

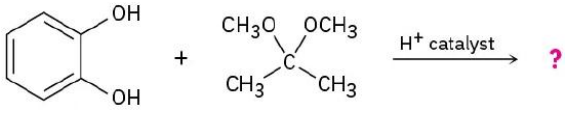
(b) 

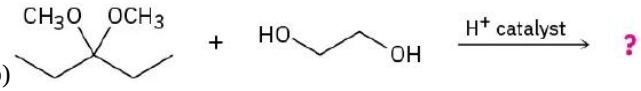
PROBLEM 5-34 Predict the product(s) and propose mechanisms for the following reactions:

(a) 

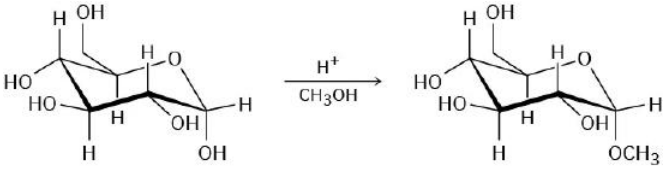
(b) 

PROBLEM 5-35 The following reaction begins with an acetal and converts it into a different acetal. Predict the product(s) and propose a mechanism.

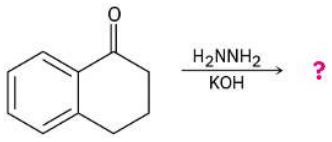
(a) 

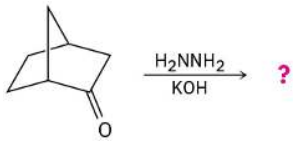
(b) 

PROBLEM 5-36 When *α*-glucose is treated with an acid catalyst in the presence of an alcohol, an acetal is formed. Propose a mechanism for this process and give the structure of the stereoisomeric acetal that you would also expect as a product.

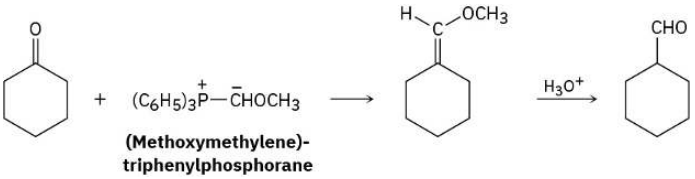


PROBLEM 5-37 Predict the products of the following Wolff–Kishner reactions. Write the mechanism for each, beginning from the hydrazone intermediate.

(a) 

(b) 

PROBLEM 5-38 Aldehydes can be prepared by the Wittig reaction using (methoxymethylene)triphenylphosphorane as the Wittig reagent, followed by hydrolysis of the product with acid. For example,

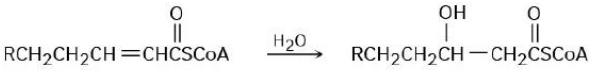


(Methoxymethylene)-triphenylphosphorane

(a) How would you prepare the necessary phosphorane?

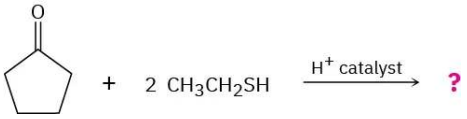
(b) Propose a mechanism for the hydrolysis step.

PROBLEM 5-39 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.

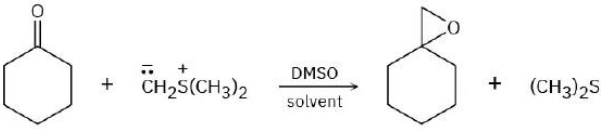


Unsaturated acyl CoA **β-Hydroxyacyl CoA**

PROBLEM 5-40 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:

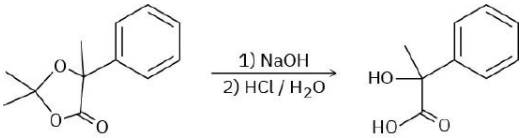


PROBLEM 5-41 Ketones react with dimethylsulfonium methylide to yield epoxides. Suggest a mechanism for the reaction.

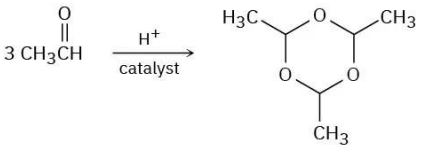


Dimethylsulfonium methylide

PROBLEM 5-42 Propose a mechanism for the following reaction.

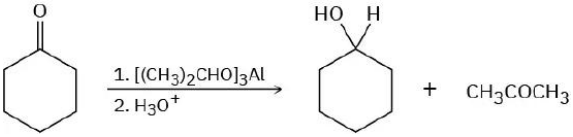


PROBLEM 5-43 Paraldehyde, a sedative and hypnotic agent, is prepared by treatment of acetaldehyde with an acidic catalyst. Propose a mechanism for the reaction.

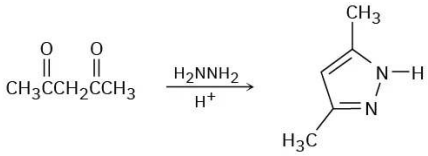


Paraldehyde

PROBLEM 5-44 The Meerwein–Ponndorf–Verley reaction involves reduction of a ketone by treatment with an excess of aluminum triisopropoxide, $[(CH_3)_2CHO]_3Al$. 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.

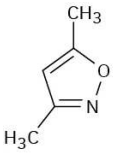


PROBLEM 5-45 Propose a mechanism to account for the formation of 3,5-dimethylpyrazole from hydrazine and 2,4-pentanedione. What has happened to each carbonyl carbon in going from starting material to product.



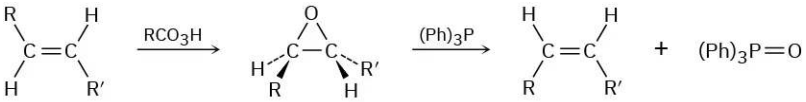
2,4-Pentanedione **3,5-Dimethylpyrazole**

PROBLEM 5-46 In light of your answer to PROBLEM 5-45, propose a mechanism for the formation of 3,5-dimethylisoxazole from hydroxylamine and 2,4-pentanedione.

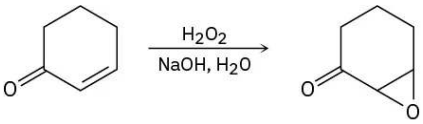


3,5-Dimethylisoxazole

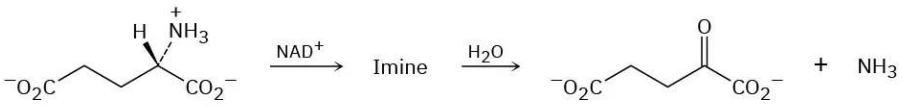
PROBLEM 5-47 Trans alkenes are converted into their cis isomers and vice versa on epoxidation followed by treatment of the epoxide with triphenylphosphine. Propose a mechanism for the reaction.



PROBLEM 5-48 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.

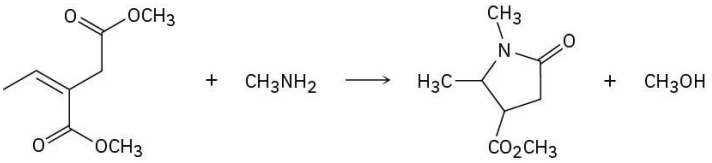


PROBLEM 5-49 One of the biological pathways by which an amine is converted to a ketone involves two steps: (1) oxidation of the amine by NAD^+ to give an imine and (2) hydrolysis of the imine to give a ketone plus ammonia. Glutamate, for instance, is converted by this process into α-ketoglutarate. Show the structure of the imine intermediate, and propose mechanisms for both steps.

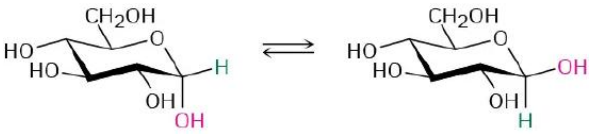


Glutamate **α-Ketoglutarate**

PROBLEM 5-50 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.

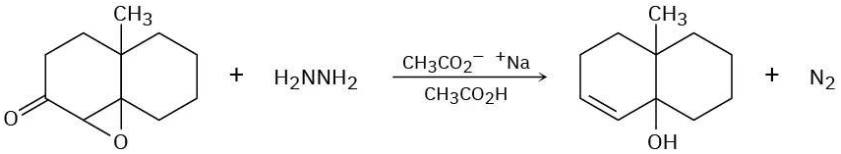


PROBLEM 5-51 When crystals of pure α-glucose are dissolved in water, isomerization occurs slowly to produce β-glucose. Propose a mechanism for the isomerization.



α-Glucose **β-Glucose**

PROBLEM 5-52 The Wharton reaction converts an epoxy ketone to an allylic alcohol by reaction with hydrazine. Review the Wolff–Kishner reaction in Section 19.9 and then propose a mechanism.



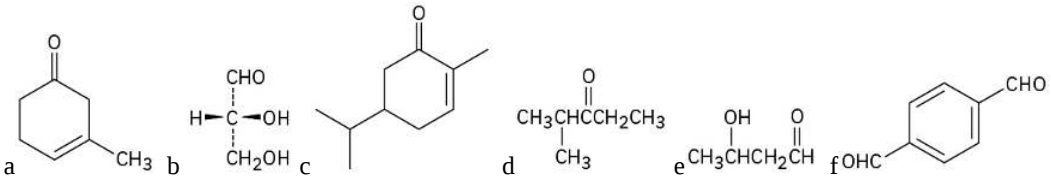
Naming Aldehydes and Ketones

PROBLEM 5-53 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

PROBLEM 5-54 Draw and name the seven aldehydes and ketones with the formula $C_5H_{10}O$. Which are chiral?

PROBLEM 5-55 Give IUPAC names for the following compounds:



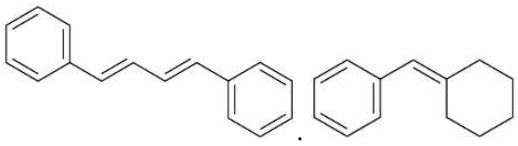
PROBLEM 5-56 Draw structures of compounds that fit the following descriptions:

(a)An α,β-unsaturated ketone, C6H8O (b) An α-diketone (c) An aromatic ketone, $C_9H_{10}O$ (d) A diene aldehyde, C_7H_8O

PROBLEM 5-57 Predict the products of the reaction of (1) phenylacetaldehyde and (2) acetophenone with the following reagents:

(a) NaBH4, then H3O+, (b) Dess–Martin reagent (c) NH_2OH, HCl catalyst (d) CH_3MgBr, then H_3O^+ (e) 2 CH_3OH, HCl catalyst (f) H_2NNH_2, KOH (g) $(C_6H_5)_3P$=Math input errorCH_2 (h) HCN, KCN

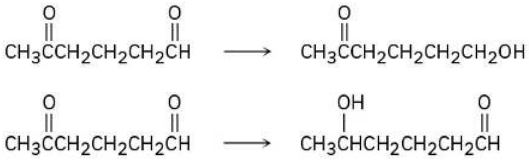
PROBLEM 5-58 Show how you might use a Wittig reaction to prepare the following alkenes. Identify the alkyl halide and the carbonyl components.



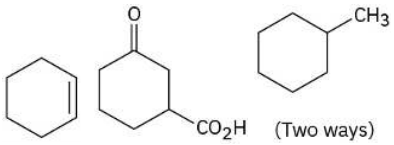
PROBLEM 5-59 How would you use a Grignard reaction on an aldehyde or ketone to synthesize the following compounds?

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

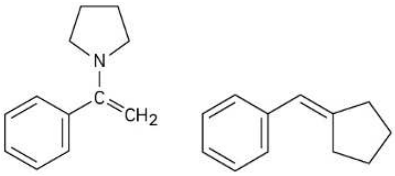
PROBLEM 5-60 How might you carry out the following selective transformations? One of the two schemes requires a protection step. (Recall from Section 19.4 that aldehydes are more reactive than ketones toward nucleophilic addition.)



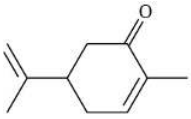
PROBLEM 5-61 How would you prepare the following substances from 2-cyclohexenone? More than one step may be needed.



PROBLEM 5-62 How would you synthesize the following substances from benzaldehyde and any other reagents needed?



PROBLEM 5-63 Carvone is the major constituent of spearmint oil. What products would you expect from the reaction of carvone with the following reagents?



Carvone

(a) (CH3)2Cu–Li+, then H_3O^+

(b) $LiAlH_4$, then H_3O^+

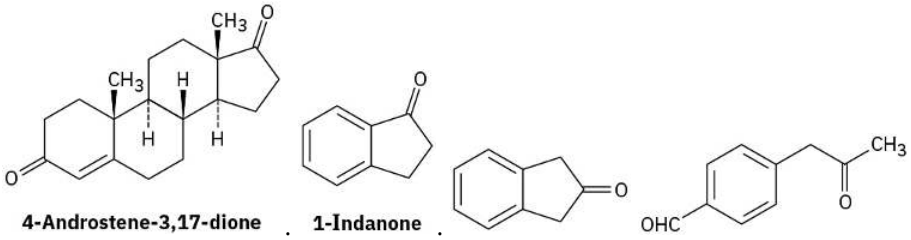
(c) CH_3NH_2 (d) C_6H_5MgBr, then H_3O^+ (e) H_2/Pd (f) $HOCH_2CH_2OH$, HCl (g) $(C_6H_5)_3\overset{+}{T}eXAtom\overset{-}{T}eXAtomHCH_3$

PROBLEM 5-64 How would you synthesize the following compounds from cyclohexanone?

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

Spectroscopy

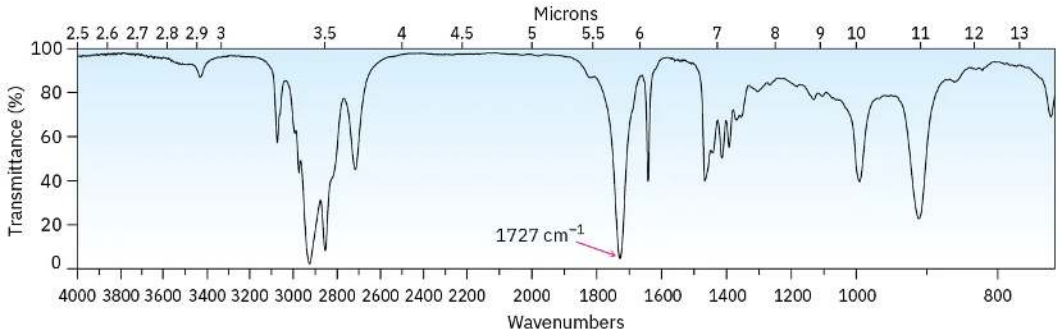
PROBLEM 5-65 At what position would you expect to observe IR absorptions for the following molecules?

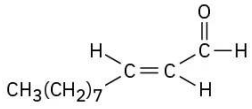


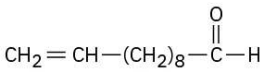
4-Androstene-3,17-dione . **1-Indanone** .

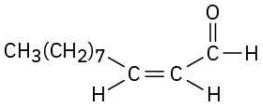
PROBLEM 5-66 Acid-catalyzed dehydration of 3-hydroxy-3-phenylcyclohexanone leads to an unsaturated ketone. What possible structures are there for the product? At what position in the IR spectrum would you expect each to absorb? If the actual product has an absorption at 1670 cm^{–1}, what is its structure?

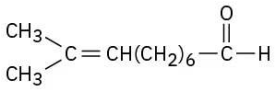
PROBLEM 5-67 Choose the structure that best fits the IR spectrum shown.



a- 

b- 

c- 

d- 

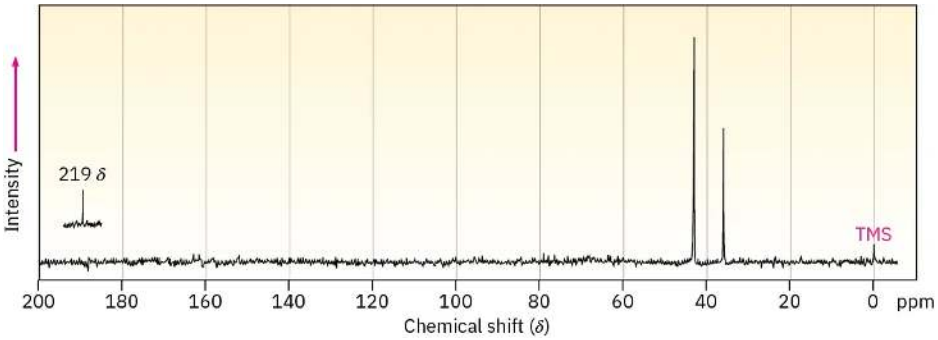
PROBLEM 5-68 Propose structures for molecules that meet the following descriptions. Assume that the kinds of carbons (1°, 2°, 3°, or 4°) have been assigned by DEPT–NMR.

$C_6H_{12}O$; 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°)

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

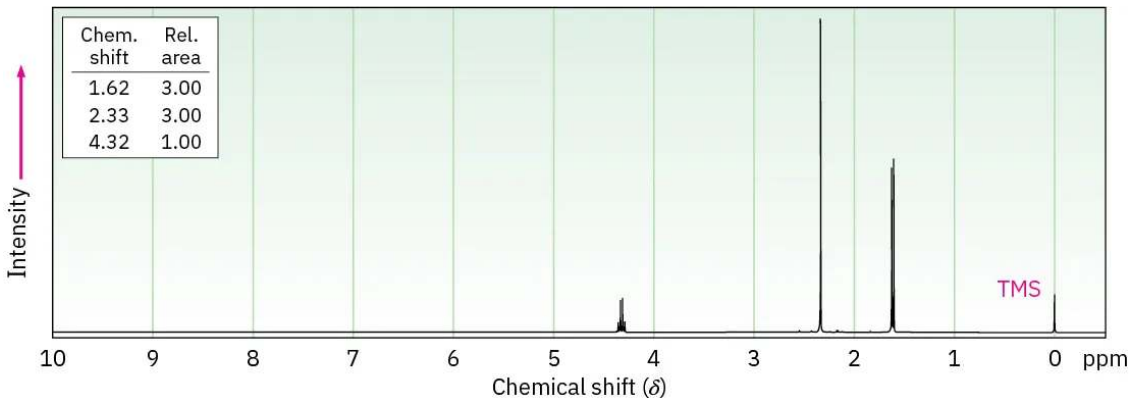
C_6H_8O; IR: 1680 cm^{-1}; ^{13}C NMR: 22.9 δ (2°), 25.8 δ (2°), 38.2 δ (2°), 129.8 δ (3°), 150.6 δ (3°), 198.7 δ (4°)

PROBLEM 5-69 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.

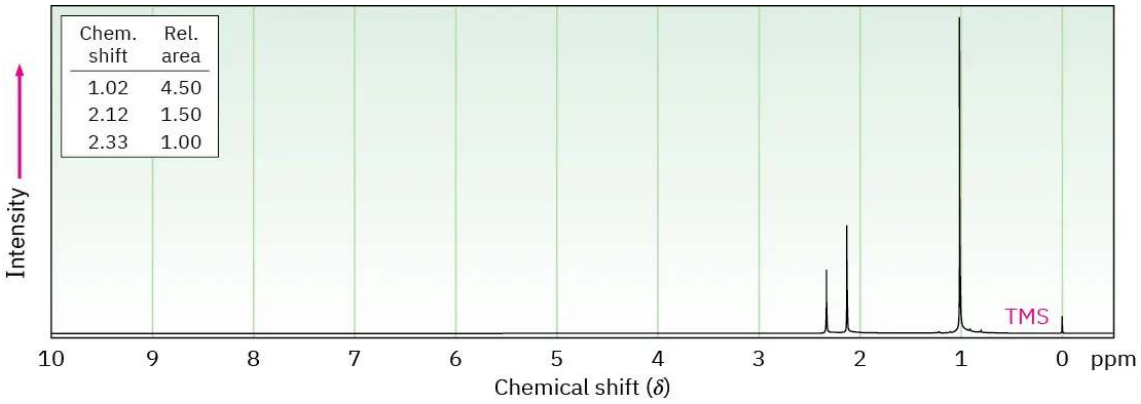


PROBLEM 5-70 Propose structures for ketones or aldehydes that have the following ^1H NMR spectra:

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

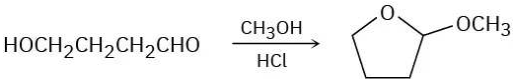


(b) $C_7H_{14}O$ IR: 1710 cm^{-1}



General Problems

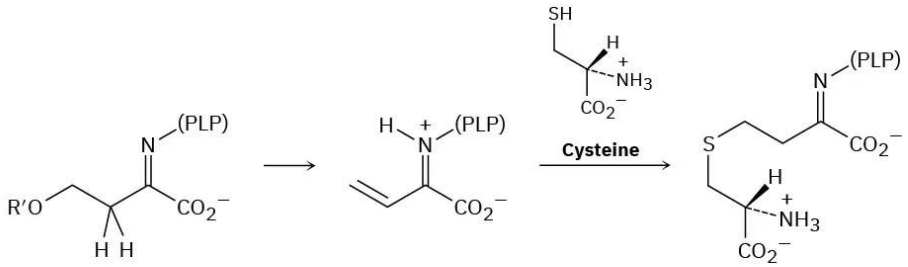
PROBLEM 5-71 When 4-hydroxybutanal is treated with methanol in the presence of an acid catalyst, 2-methoxytetrahydrofuran is formed. Explain.



PROBLEM 5-72 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.

PROBLEM 5-73 Reaction of 2-butanone with HCN yields a chiral product. What stereochemistry does the product have? Is it optically active?

PROBLEM 5-74 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?



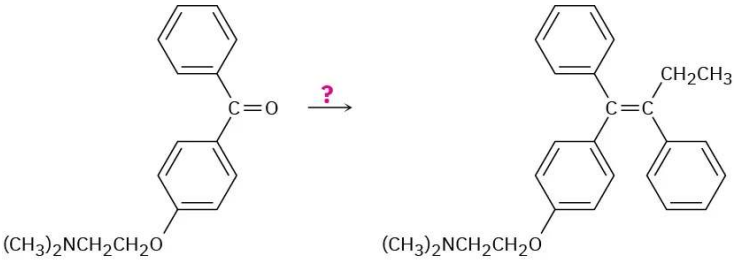
***O*-Succinylhomoserine–PLP imine** **Unsaturated imine**

PROBLEM 5-75 Each of the following reaction schemes has one or more flaws. What is wrong in each case? How would you correct each scheme?

PROBLEM 5-76 6-Methyl-5-hepten-2-one is a constituent of lemongrass oil. How could you synthesize this substance from methyl 4-oxopentanoate?

PROBLEM 5-77 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?

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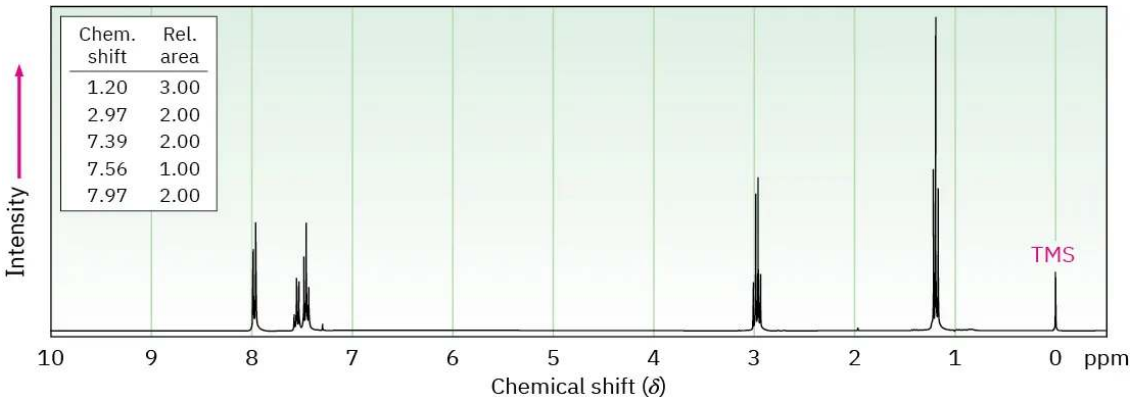


Tamoxifen

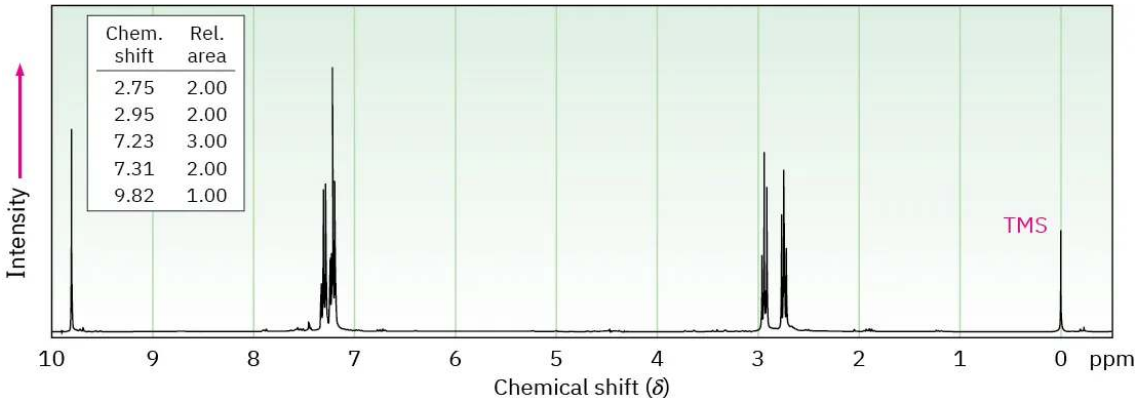
PROBLEM 5-78 Compound A, MW = 86, shows an IR absorption at 1730 cm^{-1} and a very simple ^1H NMR spectrum with peaks at 9.7 δ (1 H, singlet) and 1.2 δ (9 H, singlet). Propose a structure for A.

PROBLEM 5-79 Compound B is isomeric with A (Problem 5-78) 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?

PROBLEM 5-80 The ^1H NMR spectrum shown is that of a compound with the formula $C_9H_{10}O$. How many double bonds and/or rings does this compound contain? If the unknown compound has an IR absorption at 1690 cm^{-1}, what is a likely structure?

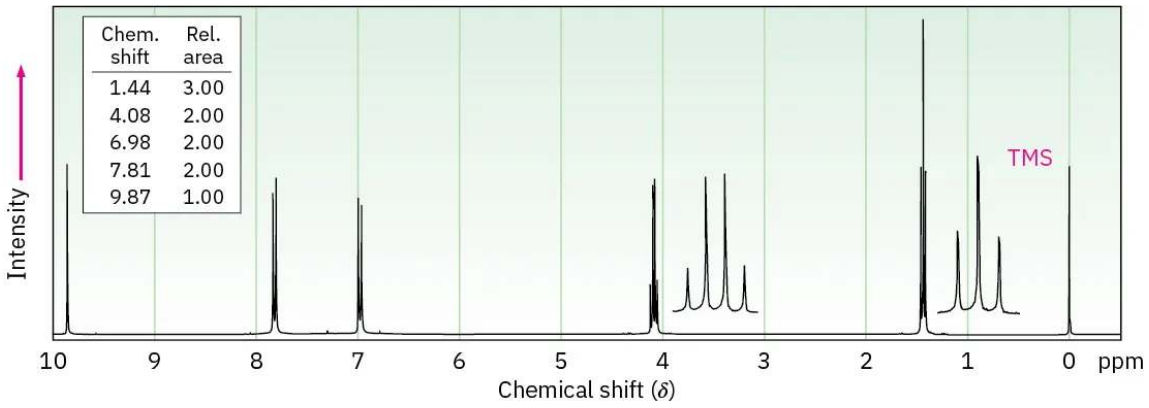


PROBLEM 5-81 The ^1H NMR spectrum shown is that of a compound isomeric with the one in Problem 5-80. This isomer has an IR absorption at 1730 cm^{-1}. Propose a structure. [*Note:* Aldehyde protons (CHO) often show low coupling constants to adjacent hydrogens, so the splitting of aldehyde signals is not always apparent.]

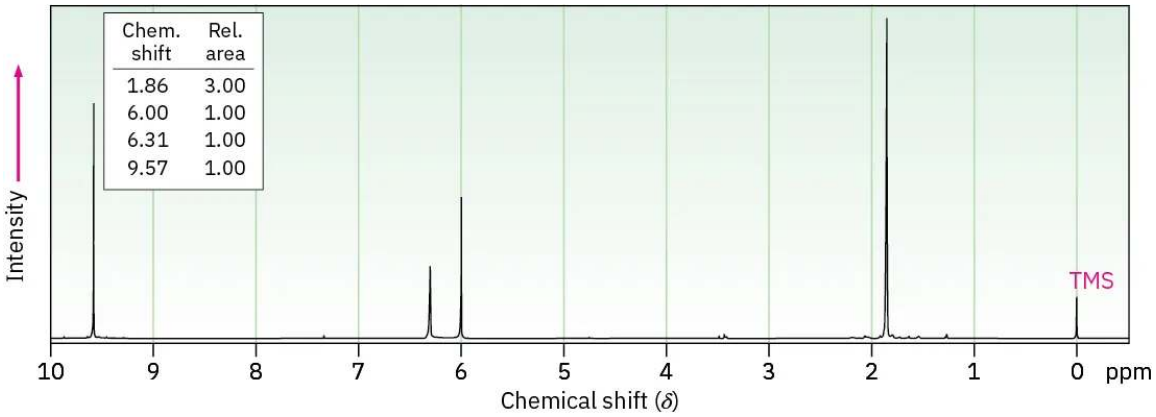


PROBLEM 5-82 Propose structures for ketones or aldehydes that have the following ^1H NMR spectra:

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

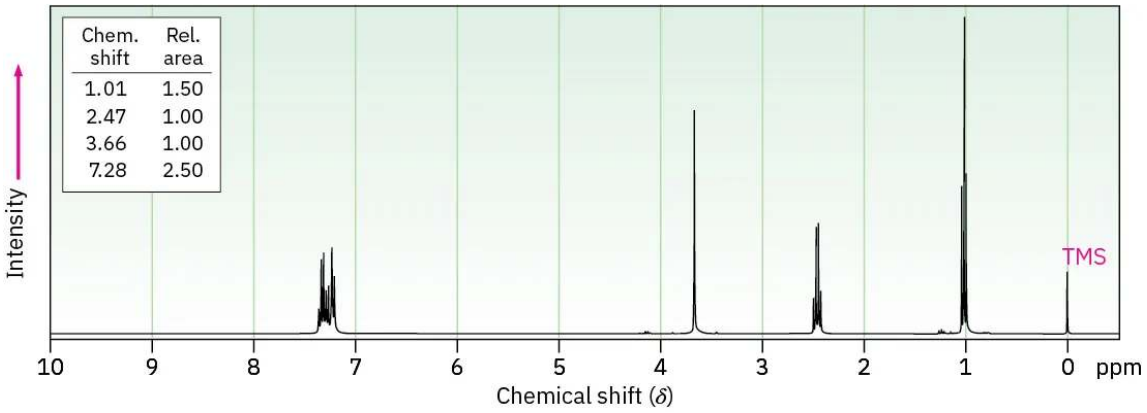


(b) C_4H_6O - IR: 1690 cm^{-1}

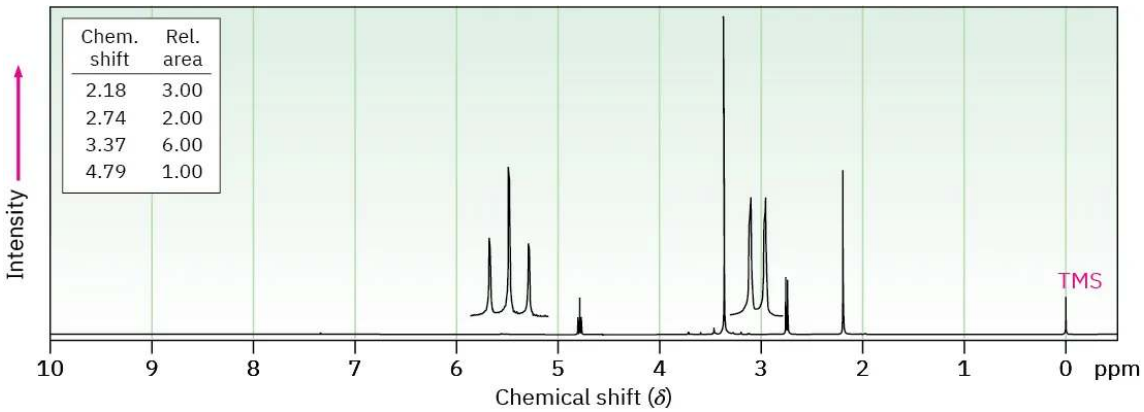


PROBLEM 5-83 Propose structures for ketones or aldehydes that have the following ^1H NMR spectra.

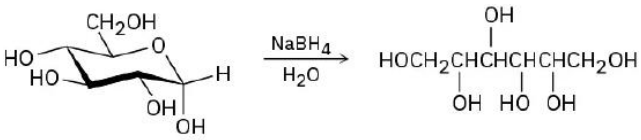
(a) $C_{10}H_{12}O$: IR: 1710 cm^{-1}



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

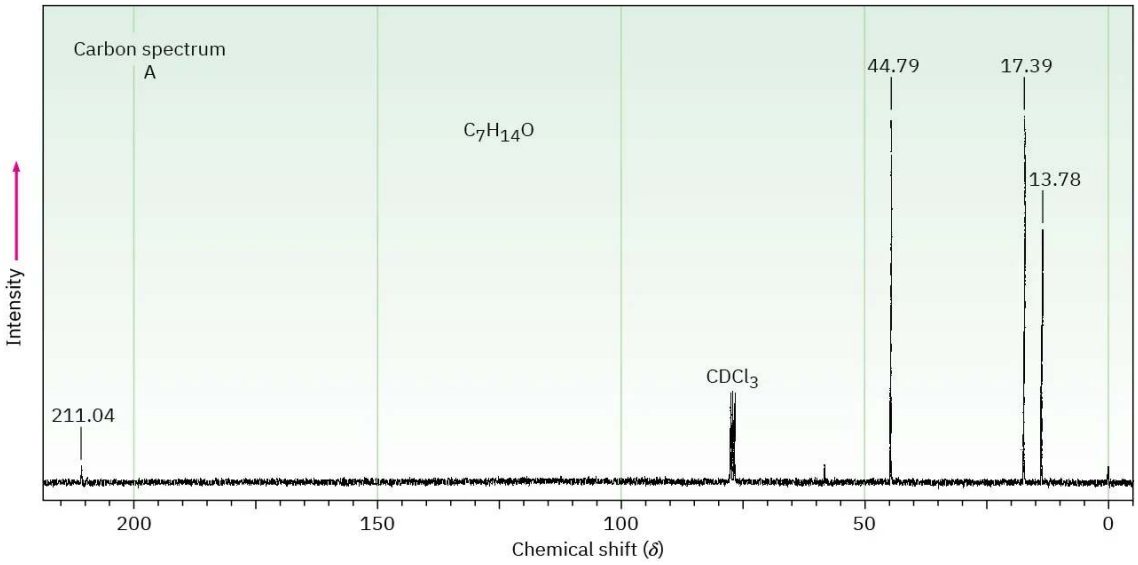


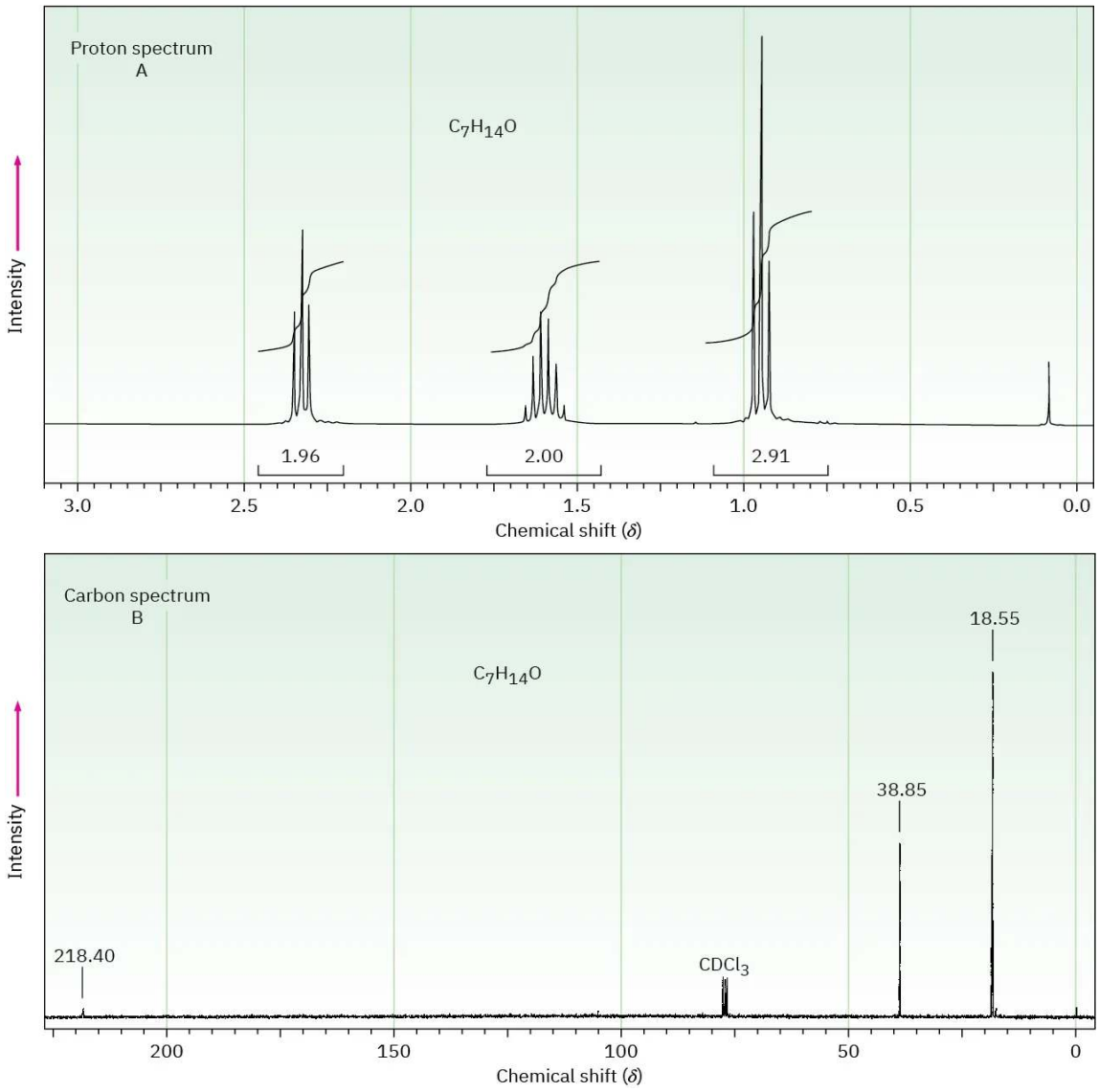
PROBLEM 5-84 When glucose (Problem 5-51) is treated with $NaBH_4$, reaction occurs to yield *sorbitol*, a polyalcohol commonly used as a food additive. Show how this reduction occurs.



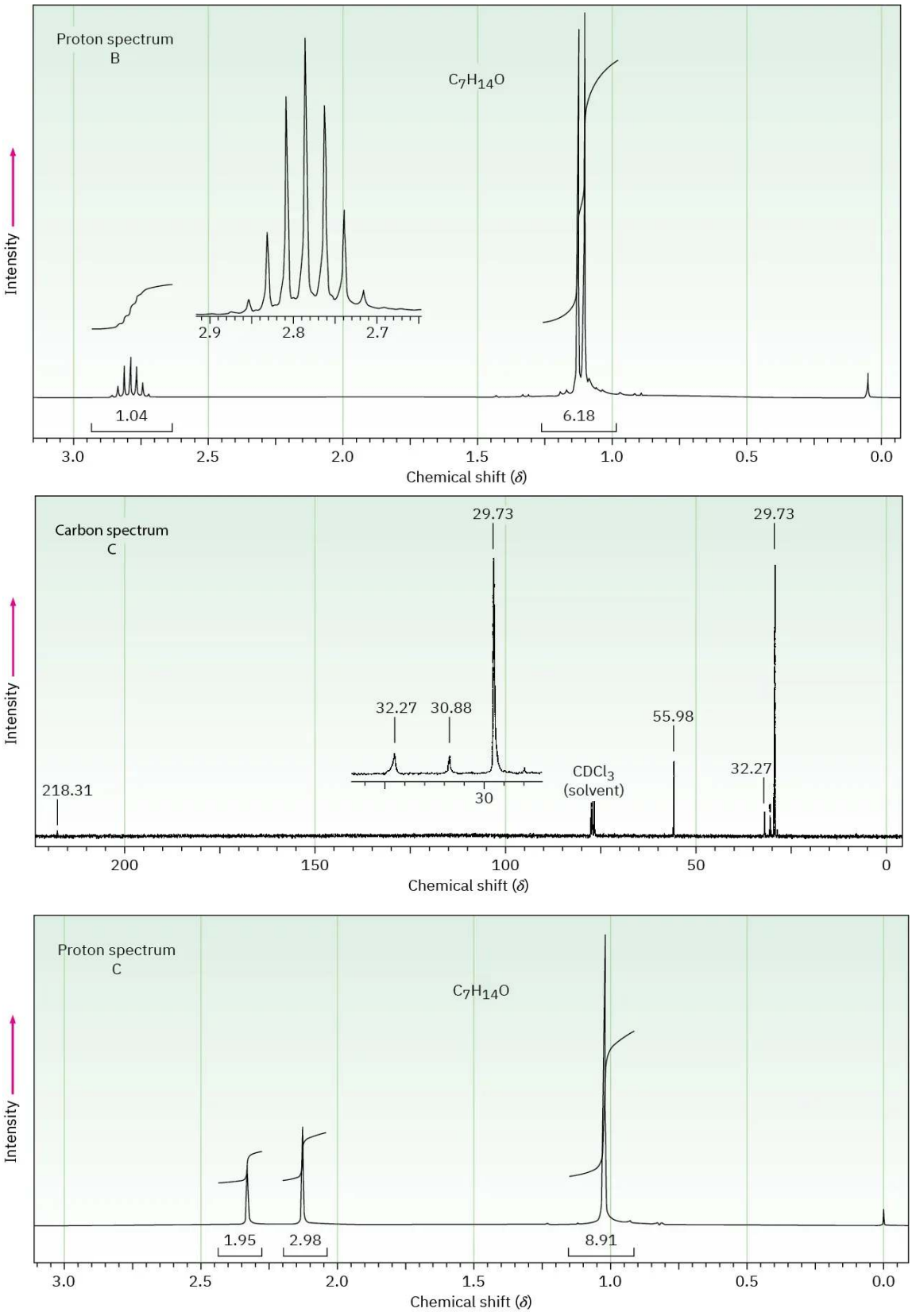
Glucose **Sorbitol**

PROBLEM 5-85 The proton and carbon NMR spectra for each of the three isomeric ketones with the formula $C_7H_{14}O$ are shown. Assign a structure to each pair of spectra.

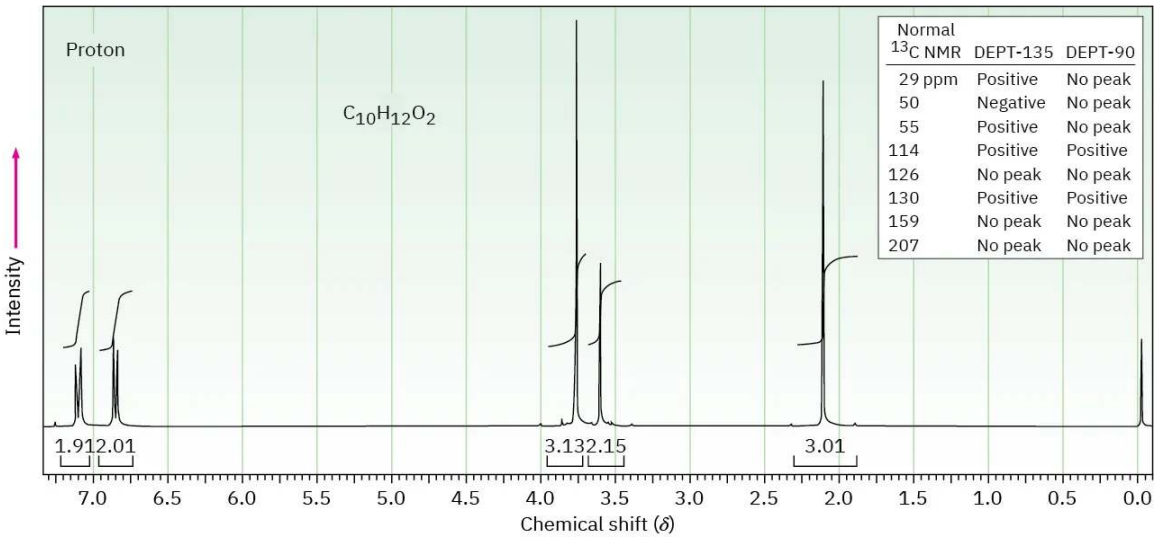




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PROBLEM 5-86 The proton NMR spectrum for a compound with formula $C_{10}H_{12}O_2$ is shown below. The infrared spectrum has a strong band at 1711 cm^{-1}. The broadband-decoupled ^{13}C NMR spectral results are tabulated along with the DEPT-135 and DEPT-90 information. Draw the structure of this compound.



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5.S: Aldehydes and Ketones (Summary)

Concepts & Vocabulary

19.0 Chapter Objectives and Preview of Carbonyl Chemistry

- Aldehydes are carbonyl compounds with an R group and a hydrogen attached to the carbonyl carbon.
- Ketones are carbonyl compounds with two R groups attached to the carbonyl carbon.

19.1 Naming Aldehydes and Ketones

- Aldehydes are named following IUPAC rules with the standard ending -al.
- Ketones are named following IUPAC rules with the standard ending -one.
- Aldehydes have priority over ketones when both appear in the same molecule.

19.2 Preparing Aldehydes and Ketones

- Primary alcohols can be oxidized to aldehydes with PCC (pyridinium chlorochromate) or DMP (Dess-Martin Periodinane).
- Terminal alkynes can be hydrated to form aldehydes through hydroboration-oxidation reactions.
- Esters can be reduced to aldehydes with DIBAL-H.
- Acid chlorides can be reduced to aldehydes with hydrides.
- Nitriles can be reduced to aldehydes with DIBAL-H.
- Secondary alcohols can be oxidized to ketones with chromic acid/Jones reagent.
- Alkynes can be hydrated to form ketones.
- Aryl ketones can be formed by Friedel-Crafts acylation of aromatic rings.
- Nitriles can be reacted with Grignard reagents to form ketones.
- Alkenes can be cleaved with ozone to form aldehydes or ketones.
- Acid halides can be converted to ketones by reacting with Gilman reagents.

19.3 Oxidation of Aldehydes and Ketones

- Aldehydes can be oxidized more easily than ketones due to the aldehyde hydrogen.
- Jones reagent is a mixture of CrO_3 and aqueous acid.
- Aldehydes can be oxidized to carboxylic acids with chromium trioxide/Jones reagent.
- Ketones can undergo oxidative cleavage with very strong oxidizing agents such as potassium permanganate.
- Ketones can be oxidized to esters by peroxycarboxylic acids in a reaction known as Baeyer-Villiger oxidation.

19.4 Nucleophilic Addition Reactions of Aldehydes and Ketones

- Carbonyl bonds are polarized with a partial positive charge on the carbon making it an electrophile and a target for attack by nucleophiles.
- Neither aldehydes nor ketones have a good leaving group causing both to undergo nucleophilic addition reactions.
- Aldehydes are more reactive than ketones to nucleophilic addition reactions.

19.5 Nucleophilic Addition Reactions of Water: Hydration

- Gem-diols are molecules that have two hydroxide groups attached to the same carbon.
- Aldehydes and ketones can react with water under either acidic or basic conditions to form gem-diols.

19.6 Nucleophilic Addition Reactions of HCN: Cyanohydrin Formation

- Cyanohydrins are molecules with a cyanide and a hydroxide attached to the same carbon.
- Cyanohydrins can be formed from aldehydes or ketones by reacting with cyanide ion and a weak acid.

19.7 Nucleophilic Addition Reactions of Hydride and Grignard Reagents: Alcohol Formation

- Metal hydrides can reduce aldehydes and ketones to alcohols.
- Organometallic reagents include carbon bonds to metals which react similarly to carbanions.
- Grignard reagents (R-Mg-X) and organolithium compounds add to aldehydes and ketones to form alcohols.

19.8 Nucleophilic Addition of Amines: Imine and Enamine

- Imines are characterized by a carbon-nitrogen double bond.
- Reaction of aldehydes and ketones with primary amines can form imines.
- Reaction of aldehydes and ketones with secondary amines can form enamines.

19.9 Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction

- Hydrazine will react with aldehydes and ketones to form hydrazones (similar to imine formation). Heating of the hydrazone with base converts it to an alkane.
- The combination of hydrazone formation and reduction (of aldehydes and ketones) is called the Wolff-Kishner reaction.

19.10 Nucleophilic Addition of Alcohols: Acetal Formation

- Hemiacetals have one hydroxide and one ether attached to a carbon.
- Acetals have two ethers attached to a carbon.
- Reaction of an aldehyde or ketone with an alcohol under acidic conditions forms a hemi-acetal. Continuation of the same reaction results in an acetal.
- Acetals can reform the aldehyde or ketone by reacting with acid.
- Acetals are useful as protecting groups due to the reversible nature of acetal formation.

19.11 Nucleophilic Addition of Phosphorun Ylides: The Wittig Reaction

- A molecule with positive and negative charges on adjacent atoms is called an ylide.
- Wittig reagents are organophosphorus ylides which can be drawn as a double bonded structure called a phosphorane.
- The Wittig reaction is used to convert an aldehyde or ketone into an alkene by reacting with an organophosphrous ylide.
- Oxaphosphetane intermediates containing a 4 membered ring including one oxygen and one phosphorus atom occur during the Wittig reaction.

19.12 Biological Reductions

- The Cannizzaro reaction allows an aldehyde to react with another like molecule in strong base to form one oxidized molecule (carboxylic acid) and one reduced molecule (alcohol).
- NADH, one of the most important biological reducing agents, uses a similar mechanism to the Cannizzaro reaction while reducing ketones in biological systems to alcohols while being converted to NAD^+.

19.13 Conjugate Nucleophilic Addition of alpha, beta-Unsaturated Aldehydes and Ketones

- α, β-unsaturated carbonyls have an alkene attached to the carbonyl carbon.
- Due to resonance delocalization, the β-carbon of an α, β-unsaturated carbonyl is electrophilic and will react with nucleophiles.
- α, β-unsaturated carbonyls can undergo 1,2 or 1,4 addition.
- 1,4 addition is also called conjugate addition.
- Lithium diorganocopper reagents are called Gilman reagents.
- Gilman reagents typically react with α, β-unsaturated carbonyls via conjugate addition.

19.14 Spectroscopy of Aldehydes and Ketones

- IR of aldehydes and ketones is defined strongly by the carbonyl stretching vibration.
- ^1H NMR of aldehydes show the aldehyde proton between 10 and 11 ppm as well as the protons on carbon adjacent to the carbonyl at about 2.5 ppm.
- ^1H NMR of ketones show the protons on carbon adjacent to the carbonyl at about 2.5 ppm.
- ^{13}C NMR of aldehydes and ketones show the carbonyl carbon at about 200 ppm.
- Mass spectra of aldehydes and ketones typically yield moderately intense molecular ions, M^+. They also can undergo some rearrangements that yield common fragmentation patterns.

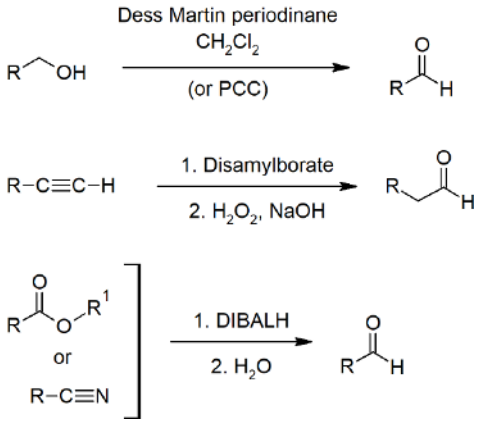
Skills to Master

- Skill 19.1 Explain the relative reactivity of aldehydes vs. ketones to nucleophiles, based on carbonyl bond polarity.
- Skill 19.2 Name aldehydes and ketones using IUPAC rules.

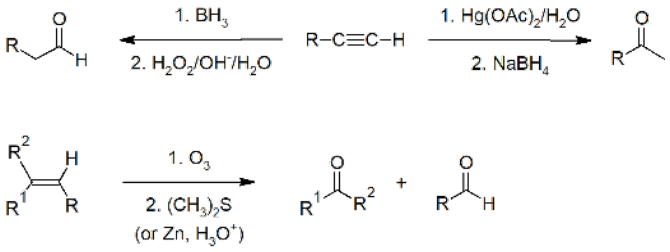
- Skill 19.3 Draw the structure of an aldehyde or ketone from the IUPAC name.
- Skill 19.4 Interpret common names of aldehydes and ketones.
- Skill 19.5 Describe methods for preparing aldehydes and ketones.
- Skill 19.6 Draw mechanisms for oxidations of aldehydes and ketones.
- Skill 19.7 Explain general reactivity of aldehydes and ketones through the nucleophilic addition mechanism.
- Skill 19.8 Draw mechanisms for nucleophilic addition reactions to aldehydes and ketones including
  - Hydration
  - Cyanohydrin formation
  - Hydride Reduction
  - Organometallic reactions
  - Addition of amines
  - Wolff-Kishner reaction
  - Acetal formation
  - Wittig reaction
  - Cannizzaro reaction
  - Conjugate addition
- Skill 19.9 Use IR, NMR and MS to identify aldehydes and ketones.

Summary of Reactions

Aldehyde Preparation

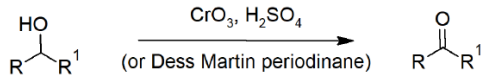


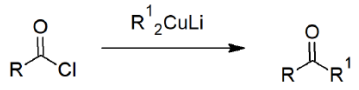
Aldehyde and Ketone Preparation

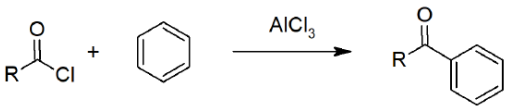


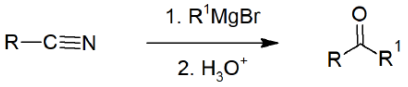
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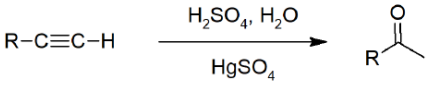
Ketone Preparation



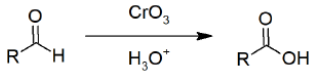


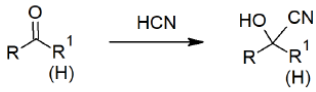


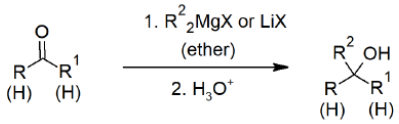


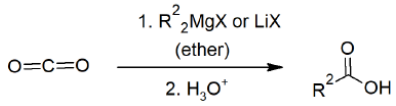


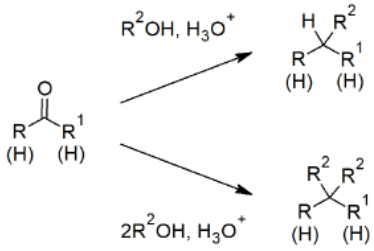
Aldehyde and Ketone Reactions



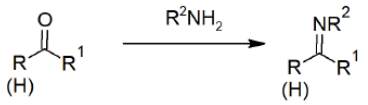


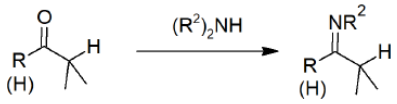


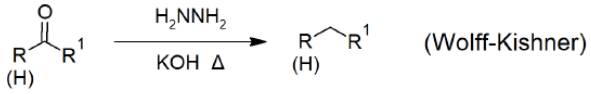


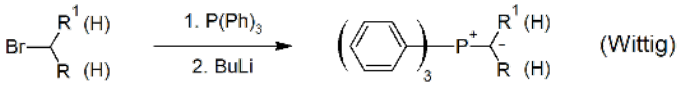


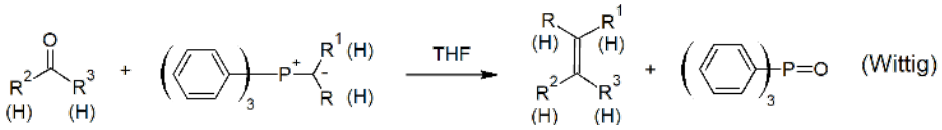
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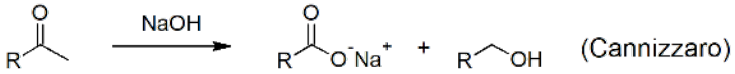




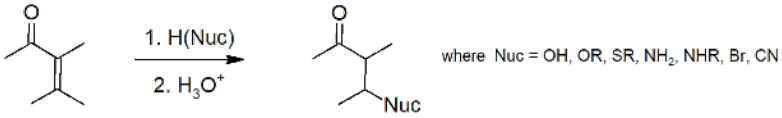


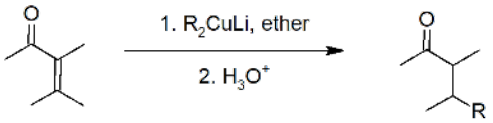






Conjugated Addition Reactions





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CHAPTER OVERVIEW

6: Carboxylic Acids and Nitriles

This chapter presents a straightforward discussion of the chemistry of carboxylic acids (formerly called “fatty acids”) and nitriles. As usual, we begin with a description of how the compounds are named. We then consider the subtleties of their structure, and how these structural features influence physical properties, such as boiling point. We place considerable emphasis on the dissociation of carboxylic acids and the effect of substituents on acid strength.

We have already encountered a number of methods for preparing carboxylic acids. We shall review these methods, and learn about two additional procedures. The only reactions of carboxylic acids that we study in detail in this chapter are reduction and decarboxylation, although two other common reactions of carboxylic acids, alpha substitution and nucleophilic acyl substitution, will be described in later chapters.

We will then look at the formation of nitriles and their chemical reactivity; and our discussion of carboxylic acid and nitrile chemistry concludes with a look at the infrared and NMR spectra of these compounds, with emphasis on the characterization of carboxylic acids.

6.0: Chapter Objectives and Introduction to Carboxylic Acids
6.1: Naming Carboxylic Acids and Nitriles
6.2: Structure and Properties of Carboxylic Acids
6.3: Substituent Effects on Acidity
6.4: Preparing Carboxylic Acids
6.5: Reactions of Carboxylic Acids - An Overview
6.6: Chemistry of Nitriles
6.7: Spectroscopy of Carboxylic Acids and Nitriles
6.8: Additional Problems
6.S: Carboxylic Acids and Nitriles (Summary)

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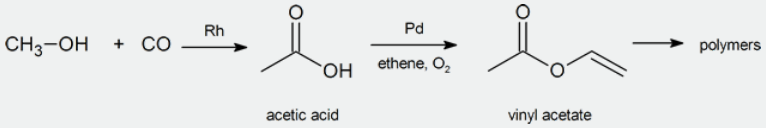
6.0: Chapter Objectives and Introduction to Carboxylic Acids

Objectives

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this chapter are used in conjunction with any of the reactions described in previous chapters.
- solve road-map problems which require a knowledge of the chemistry of carboxylic acids.
- define, and use in context, the key terms introduced in this chapter.

Study Notes

The global demand for acetic acid is about 6.5 million tonnes per year. A common industrial preparation of acetic acid is the catalytic oxidation of methanol with carbon monoxide. Much of the acetic acid produced is converted to vinyl acetate polymer and used in adhesives and paints.

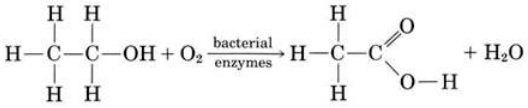


acetic acid vinyl acetate

Not only are carboxylic acids valuable, but they and their derivatives are useful starting materials for many synthetic products. Finally, carboxylic acids and their derivatives are also found in a variety of natural systems and important biological pathways.

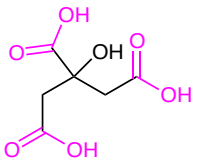
Carboxylic Acids

Carboxylic acids have been known throughout human history. Prehistoric people likely made acetic acid when their fermentation reactions went awry and produced vinegar instead of wine. The Sumerians (2900–1800 BCE) used vinegar as a condiment, a preservative, an antibiotic, and a detergent. Vinegar contains 4 to 5 percent acetic acid. Acetic acid gives vinegar its sour taste and pungent odor and can do the same thing to wine. Acetic acid, CH_3COOH, is an example of the class of compounds called **carboxylic acids**, each of which contains one or more carboxyl groups, COOH. The general formula of a carboxylic acid is RCOOH.



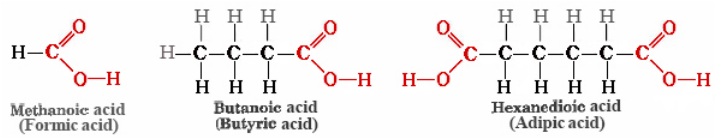
Ethanol **Ethanoic Acid (Acetic Acid)**

Citric acid was discovered by an Islamic alchemist, Jabir Ibn Hayyan (also known as Geber), in the 8th century, and crystalline citric acid was first isolated from lemon juice in 1784 by the Swedish chemist Carl Wilhelm Scheele. Medieval scholars in Europe were aware that the crisp, tart flavor of citrus fruits is caused by citric acid.



Citric acid

Naturalists of the 17th century knew that the sting of a red ant's bite was due to an organic acid that the ant injected into the wound. Formic acid (the name comes from Latin word *formica* meaning "ant") is present in ants and bees and is responsible for the burning pain of their bites and stings. Butyric acid, a component of rancid butter and Limburger cheese, has a vile odor. Adipic acid is an example of a dicarboxylic acid—it has two functional groups—and is used to make nylon



Naturally Occurring Carboxylic Acids

Carboxylic acids are widespread in nature, often combined with other functional groups. Simple alkyl carboxylic acids, composed of four to ten carbon atoms, are liquids or low melting solids having very unpleasant odors. The **fatty acids** are important components of the biomolecules known as lipids, especially fats and oils. As shown in the following table, these long-chain carboxylic acids are usually referred to by their common names, which in most cases reflect their sources. A mnemonic phrase for the C_{10} to C_{20} natural fatty acids capric, lauric, myristic, palmitic, stearic and arachidic is: "**C**urly, **L**arry & **M**oe **P**erform **S**illy **A**ntics" (note that the names of the three stooges are in alphabetical order).

Table 17.4.1: Common Saturated Fatty Acids

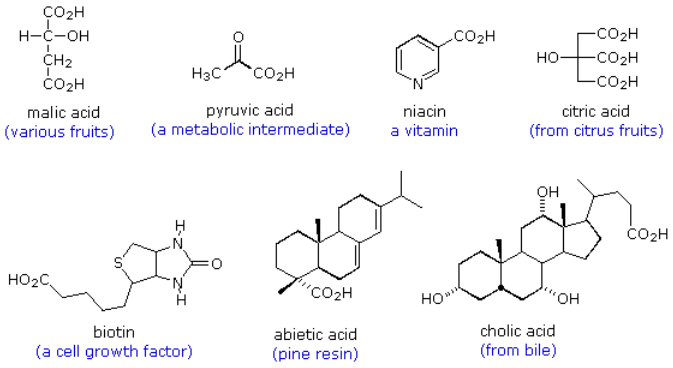
Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC

Interestingly, the molecules of most natural fatty acids have an *even number of carbon atoms*. Since nature makes these long-chain acids by linking together acetate units, it is not surprising that the carbon atoms composing the natural products are multiples of two. Analogous compounds composed of odd numbers of carbon atoms are perfectly stable and have been made synthetically. All the double bonds in the unsaturated compounds listed on the table have *cis* (or Z) stereochemistry.

Table 17.4.2: Common Unsaturated Fatty Acids

Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

The following formulas are examples of other naturally occurring carboxylic acids. The molecular structures range from simple to complex, often incorporate a variety of other functional groups, and many are chiral.



Naturally occurring carboxylic acids

Carboxylic Acid Derivatives

Other functional group combinations with the carbonyl group can be prepared from carboxylic acids, and are usually treated as related derivatives. The chemistry behind the conversion of carboxylic acids to carboxylic acid derivatives will be discussed in then next chapter. Five common classes of these **carboxylic acid derivatives** are listed in the following table. Although nitriles do not have a carbonyl group, they are included here because the functional carbon atoms all have the same oxidation state. The top row shows the general formula for each class, and the bottom row gives a specific example of each. As in the case of amines, amides are classified as 1º, 2º or 3º, depending on the number of alkyl groups bonded to the nitrogen.

acyl halide	anhydride	ester	amide	nitrile
X = F, Cl, Br or I			R′ = H or alkyl	
propanoyl chloride	acetic anhydride	ethyl acetate	formamide	acetonitrile

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6.1: Naming Carboxylic Acids and Nitriles

Objectives

After completing this section, you should be able to

1. write the IUPAC name of a carboxylic acid, given its Kekulé, condensed or shorthand structure.
2. draw the condensed or shorthand structure of a carboxylic acid, given its IUPAC name.
3. draw the structure of the following carboxylic acids, given their trivial names: formic acid and acetic acid.
4. provide an acceptable name for a nitrile of given structure.
5. draw the condensed or shorthand structure of a nitrile, give either its trivial or IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- carboxylic acid
- nitrile

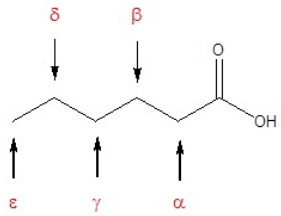
Study Notes

You need not memorize all the trivial names listed in the table, just remember the two names identified in Objective 3, above.

Carboxylic Acids, RCO_2H

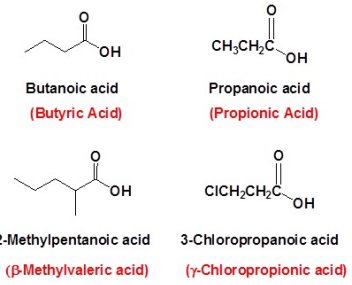
The IUPAC system of nomenclature assigns a characteristic suffix to these classes. The **–e** ending is removed from the name of the parent chain and is replaced **-oic acid**. Since a carboxylic acid group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name.

Many carboxylic acids are called by the common names. These names were chosen by chemists to usually describe a source of where the compound is found. In common names of carboxylic acids, carbon atoms near the carboxyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



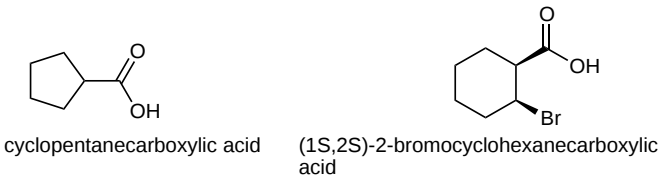
Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

Example (Common Names Are in Red)



Naming carboxyl groups added to a ring

When a carboxyl group is added to a ring, the suffix **-carboxylic acid** is added to the name of the cyclic compound. The ring carbon attached to the carboxyl group is given the #1 location number.

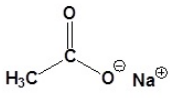


The acid with the carboxyl group attached directly to a benzene ring is called benzoic acid (C_6H_5COOH).

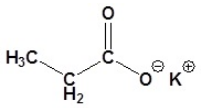


Naming carboxylates

Salts of carboxylic acids are named by writing the name of the cation followed by the name of the carboxylic acid with the **–ic acid** ending replaced by an **–ate** ending. This is true for both the IUPAC and Common nomenclature systems.



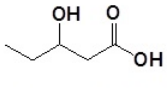
Sodium ethanoate
(Sodium Acetate)



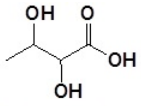
Potassium Propanoate
(Potassium propionate)

Naming carboxylic acids which contain other functional groups

Carboxylic acids are given the highest nomenclature priority by the IUPAC system. This means that the carboxyl group is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of molecules containing carboxylic acid and alcohol functional groups, the OH is named as a hydroxyl substituent. However, the **l** in hydroxyl is generally removed.

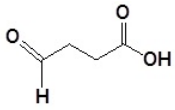


3-Hydroxypentanoic acid

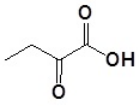


2,3-Dihydroxybutanoic acid

In the case of molecules containing a carboxylic acid and aldehydes and/or ketones functional groups, the carbonyl is named as an "Oxo" substituent.

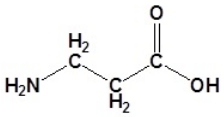


4-Oxobutanoic acid

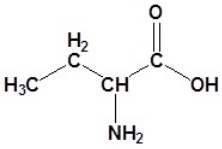


2-Oxobutanoic acid

In the case of molecules containing a carboxylic acid an amine functional group, the amine is named as an "amino" substituent.



3-Aminopropanoic acid

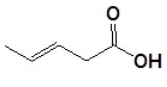


2-Aminobutanoic acid

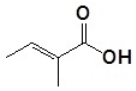
When carboxylic acids are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the -ane ending)-(an –enoic acid ending to indicate the presence of an alkene and carboxylic acid)

Remember that the carboxylic acid has priority so it should get the lowest possible location number. Also, remember that *cis/tran* or E/Z nomenclature for the alkene needs to be included if necessary.



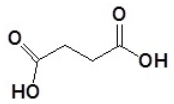
Trans-3-pentenoic acid



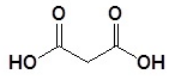
(E)-2-Methyl-2-butenoic acid

Naming dicarboxylic acids

For dicarboxylic acids the location numbers for both carboxyl groups are omitted because both functional groups are expected to occupy the ends of the parent chain. The ending **–dioic acid** is added to the end of the parent chain name.



Butanedioic acid

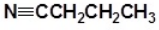


Propanedioic acid

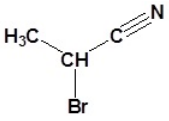
Naming Nitriles, R−C≡N

A **nitrile** is any organic compound with a −C≡N functional group. In literature the prefix **cyano-** is used interchangeably with the term nitrile to refer to the functional group. Nitriles used to be known as cyanides; the smallest organic nitrile is ethanenitrile, CH_3CN, (old name: methyl cyanide or acetonitrile).

Open chain nitriles are named with the word **-nitrile** after the name of the parent alkane name. Remmber to include the carbon atom of the nitrile as part of the parent chain. For example, CH_3CN has two carbons including the nitrile carbon, therefore it is ethanenitrile. The carbon in the nitrile is given the #1 location position. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

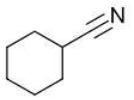


Butane nitrile

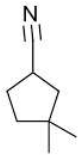


2-Bromopropane nitrile

When a nitrile is the highest priority functional group attached to a cycloalkane, the name of the parent cycloalkane is followed by the word **-carbonitrile**. The ring carbon attached to the nitrile is numbered C1 and the nitrile is not given a number in the name.

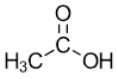


Cyclohexanecarbonitrile

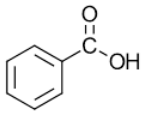


3,3-Dimethylcyclopentanecarbonitrile

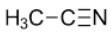
Nitriles are often named based off the common name of the corresponding carboxylic acid. This is done by replacing the -ic acid or -oic acid ending with **-onitrile**. In these cases the nitrile carbon is numbered C1 but the nitrile itself is not given a number in the name.



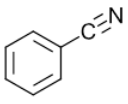
Acetic Acid



Benzoic Acid

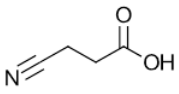


Acetonitrile



Benzonitrile

In the case of molecules containing a carboxylic acid and nitrile functional group, the nitrile is named as a "cyano" substituent. Note! The carbon in the nitrile is not counted as part of the parent chain when named as a cyano substituent.



3-Cyanopropanoic Acid

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6.2: Structure and Properties of Carboxylic Acids

Objectives

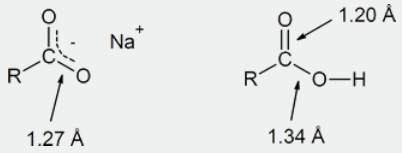
After completing this section, you should be able to

1. describe the geometry and electronic structure of a simple carboxylic acid; for example, acetic acid.
2. describe the hydrogen bonding that occurs between carboxylic acid molecules, and hence account for the relatively high boiling points of these compounds.
3. write an expression for the dissociation constant of a given carboxylic acid, and use it to calculate dissociation constants, percentage dissociation, etc.
4. identify carboxylic acids as being weaker acids than mineral acids, such as hydrochloric acid, but stronger acids than alcohols.
5. use the concept of resonance to explain why carboxylic acids are stronger acids than alcohols.
6. draw an orbital picture of a carboxylate anion to show the equivalence of the two oxygen atoms.
7. explain why the two carbon-oxygen bond lengths are identical in sodium carboxylate, but different in carboxylic acid.
8. write an equation for the reaction of a carboxylic acid with a base, such as sodium hydroxide.

Study Notes

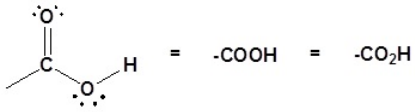
It might be convenient to review Sections 2.7, “Acids and Bases: The Brønsted-Lowry Definition” and 6.7, “Describing a Reaction: Equilibria, Rates, and Energy Changes” from CHEM 231 Textbook in conjunction with this section.

In the reading, the discussion of the role of resonance in the acidity of a carboxylic acid explains that the two carbon-oxygen bonds in the delocalized carboxylate anion are identical (both 1.27 Å). However, in the structure of a carboxylic acid the **C–O** bond (1.20 Å) is shorter than the **C–OH** bond (1.34 Å).



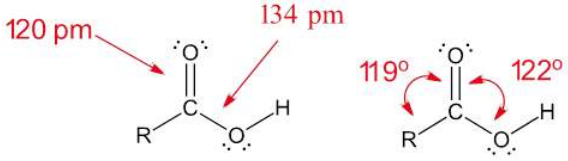
Structure of the carboxyl acid group

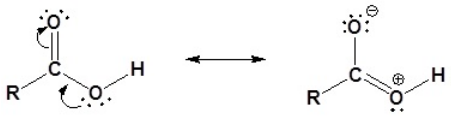
Carboxylic acids are organic compounds which incorporate a carboxyl functional group, CO_2H. The name carboxyl comes from the fact that a carbonyl and a hydroxyl group are attached to the same carbon.



Carboxyl Group

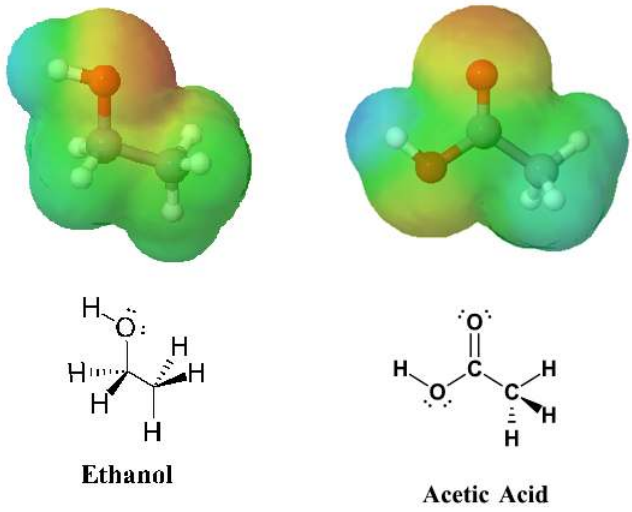
The carbon and oxygen in the carbonyl are both sp^2 hybridized which gives a carboxylic acid a trigonal planar shape (around the carbonyl carbon) making the bond angles roughly 120°. A resonance structure exists where one of the lone pairs of the hydroxyl oxygen (OH) is conjugated with the pi bond system of the carbonyl group. The conjugation can be represented by the resonance structure shown below which holds all the atoms in the carboxylic acid in a co-planar arrangement.





Major Contributor Minor Contributor

The effects of conjugation in a carboxylic acid can be seen when comparing the electrostatic potential maps of ethanol and acetic acid. Conjugation creates a greater polarization in the O-H bond in acetic acid, as shown by its darker blue color, which subsequently leads to a greater acidity in carboxylic acids.



Ethanol Acetic Acid

Physical Properties of Some Carboxylic Acids

Carboxylic acids tend to have higher boiling points when compared to ethers, alcohols, aldehydes, or ketones with a similar molecular weight. For example acetic acid and ethanol have boiling points of 117.9 ºC and 78.3 ºC respectively despite the fact that they both contain two carbons. Because carboxylic acids and alcohols both contain an O-H bond they are strongly associated by a hydrogen-bonding intermolecular force. The difference is that for carboxylic acids, two molecules of a carboxylic acid form two hydrogen bonds with each other to create a cyclic dimer (pair of molecules). Two alcohol molecules can only form one hydrogen bond between each other. Thus, carboxylic acids have stronger intermolecular forces and higher boiling points than their corresponding alcohols.

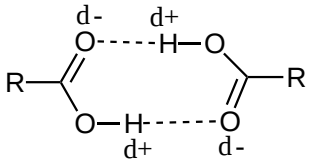


Table **6.2.2**: Intermolecular hydrogen bonding in carboxylic acids.

Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

Acidity of Carboxylic Acids

Carboxylic acids are named such because they tend to be more acidic than other functional groups in organic chemistry. In dilute aqueous solutions, they act as Brønsted–Lowry acids and partially dissociate to produce the corresponding carboxylate ion and hydronium (H_3O^+).



Carboxylic acid — Carboxylate ion

The extent of this dissociation is described by the K_a value of the carboxylic acid. In a 0.1 M solution of acetic acid ($K_a = 1.75 \times 10^{-5}$ @ 25 °C) only about 0.1% of the molecules are dissociated.

$$K_{eq} = K_a = \frac{[RCOO^-][H_3O^+]}{[RCOOH]} = 1.75 \times 10^{-5}$$

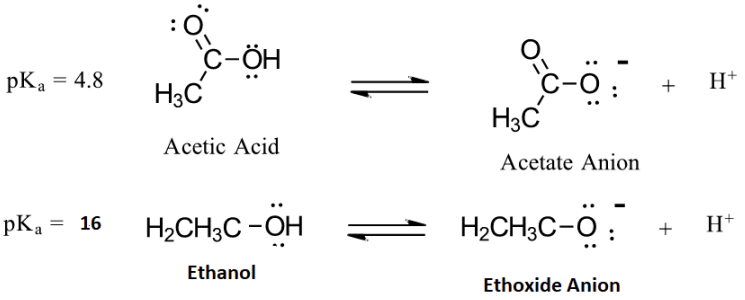
with $pK_a = -\log K_a$.

The pK_a's of some typical carboxylic acids are listed in Table 6.2.1. The factors which affect the acidity of different carboxylic acids will be discussed in the next section of this text.

Table 6.2.1: Acidity of example carboxylic acids

Compound	K_a	pK_a
F_3CCO_2H	0.59	0.23
Cl_3CCO_2H	0.22	0.66
$p\text{-}O_2NC_6H_4CO_2H$	3.39×10^{-4}	3.47
HCO_2H	1.78×10^{-4}	3.75
$C_6H_5CO_2H$	6.31×10^{-5}	4.20
$p\text{-}CH_3OC_6H_4CO_2H$	3.55×10^{-5}	4.45
CH_3CO_2H	1.75×10^{-5}	4.76
$CH_3CH_2CH_2CO_2H$	1.51×10^{-5}	4.82

The acidity of carboxylic acids comes about, in part, due to resonance stabilization of the carboxylate conjugate base. A classic example compares the relative acidity of ethanol and acetic acid, but the conclusions we reach will be equally valid for all alcohol and carboxylic acid groups. Despite the fact that they are both oxygen acids, the pK_a values of ethanol and acetic acid are very different (acetic acid is more than 10^{11} times more acidic than ethanol). In both species, the negative charge on the conjugate base is held by an oxygen so electronegativity does not explain the difference in acidity.



For acetic acid, however, there is a key difference: a resonance contributor can be drawn in which the negative charge is localized on the second oxygen of the group. The two resonance forms for the conjugate base are equal in energy allowing for the negative charge on the acetate ion to be equally shared between two oxygens. In the ethoxide anion, by contrast, the negative charge is 'locked' on the single oxygen. (Figure **6.2.1**) This stabilization leads to a marked increase in stability of the acetate anion, as illustrated by the energy diagram shown below. The increased stabilization of the acetate anion conjugate base promotes the acidity of acetic acid.

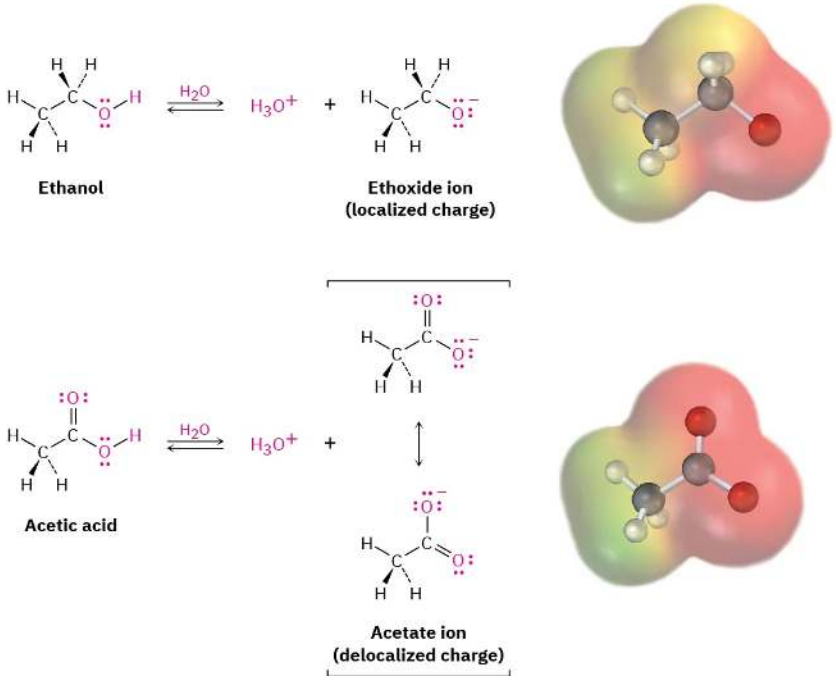
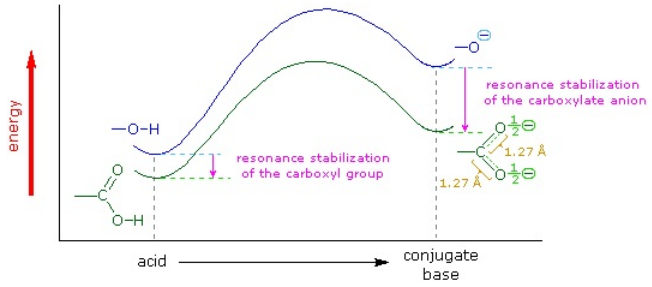


Figure **6.2.1**: An alkoxide ion has its charge localized on one oxygen atom and is less stable, while a carboxylate ion has the charge spread equally over both oxygens and is therefore more stable.



The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of over 11 pK_a units between ethanol and acetic acid (and remember, pK_a is a log expression, so this represents a difference of over 10^{11} between the acidity constants for the two molecules). The acetate anion is that much more stable than the ethoxide anion, all due to the effects of resonance delocalization.

X-ray crystallographic studies provide experimental evidence of the acetate anion resonance hybrid (Figure **6.2.2**). Both C-O bonds in acetate are 127 pm which is roughly the average of C=O double bond (120 pm) and the C-O single bond (134 pm) of acetic acid. Both of the C-O bonds in the acetate anion are considered to have a bond order of 1 1/2. The negative charge is equally spread between the two oxygens giving them each a charge of -1/2.

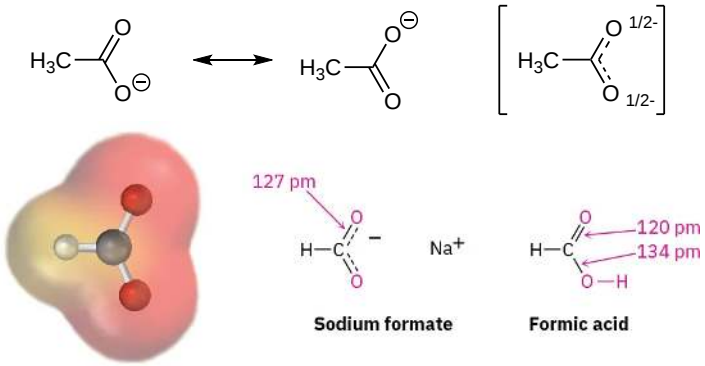
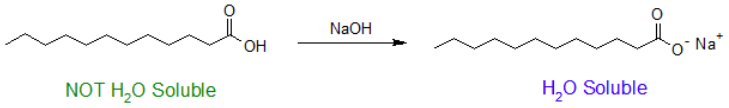


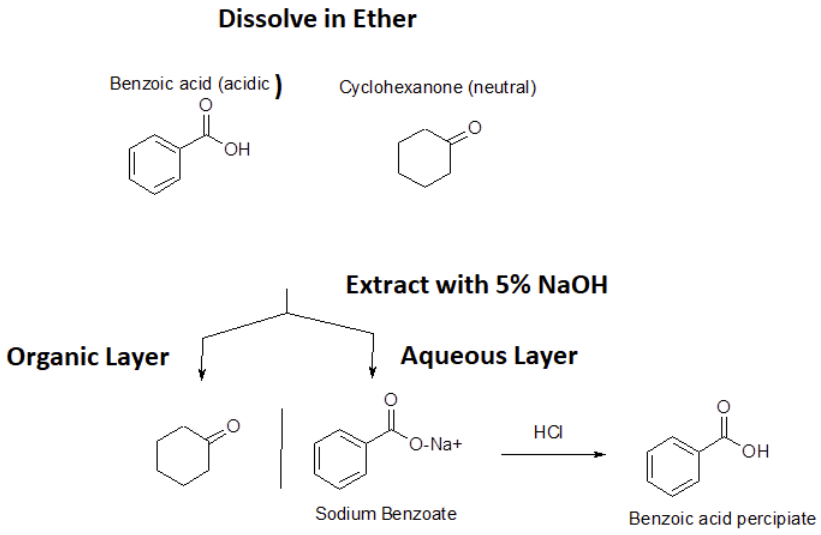
Figure **6.2.2**: Resonance structures and resonance hybrid of acetate ion.

Water Solubility of Carboxylic Acids

The ability to form hydrogen bonds gives carboxylic acids with low molecular weights some measure of solubility in water. Carboxylic acids with six or more carbons tend to only be slightly soluble in water. However, conversion to the corresponding carboxylate anion tends to immensely increase water solubility due to the creation of an ion-dipole intermolecular force. Typically a strong base is used to deprotonate a carboxylic acid and drive this reaction to completion as shown below.



This property of carboxylic acids allows many carboxylic acids to be purified by a technique called acid/base extraction. The figure below shows how a carboxylic acid (benzoic acid) can easily be separated from non-acidic water insoluble compounds (cyclohexanone) using an acid/base extraction. First, the two compounds are dissolved in an organic solvent immiscible with water (ether). Then a basic aqueous solution (5% NaOH) is added and two liquid layers are formed. As the layers are mixed, benzoic acid reacts with the basic solution to become sodium benzoate. Because sodium benzoate is soluble in water it is extracted into the aqueous layer while the non-acidic cyclohexanone remains in the organic layer. The two layers can be separated using a separatory funnel effectually removing the cyclohexanone. The aqueous layer can then be acidified with a strong acid causing sodium benzoate to become protonated, reforming benzoic acid. Because benzoic acid is insoluble in water it will form a precipitate which can easily be filtered off.



Carboxylic Acids in Buffered Solutions

Due to the acidic nature of carboxylic acids, their level of dissociation is directly related to the pH of the solution. Under acidic conditions (low pH), carboxylic acids are almost completely undissociated and exist primarily in their protonated form (**RCOOH**). Under, basic conditions (high pH), carboxylic acids become nearly completely dissociated into their deprotonated carboxylate form ($\mathbf{RCOO^-}$). Because the environment inside a living cell is an aqueous buffer with a nearly neutral pH = 7.3 (sometimes referred to as the **physiological pH**), then in what form do carboxylic acids exist? An important part of answering this question lies in the **Henderson-Hasselbalch equation**:

$$pH = pK_a + \log\left(\frac{[\text{ concentration of conjugate base }]}{[\text{ concentration of weak acid }]}\right) \tag{6.2.1}$$

This equation shows that the amount of dissociation in a carboxylic acid is related to the pH of the solution and the pK_a of the acid. In particular, the Henderson-Hasselbalch equation shows that when the concentration of a carboxylic acid is equal to the concentration of carboxylate then the pH of the solution equals the pK_a of the acid. Also, the Henderson-Hasselbalch allows for the pH of the solution to be calculated when the pK_a of the acid is known along with the concentrations of the carboxylic acid and carboxylate are known.

Example 6.2.1

What is the pH of an aqueous buffer solution that is 30 mM in acetic acid and 40 mM in sodium acetate? The pK_a of acetic acid is 4.8.

Solution

This is a direct application of the Henderson-Hasselbalch equation (Equation 6.2.1).

$$pH = pK_a + \log\left(\frac{[\text{ concentration of conjugate base }]}{[\text{ concentration of weak acid }]}\right)$$

The ratio of base to acid is 40/30, or 1.33. Therefore, substituting these values and the pK_a results in

$$\begin{aligned} pH &= 4.8 + \log\left(\frac{40}{30}\right) \\ &= 4.8 + \log 1.33 \\ &= 4.8 + 0.125 \\ &= 4.9 \end{aligned}$$

The Henderson-Hasselbalch equation is particularly useful when determining the protonation state of different biomolecule functional groups under physiological pH conditions. This is done under the assumption that the concentration of the biomolecule is small compared to the concentration of the buffer components. (The actual composition of a physiological buffer is complex, but it is primarily based on phosphoric and carbonic acids.).

Aspartic acid is an amino acid with a carboxylic acid functional group as part of its side chain. When aspartic acid comprises an amino acid residue of a protein in a human cell, it's side chain is in full contact with the physiological buffer. In what state is the side chain functional group: the protonated state (a carboxylic acid) or the deprotonated state (a carboxylate ion)?

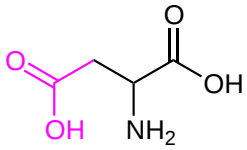


Figure **6.2.3**: Aspartic acid with the carboxylic acid side-chain highlighted. (CC BY-SA 4.0; Layne Morsch via LibreTexts)

Using the buffer pH of 7.3 and a rough approximation of pK_a = 5 for the carboxylic acid side chain, we find that the ratio of carboxylate to carboxylic acid is about 200 to 1. The carboxylic acid is almost completely ionized to the carboxylate inside the cell. This result extends to all other carboxylic acid groups you might find on natural biomolecules or drug molecules. In the physiological environment, carboxylic acids are almost completely deprotonated. Indeed, cellular carboxylic acids are often referred to by the name of their anion. So rather than pyruvic acid, or acetic acid or lactic acid, they are discussed as pyruvate, acetate or lactate.

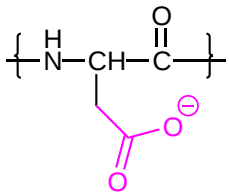


Figure **6.2.4**: Aspartate (as part of a protein or polypeptide). (CC BY-SA 4.0; Layne Morsch via LibreTexts)

Using the same process, the Henderson-Hasselbalch equation (Equation **6.2.1**) can also be used to determine the protonation state of carboxylic acids in solutions buffered to other pH levels.

$$pH = pK_a + \log\left(\frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}\right)$$

$$7.3 = 5 + \log\left(\frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}\right)$$

$$2.3 = \log\left(\frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}\right)$$

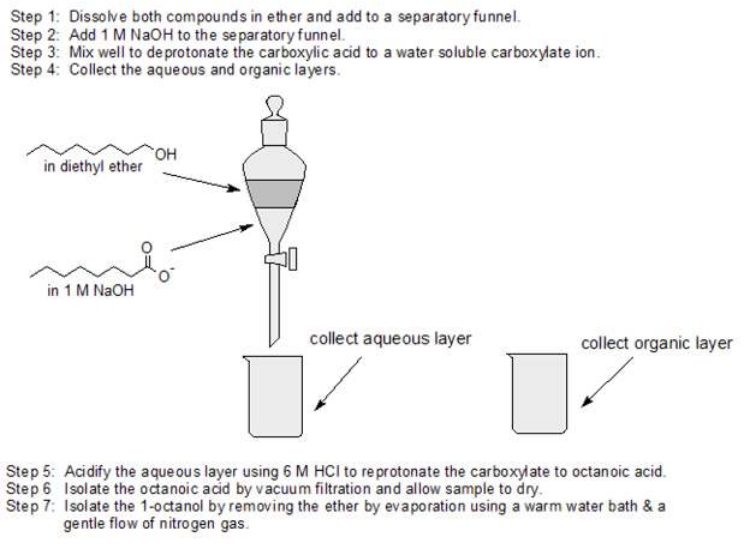
$$199 = \frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}$$

Therefore at physiological pH, the carboxylate anion is found with a 199-fold higher concentration than the protonated carboxylic acid. Naturally, changing the pH will alter this ratio.

? Exercise 6.2.1

Use acid-base chemistry and differences in water solubility to separate 1-octanol from octanoic acid using the following solutions: 1 M NaOH, ether, and 6 M HCl and any lab equipment.

Answer



Exercise 6.2.2

What percentage of propanoic acid (CH_3CH_2COOH) is dissociated into its conjugate base in a 0.20 M aqueous solution? K_a = 1.32 x 10^{-5}

Answer

From the acid equilibrium expression we get that:

$[CH_3CH_2COO^-][H_3O^+]/[CH_3CH_2COOH] = K_a = 1.32 \times 10^{-5}$

$[X][X]/[0.20\ M - X] = 1.32 \times 10^{-5}$

Assume X is small compared to 0.20 M

$[X]^2/[0.20\ M] = 1.32 \times 10^{-5}$

$X = [CH_3CH_2COO^-] = 1.62 \times 10^{-3}$ M

$[CH_3CH_2COO^-] / [CH_3CH_2COOH] \times 100 = \%Disassociation$

1.62×10^{-3} M / 0.20 M X 100 = **0.812%**

Exercise 6.2.3

What is the ratio of acetate ion to neutral acetic acid when a small amount of acetic acid (pK_a = 4.8) is dissolved in a buffer of pH 2.8? pH 3.8? pH 4.8? pH 5.8? pH 6.8?

Answer

We use the Henderson-Hasselbalch equation (Equation 6.2.1) and let the base to acid ratio be x.

For pH = 2.8:

$$2.8 = 4.8 + \log x$$

$x = 0.01 to 1$

- pH 3.8, the ratio is 0.10 to 1
- pH 4.8, the ratio is 1.0 to 1
- pH 5.8, the ratio is 10 to 1
- pH 6.8, the ratio is 100 to 1

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6.3: Substituent Effects on Acidity

Objectives

After completing this section, you should be able to

1. list a given series of carboxylic acids in order of increasing or decreasing acidity.
2. explain the difference in acidity between two or more given carboxylic acids.
3. arrange a series of substituted benzoic acids in order of increasing or decreasing acidity.
4. determine whether a given substituted benzoic acid will be more or less acidic than benzoic acid.
5. decide which of two or more substituted benzoic acids is the most acidic, and explain your decision on the basis of the electron-withdrawing or electron-releasing ability of the substituent.
6. use the K_a (or pK_a) of a substituted benzoic acid to predict the effect that the substituent has on the susceptibility of the benzene ring to electrophilic attack.

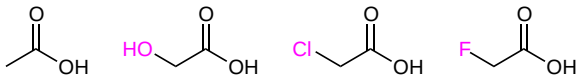
Study Notes

You have already seen how the presence of an electron-withdrawing or electron-releasing group affects the stability of a positively charged carbocation. Now you see how these groups affect the stability of carboxylate anions, and in turn, determine the dissociation constant of a carboxylic acid.

The Inductive Effect

As seen before, there can be a substantial range in the acidities of carboxylic acids. Trifluoroacetic acid (K_a = 0.59) is almost 60,000 times more acidic than butanoic acid (K_a = 1.51 X 10^{-5}). These vast differences in acidity can be explained almost exclusively by the inductive effect of substituents on the carboxylic acids.

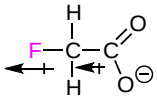
The **inductive effect** is an experimentally observed phenomenon in which charge is transmitted through a chain of atoms in a molecule, resulting in a permanent dipole in a bond. In a carboxylic acid group, the presence of halogens (such as fluorine) on adjacent carbons increases the acidity of the carboxylic acid group by stabilizing the carboxylate conjugate base.



pK_a = 4.8 pK_a = 3.9 pK_a = 2.8 pK_a = 2.6

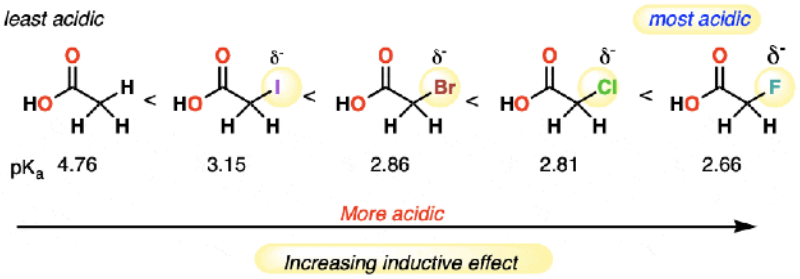
Withdrawing Inductive Effects

A fluorine atom is more electronegative than a hydrogen atom, and thus it is able to ‘induce’, or ‘pull’ the electron density of covalent bonds towards itself. In the fluoroacetate anion, the electrons in the C-F covalent bond are pulled toward the fluorine, giving the carbon a partial positive charge. The positively charged carbon, in turn, draws electron density away from the carboxylate anion, dispersing the charge, and creating a stabilizing effect. Stabilizing the carboxylate anion increases the acidity of the corresponding carboxylic acid. In this context, the fluorine substituent is acting as an **electron-withdrawing group**.

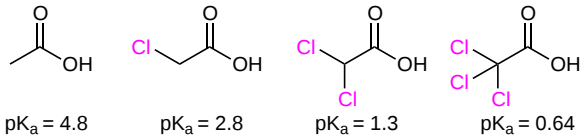


Fluoroacetate anion stabilized by electron withdrawing inductive effect of fluorine

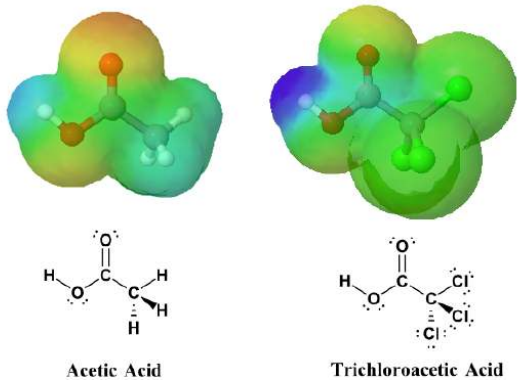
A similar effect is seen when other electron-withdrawing groups are attached to -CH_2CO_2H. As the power of the electron-withdrawing group becomes stronger, there is a corresponding drop in the pK_a of the carboxylic acid.



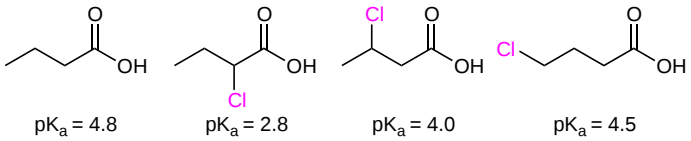
The presence of multiple electron-withdrawing groups compounds the inductive effect, further increasing the acidity of the carboxylic acid. Dichloroacetic is a stronger acid than chloroacetic acid, and trichloroacetic acid is even stronger.



The inductive effects of chlorine be clearly seen when looking at the electrostatic potential maps of acetic acid (Left) and trichloroacetic acid (Right). The O-H bond in trichloroacetic acid is highly polarized, as shown by the dark blue color making it a much stronger acid than acetic acid.

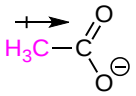


Because inductive effects are not transmitted effectively through covalent bonds, the acid-strengthening effect falls off rapidly as the number of sigma bonds between the carboxylic acid and the electron-withdrawing group increases. A distance of three sigma bonds almost completely eliminates chlorine's inductive effect in 4-chlorobutanoic acid, giving it a similar pK_a value to unsubstituted butanoic acid.

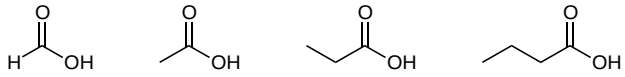


Donating Inductive Effects

Alkyl groups (hydrocarbons) are inductively electron-donating. In this case, the inductive effects push electron density onto the carboxylate anion, producing a destabilizing effect, decreasing the acidity of the carboxylic acid.



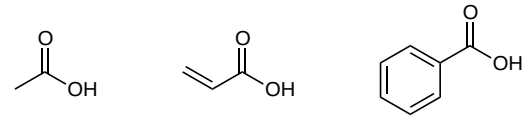
Lengthening the alkyl chain of a carboxylic acid can increase this inductive effect but it no longer decreases the acidity further after the chain is about three carbons long.



pK_a = 3.75 pK_a = 4.76 pK_a = 4.87 pK_a = 4.82

The Acidity of Substituted Benzoic Acids

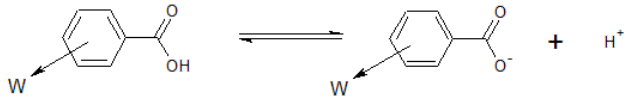
Extensive research has been performed on the acidity of substituted benzoic acids. Benzoic acid itself is a somewhat stronger acid than acetic acid. The carboxyl group of benzoic acid is attached to an sp^2-hybridized carbon, which is more electronegative and electron-withdrawing than the sp^3-hybridized carbon attached to the carboxyl group of acetic acid. In **Section 2.9** it was discussed that carbon becomes more electron-withdrawing as the s character of its hybrid orbitals increases. The same effect is seen in acrylic acid, which is also more acidic than acetic acid.



acetic acid pK_a = 4.8 acrylic acid pK_a = 4.3 benzoic acid pK_a = 4.2

In **Section 3.4** it was discussed that substituents had a marked effect on the electron density of an aromatic ring and on the rate of electrophilic aromatic substitutions. Electron-donating substituents increase the electron density of the aromatic ring, activating it, and increasing the rate of electrophilic substitutions. Electron-withdrawing groups decreased electron density, deactivating the aromatic ring, and reduced the rate of electrophilic substitution.

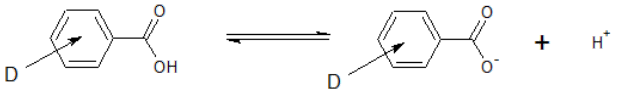
In a similar fashion, substituents have an effect on the acidity of benzoic acids. Benzoic acids with deactivating substituents, such a nitro group (-NO_2), in the *meta or para* position tend to be more acidic. The deactivating substituents remove electron density, stabilize the negative charge of the carboxylate anion, and increase the acidity of the carboxylic acid.



W = electron Withdrawing group

The carboxylate anion is stabilized by the electron withdrawing group increasing the acidity of the conjugate acid.

The opposite effect occurs with electron-donating substituents. Electron-donating substituents in the meta or para position destabilize the carboxylate anion making the benzoic acid less acidic.



D = electron Donating group

The carboxylate anion is destabilized by the electron withdrawing group decreasing the acidity of the conjugate acid.

A closer look at the effects of electron-withdrawing and electron-donating substituents in the meta or para position can be seen in the pK_a values of various benzoic acids as shown in the table below. Notice the trend in the following table, where electron-donating substituents (X) at the meta or para positions lead to weaker acids, while those having more electron-withdrawing substituents generate stronger acids.

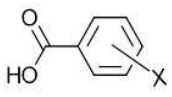


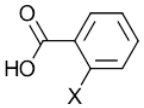
Table 6.3.1: Substituent Effects on the Acidity of *m- & p*-Substituted Benzoic Acids

Y	pK_a *o*-Substituted	pK_a *m*-Substituted	pK_a *p*-Substituted
$-NO_2$	2.17	2.45	3.44
–CN			3.55
–CHO			3.75
–Br	2.85	3.81	3.96
–Cl	2.94	3.84	4.00
–F	3.27	3.86	4.15
–H	4.19	4.19	4.19
$-CH_3$	3.91	4.25	4.37

$-OCH_3$	**4.09 - Induction**	4.09
–OH	**2.97**	4.8
$—NH_2$	4.7	4.7

The *Ortho*-Effect

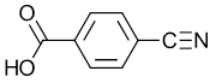
Almost all ortho-substituents increase the acid strength of a benzoic acid regardless of whether they are electron-donating or electron-withdrawing. This is called the *ortho*-effect, and its cause is not completely understood. It is theorized to be a combination of both steric and electronic factors. There are exceptions to the ortho-effect, such as an amino substituent, which still makes benzoic acid less acidic.



Dissociation Constants of *o*-Substituted Benzoic Acid

Example

The following molecule, *p*-cyanobenzoic acid, has a pK_a of 3.55. Does the cyano substituent activate or deactivate the aromatic ring towards electrophilic aromatic substitution?



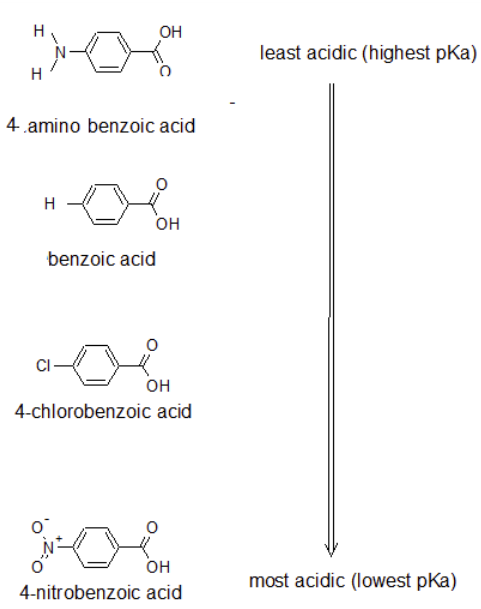
p-cyanobenzoic acid

The pK_a of benzoic acid is 4.2, which means it is a weaker acid than *p*-cyanobenzoic acid. This means the cyano substituent deactivates the ring.

? Worked Example

Draw the bond-line structures and arrange the following compounds in order of increasing acidity: 4-nitrobenzoic acid; 4-aminobenzoic acid; 4-chlorobenzoic acid; and benzoic acid. Try to use the expected inductive effects of the substituents to determine the acidity rather than looking at the pK_a table.

Answer



Exercises

Exercise 6.3.1

For the following pairs, which is expected to be the stronger acid? Explain your answer.

(a) $(CH_3)_3CCH_2CO_2H$ or $(CH_3)_3\overset{+}{N}CH_2CO_2H$

(b) $CH_3CH_2CO_2H$ or $CH_3\underset{\underset{OH}{|}}{C}HCO_2H$

(c) $CH_3\overset{\overset{O}{\|}}{C}CO_2H$ or $CH_2{=}CHCO_2H$

Answer

a) Consider the inductive effects of the substituents attached to the carboxylic acid. The *tert*-butyl group is electron-donating, which should decrease the acidity of the carboxylic acid. The trimethylammonium substituent is positively charged and can be a powerful electron-withdrawing substituent. This should increase the acidity of the carboxylic acid. The compound $(CH_3)_3NCH_2CO_2H$ is expected to be a stronger acid than $(CH_3)_3CCH_2CO_2H$. The acidity constants for these two compounds match the predictions.

b) Lactic acid, the second molecule has an electron-withdrawing hydroxyl group at the C-2. This group stabilizes the carboxylate ion of lactic acid through inductive effects. This should make lactic acid more acidic than propanoic acid.

c) Due to the presence of a highly electronegative oxygen in the first molecule (pyruvic acid), the carbonyl group is expected to be more strongly electron-withdrawing than a carbon–carbon double bond. Thus, pyruvic acid should be a stronger acid than acrylic acid.

Exercise 6.3.2

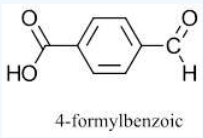
Oxalic acid is a dicarboxylic acid with two acidic protons. The first proton is much more acidic (pK_a = 1.20) than a typical carboxylic acid. However, Heptanedioic acid's first acidic proton has a pK_a much closer to that of a typical carboxylic acid. Explain these differences.

Answer

With oxalic acid, one carboxyl group acts as an inductive electron-withdrawing group, which increases the acidity of the other carboxylic acid. This inductive effect is only relevant when the two carboxyl groups are separated by only a few bonds. In heptanedioic acid, the carboxyl groups are separated by five carbon atoms, which effectively negates the inductive effect.

? Exercise 6.3.3

The carboxylic acid of 4-formylbenzoic acid has a pK_a of 3.75. Is this molecule likely to be more reactive or less reactive than benzene toward electrophilic aromatic substitution?



4-formylbenzoic

Answer

Benzoic acid (pK_a = 4.2) has a higher pK_a and is more acidic than 4-formylbenzoic acid (pK_a = 3.75). This means that the formyl group is removing electrons from the aromatic ring, making it deactivated toward electrophilic aromatic substitution.

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6.4: Preparing Carboxylic Acids

Objectives

After completing this section, you should be able to

1. describe in detail the methods of preparing carboxylic acids discussed in previous chapters:
   a. the oxidation of alkylbenzenes.
   b. the oxidative cleavage of alkenes.
   c. the oxidation of primary alcohols and aldehydes.
2. discuss, in detail, the hydrolysis of nitriles:
   a. write an equation to illustrate the preparation of a carboxylic acid through nucleophilic attack by cyanide ion on an alkyl halide and hydrolysis of the nitrile which results.
   b. identify the carboxylic acid formed from the hydrolysis of a given nitrile, or from the reaction of a given alkyl halide with cyanide ion followed by hydrolysis of the resulting nitrile.
   c. identify the alkyl halide needed to prepare a given carboxylic acid by the formation and subsequent hydrolysis of a nitrile.
   d. identify the reagents needed to convert a given alkyl halide into a carboxylic acid containing one more carbon atom.
3. discuss, in detail, the carboxylation of Grignard reagents:
   a. write an equation describing the formation of a carboxylic acid from a Grignard reagent.
   b. identify the carboxylic acid obtained through the treatment of a given Grignard reagent with carbon dioxide followed by dilute acid.
   c. identify the Grignard reagent (or the alkyl halide required to form the Grignard reagent) that must be used to produce a given carboxylic acid by reaction with carbon dioxide.
   d. write the detailed mechanism for the formation of a carboxylic acid using a Grignard reagent.

Study Notes

Review the methods of obtaining carboxylic acids presented in earlier sections:

1. oxidation of aromatic compounds—Section 16.9.
2. oxidative cleavage of alkenes—Section 8.8.
3. oxidation of primary alcohols and aldehydes—Sections 17.7 and 19.3.

Carboxylic acids can be prepared using a wide variety of reactions. Many carboxylic acid derivatives such as esters, amides, and anhydrides can undergo hydrolysis to form the parent carboxylic acids. The most common methods for synthesizing carboxylic acids can be separated into three major groups.

1. Oxidations
2. Carboxylation of Grignard Reagents
3. Hydrolysis of Nitriles

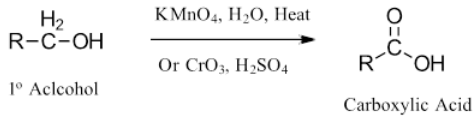
Forming Carboxylic Acids Through Oxidations

The carbon atom of a carboxyl group has a high oxidation state. It is not surprising, therefore, that many of the chemical reactions used for their preparation are oxidations. Such reactions have been discussed in previous sections of this text.

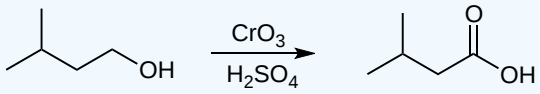
Oxidation of 1° Alcohols

The oxidation of 1° alcohols to carboxylic acids can be performed with a wide variety of oxidizing agents including potassium permanganate ($KMnO_4$) and Jones reagent (CrO_3 & H_2SO_4). One of the main synthetic limitations of alcohol oxidations is that the necessary oxidizing agents often react with other oxidizable functional groups, such as aldehydes, alkyl arenes, and other alcohols.

Because alcohols are often readily available this reaction is the most common oxidative reaction for creating simple carboxylic acids.



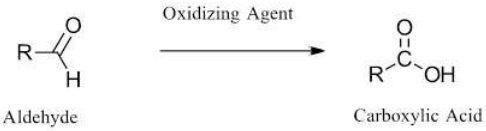
? Exercise 6.4.1



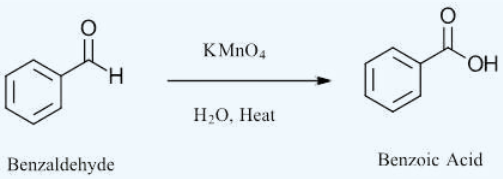
Oxidation of 3-methylbutan-1-ol to 3-methylbutanoic acid

Oxidation of Aldehydes

In a similar fashion as 1° alcohols, aldehydes are also converted to carboxylic acids using a wide variety of oxidizing agents including potassium permanganate and Jones reagent.

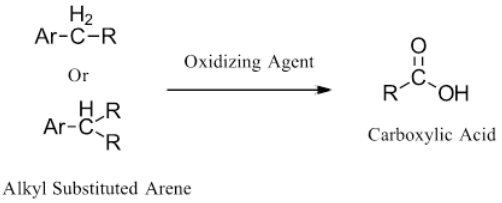


✓ Example 6.4.1



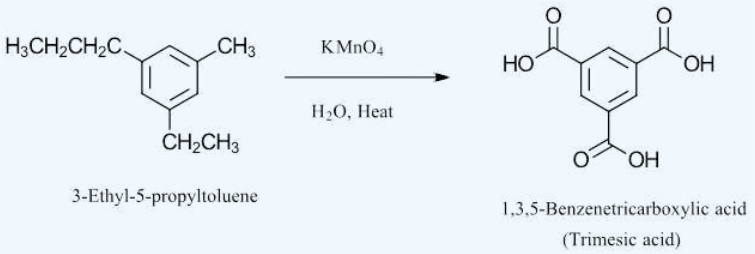
Oxidation of Alkyl Arene Side-Chains

Primary and secondary carbons directly attached to an aromatic ring can be converted to carboxylic acids by reaction with strong oxidizing agents including potassium permanganate and Jones reagent. Tertiary carbons attached to an aromatic ring are not affected by these reactions. It should be noted that alkyl groups are ortho, para directors and after oxidation the carboxylic acid formed is a meta director.



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Example

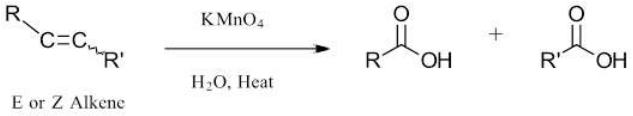


3-Ethyl-5-propyltoluene

1,3,5-Benzenetricarboxylic acid
(Trimesic acid)

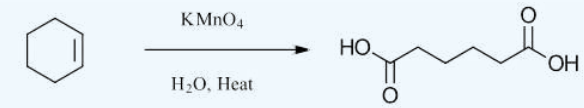
Oxidative Cleavage of Alkenes

Alkenes can undergo oxidative cleavage to form carboxylic acids by reacting with hot alkaline $KMnO_4$.



E or Z Alkene

Example

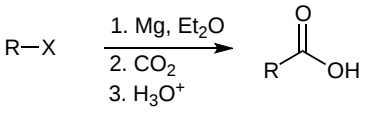


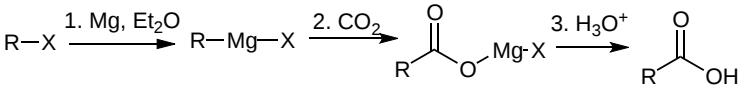
Cyclohexene

Hexanedioic Acid
(Adipic Acid)

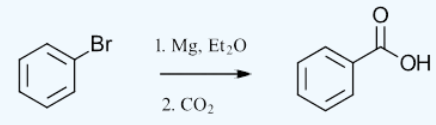
Carboxylation of Grignard Reagents

In this method, an electrophilic halide is first transformed into a strongly nucleophilic Grignard reagent. The Grignard reagent adds to the C=O bond of carbon dioxide (an electrophile) to yield the salt of of a carboxylic acid called a halomagnesium carboxylate. This intermediate is then treated with a strong aqueous acid to form the carboxylic acid. Most alkyl or aryl halides can be used for this synthesis of carboxylic acids. The main limitation is that no functional groups incompatible with Grignard reagents can be present such has O-H, N-H, S-H, or C=O bonds.





Example



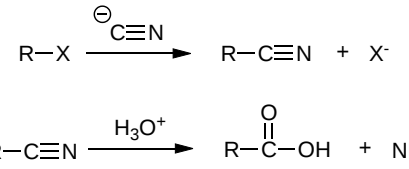
Bromobenzne

Benzoic Acid

Hydrolysis of Nitriles

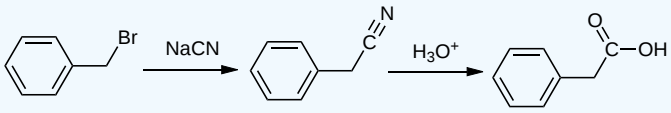
Hydrolysis of nitriles to carboxylic acids requires two steps. First, an alkyl halide is reacted with a nucleophilic cyanide anion to form a nitrile intermediate by an S_N2 reaction. Subsequent hydrolysis of the nitrile is typically performed by heating with an acidic

or basic aqueous solution and uses a mechanism discussed later in this chapter. Due to the requirements of the S_N2 reaction, only primary and secondary alkyl halides may be used for this reaction. Tertiary alkyl halides typically produce an alkene through E2 elimination reaction and aryl halides usually do not react.

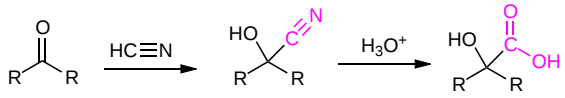


Two steps of nitrile formation and hydrolysis

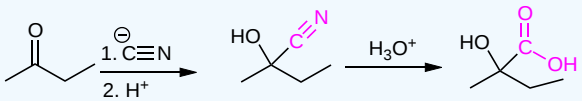
Example



Aldehydes and ketones can be converted to cyanohydrins through nucleophilic addition of a cyanide anion to the carbonyl. The -CN group of the cyanohydrin can also be hydrolized to form an alpha hydroxy carboxylic acid.



Example



conversion of butan-2-one to 2-hydroxy-2-methylbutanoic acid

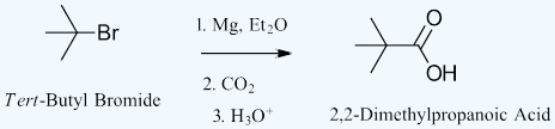
Worked Example 6.4.1: Choosing a Synthesis Pathway to a Carboxylic Acid

Thus far this chapter has discussed three main methods for the creation of a carboxylic acid functional group: the oxidation of a 1° alcohol, the carboxylation of a Grignard reagent, and the hydrolysis of a nitrile. Select one of these three methods to perform the following transformation. Briefly explain why the other two methods would be unsuccessful.

a. Tert-Butyl Bromide → 2,2-Dimethylpropanoic acid.
b. Benzyl Bromide → Benzoic Acid
c. 3-Bromo-1-propanol → 4-Hydroxybutanoic acid

Solution A

The product contains one more carbon than the reactant so the oxidation of a 1° alcohol would be an ineffective method. Also, the reactant contains a tertiary halide, so the S_N2 reaction required to form a nitrile would not be possible. The carboxylation of a Grignard reagent would be the most effective method because it allows for the addition of a carbon, it is not severely affected by the sterics of the tertiary halide, and there are no incompatible functional groups.

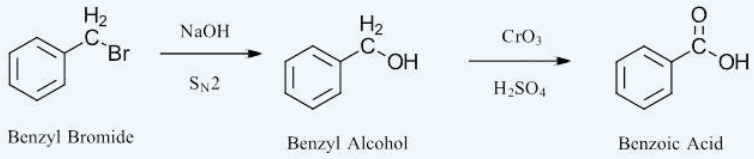


Tert-Butyl Bromide — 2,2-Dimethylpropanoic Acid

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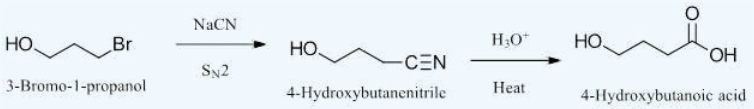
Solution B

The product and reactant have the same number of carbons so both the carboxylation of a Grignard reagent and hydrolysis of a nitrile would be ineffective for this conversion. Benzyl bromide is a primary alkyl halide which can easily be converted to a primary alcohol by an S_N2 reaction with NaOH. Once formed, the primary alcohol can be converted to a carboxylic acid using an oxidation reaction.



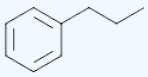
Solution C

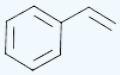
The product contains one more carbon than the reactant so the oxidation of a primary alcohol would not be an effective method. Also, the carboxylation of a Grignard reagent would not be an effect method because the presence of an incompatible alcohol functional group in the reactant. The reactant contains a primary halogen which can readily be converted to a nitrile by an S_N2 reaction with NaCN. The resulting nitrile can be converted to a carboxylic acid through hydrolysis.



Exercise 6.4.1

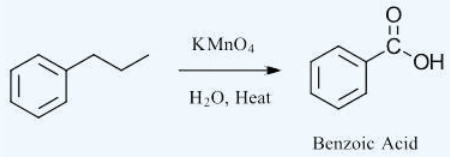
Show how the following molecules can be used to synthesize benzoic acid:

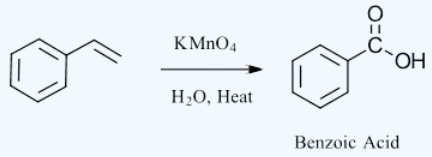
a. 

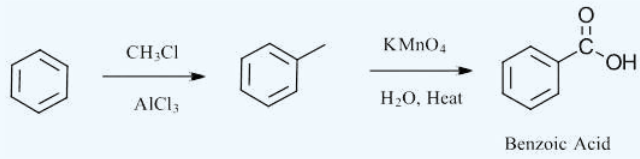
b. 

c. 

Answer

a. 

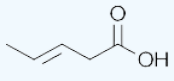
b. 

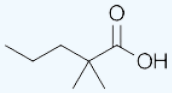
c. 

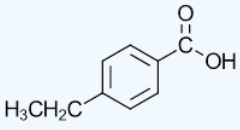
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Exercise 6.4.2

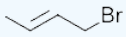
give the structure of the bromide required to make the following using the carboxylation of a Grignard reagent:

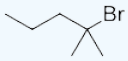
a. 

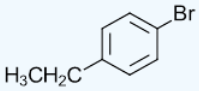
b. 

c. 

Answer

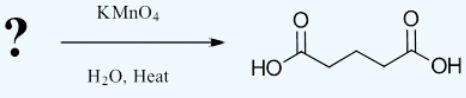
a. 

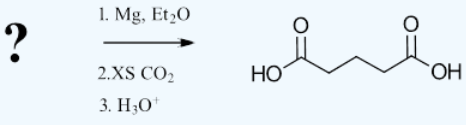
b. 

c. 

Exercise 6.4.3

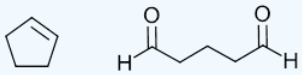
Give the possible reactants for the following reactions:

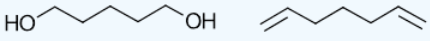
a. 

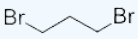
b. 

There are at least four possible answers for question a.

Answer



a. 

b. 

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6.5: Reactions of Carboxylic Acids - An Overview

Objectives

After completing this section, you should be able to identify the four types of reaction which a carboxylic acid can undergo.

Study Notes

You may wish to review the reduction of carbonyl compounds to form alcohols (OCHEM I) and the acidity of carboxylic acids, which is important to salt formation and substitution of the hydroxyl hydrogen. Nucleophilic acyl substitution (Chapter 7) and alpha substitutions (Chapter 8) are discussed later in more detail.

Four Categories of Carboxylic Acid Reactions

Carboxylic acid reactions are typically classified into four major categories:

1. As carboxylic acids are easily deprotonated, they readily form a carboxylate salt which can then potentially be reacted with an electrophile to complete a substitution of the hydroxyl hydrogen.
2. Nucleophilic acyl substitution reactions allow substitution of the hydroxyl group which leads to several carboxylic acid derivatives (e.g. acid halides, esters, amides, thioesters, acid anhydrides etc.). We will see these reactions in more detail in Chapter 7.
3. Like other carbonyl compounds, carboxylic acids can be reduced by reagents such as $LiAlH_4$.
4. While the proton on the carbon alpha to the carbonyl group is not as acidic as the hydroxyl hydrogen, it can be removed leading to substitution at the alpha position. The scheme summarizes some of the general reactions that carboxylic acids undergo.

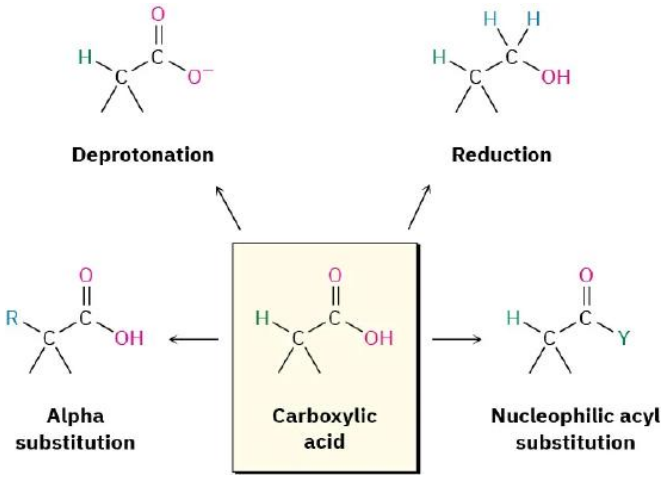


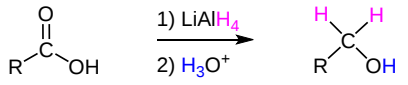
Figure **6.5.1**: Some general reactions of carboxylic acids.

Reduction of Carboxylic acids to 1° alcohols

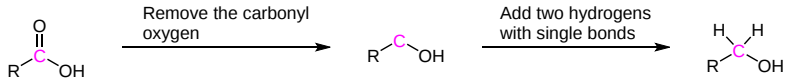
Lithium aluminum hydride ($LiAlH_4$)

Hydride nucleophiles from lithium aluminum hydride ($LiAlH_4$) can reduce carboxylic acids to 1° alcohols. Note that $NaBH_4$ is not a strong enough reducing agent to convert carboxylic acids or esters to alcohols. Because the incoming nucleophile is an “H” the reaction first produces an aldehyde intermediate which available for further hydride additions. The aldehyde intermediate is difficult to isolate because it is more reactive than the original carboxylic acid. This reaction represents the first example in this chapter where a carboxylic acid derivative can undergo a double nucleophilic addition. In the mechanism of this reaction, a nucleophilic acyl substitution is followed by a nucleophilic addition allowing for two hydride nucleophiles being added to the electrophilic carbonyl carbon of a carboxylic acid.

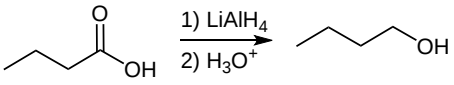
General reaction



Predicting the product of a hydride reduction



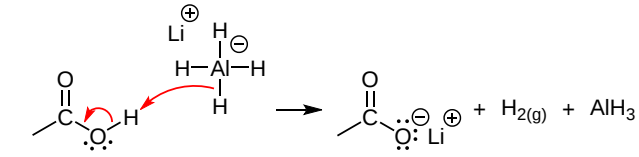
Example



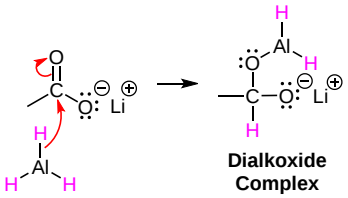
Possible Mechanism

Although the mechanism of this reaction is not precisely known, much of it is understood. Initially, a hydride deprotonates the carboxylic acid to form a lithium carboxylate, hydrogen gas (H_2), and aluminum hydride. Then a hydride nucleophile, from aluminum hydride, adds to the carbonyl carbon as part of a nucleophile acyl substitution. The resulting high-energy dianion intermediate forms a Lewis Acid/Base complex with aluminum, making one of the oxygens a good leaving group (the negative charge on the oxygen complexed to aluminum is not shown in step 2 below). The carbonyl bond is reformed along with the elimination of $OAlH_2$ as a leaving group to form an aldehyde. A hydride nucleophile from another molecule of $LiAlH_4$ adds to the re-formed carbonyl carbon as part of a nucleophilic addition. The resulting alkoxide intermediate is protonated during an acidic work-up to form the 1° alcohol product. Due to the formation of a dianion intermediate the reaction requires relatively high temperature and long reaction times.

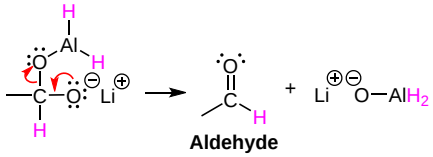
1) Deprotonation



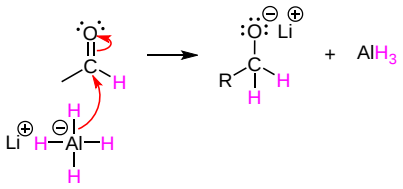
2) Nucleopilic attack by a hydride anion



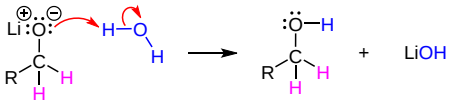
3) Leaving group removal



4) Nucleopilic attack by a hydride anion



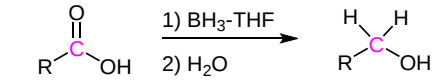
5) Alkoxide protonation



1° Alcohol

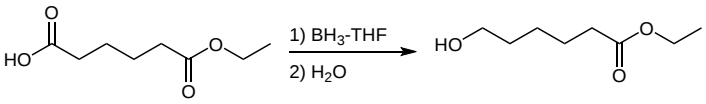
Borane tetrahydrofuran complex

Solutions of a borane tetrahydrofuran complex (BH_3-THF) rapidly reduce carboxylic acids at room temperature with often high yields. The borane tetrahydrofuran complex offers a safer and easier alternative to $LiAlH_4$ reductions.



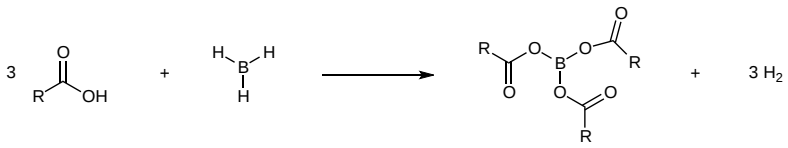
Carboxylic Acid **1° Alcohol**

Example



Adipic acid monoethyl ester **Ethyl 6-hydroxyhexanoate, (88% Yield)**

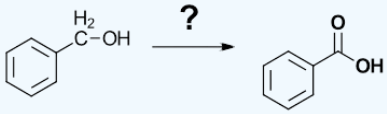
The acidic hydrogen of carboxylic acids allows them react faster with the borane tetrahydrofuran complex faster than any other functional group, allowing them to be selectively reduced in the presence of other carbonyls. In the first step of the reduction mechanism, which is rate determining, the acidic hydrogens of three carboxylic acids along with the three hydrogens from BH_3 are rapidly removed to form hydrogen gas (H_2) and a triacyloxyborane complex. A subsequent aqueous work-up converts the complex into a primary alcohol as shown in the general reaction above.



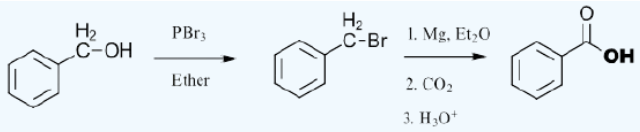
triacyloxyborane complex

? Exercise 6.5.1

Show how the following transformation can be performed. Multiple steps may be required.

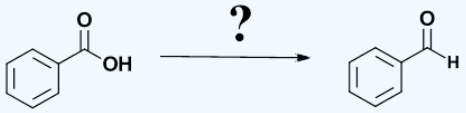


Answer

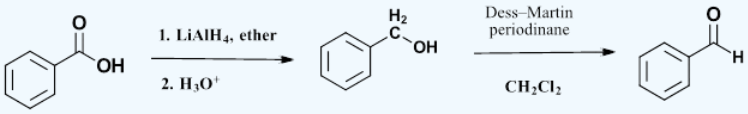


Exercise 6.5.2

Show how the following transformation can be performed. Multiple steps may be required.



Answer



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6.6: Chemistry of Nitriles

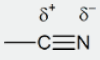
Objectives

After completing this section, you should be able to

1. discuss, in detail, the preparation of nitriles:
    a. write an equation to illustrate the formation of a nitrile by the nucleophilic attack of cyanide ion on an alkyl halide.
    b. write an equation to illustrate the formation of a nitrile by the dehydration of a primary amide.
    c. identify the product formed when a primary amide is treated with $SOCl_2$, P_2O_5, or $POCl_3$.
    d. identify the primary amide, the reagents, or both, needed to prepare a given nitrile by a dehydration reaction.
    e. write a detailed mechanism for the dehydration of a primary amide by thionyl chloride.
2. discuss, in detail, the reactions of nitriles:
    a. write an equation to describe the (acidic or basic) hydrolysis of a nitrile.
    b. write detailed mechanisms for the acidic and basic hydrolysis of nitriles.
    c. identify the products formed from the (acidic or basic) hydrolysis of a given nitrile.
    d. identify the nitrile, the reagents, or both, needed to obtain a given carboxylic acid from a hydrolysis reaction.
    e. write an equation to describe the reduction of a nitrile to give a primary amine.
    f. identify the product formed from the lithium aluminum hydride reduction of a given nitrile.
    g. identify the nitrile, the reagents, or both, needed to prepare a given amine by direct reduction.
    h. write a detailed mechanism for the reduction of a nitrile to a primary amine using lithium aluminum hydride.
    i. give an example of the reduction of a nitrile with diisobutylaluminum hydride.
    j. write an equation to illustrate the reaction of a nitrile with a Grignard reagent.
    k. identify the product formed from the reaction of a given nitrile with a given Grignard reagent.
    l. identify the nitrile, the Grignard reagent, or both, needed to prepare a given ketone.
    m. write a detailed mechanism for the reaction of a nitrile with a Grignard reagent.

Study Notes

To be able to understand the driving force behind the reactions of nitriles, you must recognize the polarity of this group:

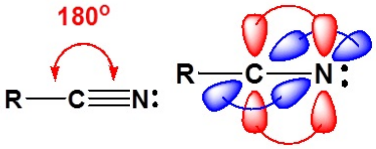


You can therefore expect to see similarities between the behaviour of the nitrile group and the similarly polarized carbonyl group:

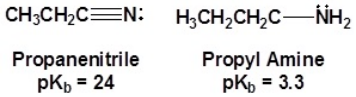


Structure of Nitriles

The electronic structure of nitriles is very similar to that of an alkyne with the main difference being the presence of a set of lone pair electrons on the nitrogen. Both the carbon and the nitrogen are *sp* hydridized which leaves them both with two p orbitals which overlap to form the two π bonds in the triple bond. The R-C-N bond angle in a nitrile is 180° which give a nitrile functional group a linear shape.

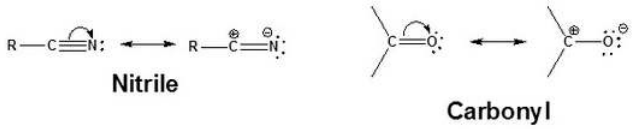


The lone pair electrons on the nitrogen of a nitrile are contained in a *sp* hybrid orbital. The 50% *s* character of an *sp* hybrid orbital makes the lone pair electrons closer to the nucleus and therefore less basic when compared to lone pair electrons on sp^3 hybridized nitrogen (25% *s* character) containing compounds such as amines.

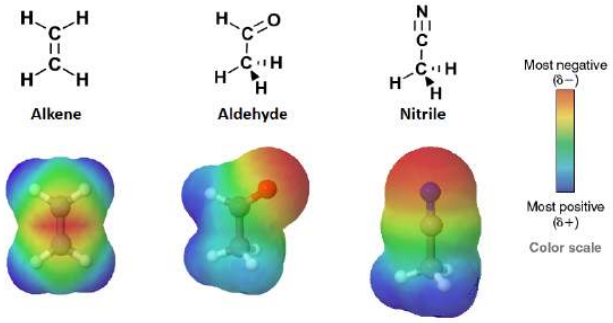


Resonance of Nitriles

Nitriles are analogous to carbonyl groups in that they contain pi bonds, are strongly polarized, and contain electrophilic carbons.

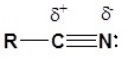


The bond polarization of a nitrile can clearly be seen when comparing the electrostatic potential maps of an alkene, an aldehyde, and a nitrile. In the maps of the aldehyde and nitrile, the electron density in the pi bonds is pulled away from the carbon toward the electronegative oxygen and nitrogen. This gives the functional group carbons a slight positive charge making them electrophilic. In the map of the alkene, the electron density is centered on the carbon making the pi bond non-polar and the carbons not electrophilic.



Properties of Nitriles

The presence of an electronegative nitrogen causes nitriles to be very polar molecules. Consequently, nitriles tend to have higher boiling points than molecules with a similar size. Also, the polar nature of nitriles promotes their solubility in water.

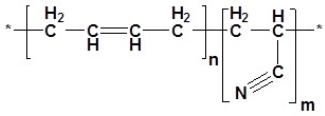


	Boiling Point
$CH_3CH_2C{\equiv}N$ Propanenitrile	96-98 °C
$CH_3CH_2C{\equiv}C{-}H$ Butyne	8.1 °C
$CH_3CH_2CH_2CH_3$ Butane	-1-1 °C

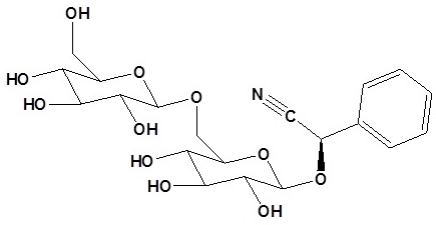
Interesting Nitriles

One of the most common occurrences of nitriles is in Nitrile rubber. Nitrile rubber is a synthetic copolymer of acrylonitrile and butadiene. This form of rubber is highly resistant to chemicals and is used to make protective gloves, hoses and seals. Amygdalin is a naturally occurring molecule contained by certain plants to protect themselves against herbivores and insects. Acting as a sort of

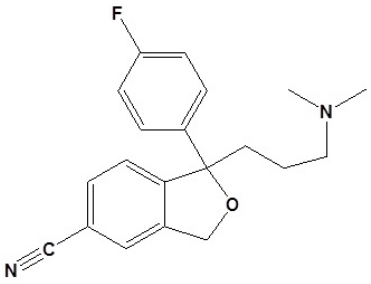
natural pesticide, amygdalin degrades to release poisonous hydrogen cyanide (HCN) when any plant material is chewed by an insect or animal. There are also several nitrile containing molecules that have medicinal uses such as Cyamemazine, which is an antipsychotic drug primarily used to treat schizophrenia and certain types of anxiety. Also, Citalopram is an antidepressant primarily used to treat depression, panic disorder, and social phobia. It is currently among the most prescribed drugs in the United States (#21 in 2019 with over 26,000,000 prescriptions).



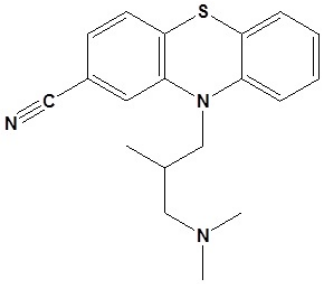
Nitrile Rubber



Amygdalin: Found in Bitter Almonds



Citalopram: an antidepressant

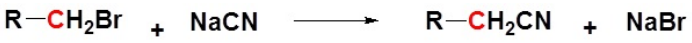


Cyamemazine: an antipsychotic

Preparation of Nitriles

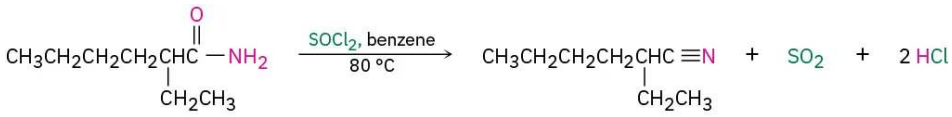
Formation of a Nitrile from an Aldehyde or Ketone

The simplest method of nitrile preparation is the S_N2 reaction of CN^- with a primary or secondary alkyl halide and sodium cyanide. Tertiary and aryl halides cannot be used for this reaction.



Formation of a Nitrile from a 1° Amide

Another method for preparing nitriles is by dehydration of a primary amide, $RCONH_2$. Thionyl chloride ($SOCl_2$) is often used for this reaction, although other dehydrating agents such as $POCl_3$ or P_2O_5 also work.

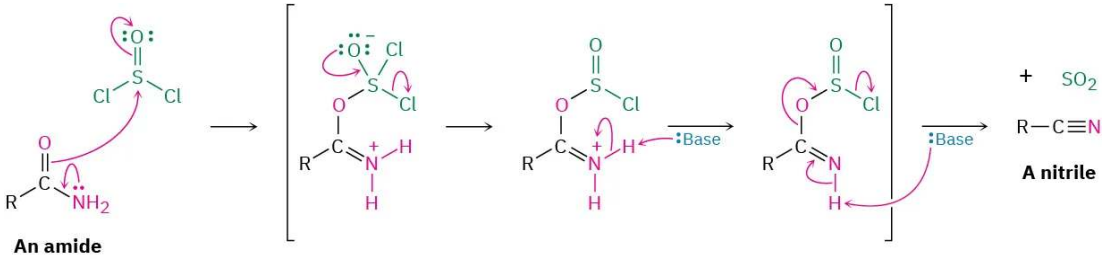


2-Ethylhexanamide **2-Ethylhexanenitrile (94%)**

Mechanism

For the reaction of primary amides with thionyl chloride, the mechanism begins with the lone pair of electrons from the nitrogen atom forming a protonated imine and pushing the pi electrons of the carbonyl to undergo nucleophilic attack on the sulfur of thionyl chloride. This forms a O-S sigma bond and causes the pi electrons of the thionyl bond (S=O) to be pushed onto the oxygen. The thionyl bond reforms in concert with the loss of a chloride leaving group (Cl^-). The protonated imine is neutralized by any

base. The nitrile is then produced by an E2-like elimination reaction with a loss of sulfur dioxide (SO_2) and another chloride as the leaving groups.



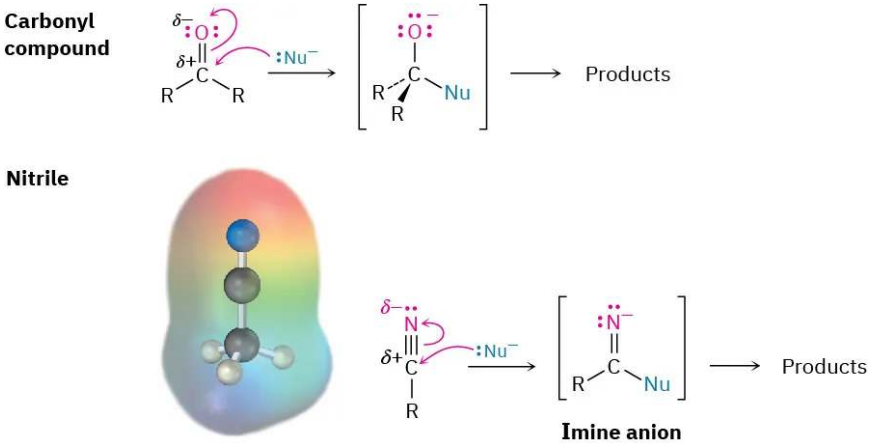
The dehydration occurs by initial reaction of $SOCl_2$ on the nucleophilic amide oxygen atom, followed by deprotonation and a subsequent E2-like elimination reaction.

Both methods of nitrile synthesis—S_N2 displacement by CN^- on an alkyl halide and amide dehydration—are useful, but the synthesis from amides is more general because it is not limited by steric hindrance.

Nucleophilic Reactions with Nitriles

The triple bond of a nitrile reacts with negatively charged nucleophiles to form an imine anion intermediate in much the same fashion that carbonyls form a tetrahedral alkoxide intermediate. Because the imine anion intermediate still contains a pi bond and an electrophilic carbon, additional nucleophilic additions can occur to form a variety of functional groups including ketones, aldehydes, and amines.

Like a carbonyl group, a nitrile group is strongly polarized and has an electrophilic carbon atom. Nitriles therefore react with nucleophiles to yield sp^2-hybridized imine anions in a reaction analogous to the formation of a sp^3-hybridized alkoxide ion by nucleophilic addition to a carbonyl group.



General Reactions of Nitriles

Nitriles undergo several types of reactions including hydrolysis to carboxylic acids, two different reductions with products that vary with the strength of the reducing agent and reaction with Grignard reagents that form ketones.

Some general reactions of nitriles are shown in Figure 6.6.1.

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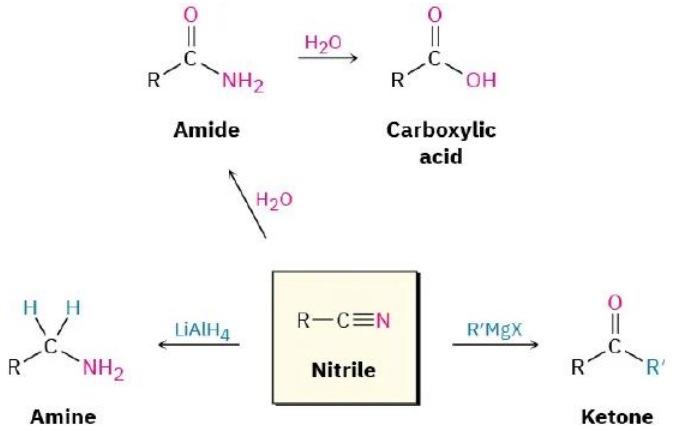


Figure 6.6.1: Some reactions of nitriles.

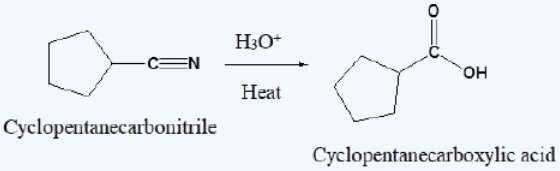
Hydrolysis: Conversion of Nitriles into Carboxylic Acids

One of the more useful reaction involving nitriles is their hydrolysis to form carboxylic acids. This reaction occurs in either acidc or basic aqueous solutions with slight differences in each mechanism. In the case of acid catalysis, the nitrile becomes protonated. Protonation increases the electrophilicity of the nitrile so that it will accept water, a poor nucleophile. With base catalyzed hydrolysis, the strongly nucleophilic hydroxide anion is capable of directl addition to the carbon-nitrogen triple bond. During both mechanisms an amide intermediate is formed which usually is not isolated.

Among the most useful reactions of nitriles is their hydrolysis to yield first an amide and then a carboxylic acid plus ammonia or an amine. The reaction occurs in either basic or acidic aqueous solution:

Acid Catalyzed Hydrolysis of Nitriles

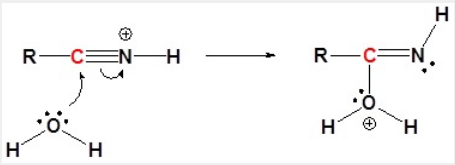
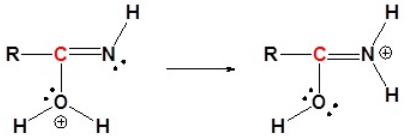
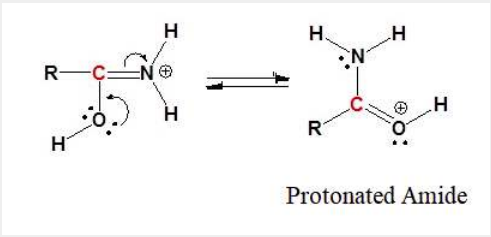
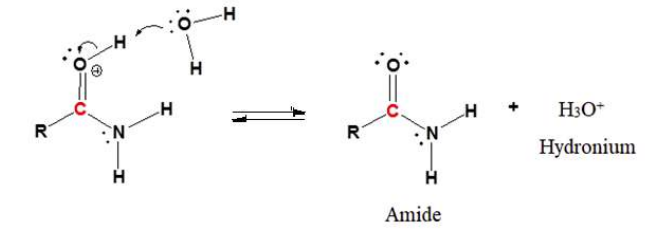
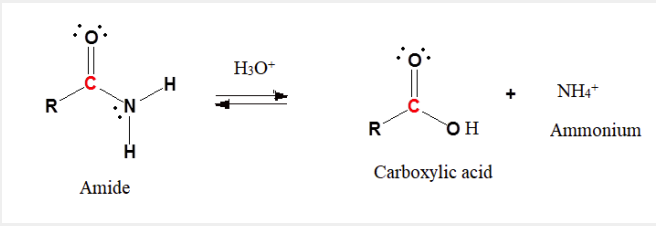
Example



Mechanism of Acid Catalyzed Hydrolysis

The mechanism begins with the protonation of the nitrile to promote the addition of the weakly nucleophilic water molecule to the C-N triple bond. Once water has reacted with the nitrile carbon, a proton transfer and resonance occur to produce a protonated amide. Water acts as a weak base, deprotonating the carbonyl to form an amide and regenerating the hydronium catalyst. Further

hydrolysis converts the amide to the carboxylic acid. The nitrile nitrogen is eventually removed as a leaving group and eventually forms ammonium (NH_4^+)

Step 1: Protonation	
Step 2: Nucleophilic addition of water	
Step 3: Proton Transfer	
Step 4: Resonance to form a protonated amide	
Step 5: Deprotonation to form an amide	
Step 6: Further hydrolysis of the amide forms a carboxylic acid. This mechanism can be found in Section 6.8	

Based Catalyzed Hydrolysis of Nitriles

As shown in Figure 6.6.2, base-catalyzed nitrile hydrolysis involves nucleophilic addition of hydroxide ion to the polar C≡N bond to give an imine anion in a process similar to the nucleophilic addition to a polar C═O bond to give an alkoxide anion. Protonation then gives a hydroxy imine, which tautomerizes to an amide in a step similar to the tautomerization of an enol to a ketone. Further hydrolysis gives a carboxylate ion.

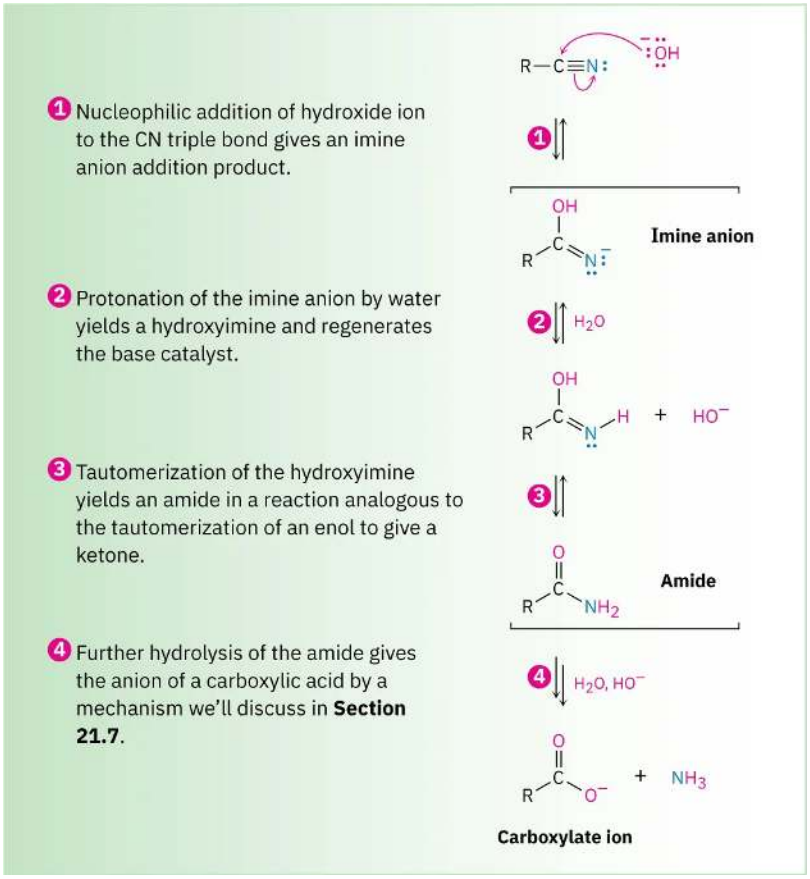
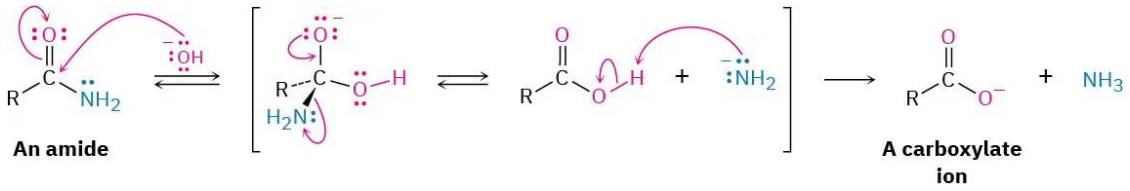


Figure 6.6.2: Mechanism for the basic hydrolysis of a nitrile to yield an amide, which is then hydrolyzed further to a carboxylic acid anion.

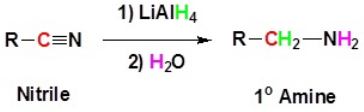
The further hydrolysis of the amide intermediate takes place by a nucleophilic addition of hydroxide ion to the amide carbonyl group, which yields a tetrahedral alkoxide ion. Expulsion of amide ion, NH_2^-, as leaving group gives the carboxylate ion, thereby driving the reaction toward the products. Subsequent acidification in a separate step yields the carboxylic acid. We'll look at this process in more detail in Section 7.8.



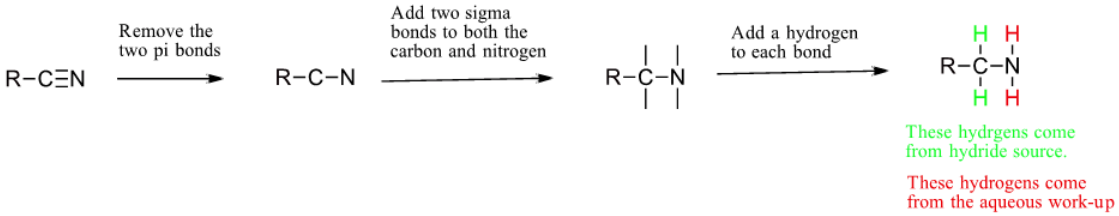
Reduction: Conversion of Nitriles into Amines

Nitriles can be reduced to 1° amines by reaction with $LiAlH_4$

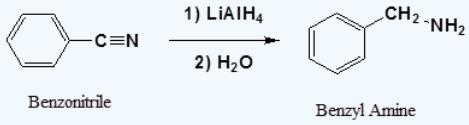
The reduction of nitriles with lithium aluminum hydride $LiAlH_4$ is an excellent method for the synthesis of primary amines. This reaction occurs via two nucleophilic additions of a hydride to the electrophilic carbon in the nitrile. Subsequent protonation with an aqueous work-up leads to the primary amine.



Predicting the Product of a Hydride Reduction

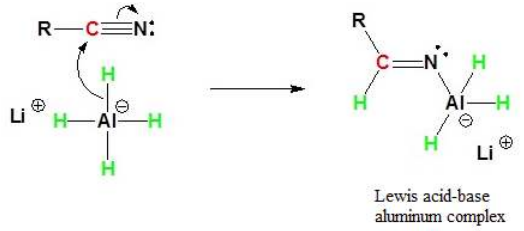
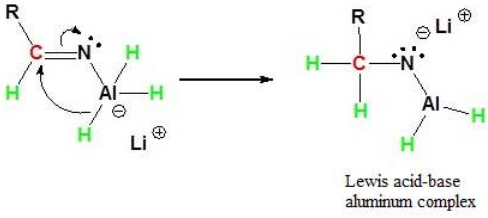
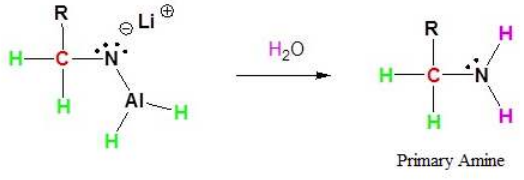


Example 6.6.1



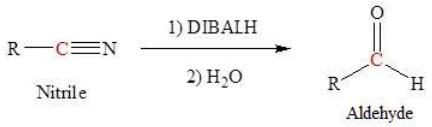
Mechanism

During this reaction the hydride nucleophile reacts with the electrophilic carbon in the nitrile to form an imine anion. The imine ion is stabilized through formation of an anionic Lewis acid-base aluminum complex. The complex is vital for the continuation of the reaction because it shifts the negative charge from the nitrogen to the aluminum allowing for the imine carbon to remain electrophilic. Because the imine-aluminum complex still contains a pi bond and an electrophilic carbon, it can undergo a second nucleophilic addition of a hydride to form a dianion. The dianion is also stabilized through the formation of an anionic Lewis acid-base aluminum complex. During the aqueous work-up, the dianion is protonated by water to form a primary amine.

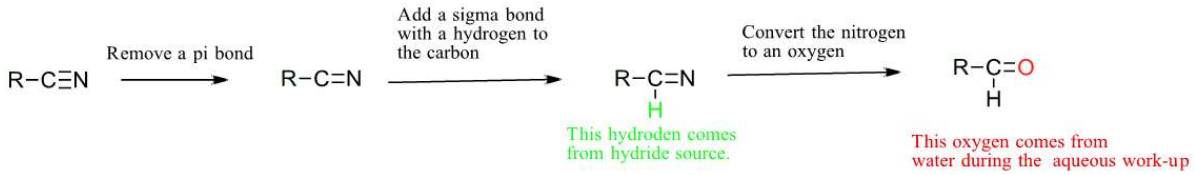
Step 1: Nucleophilic Attack by the Hydride	
Step 2: Second nucleophilic attack by the hydride.	
Step 3: Protonation by addition of water to give a primary amine	

The Conversion of Nitriles to Aldehydes by Reaction with DIBALH

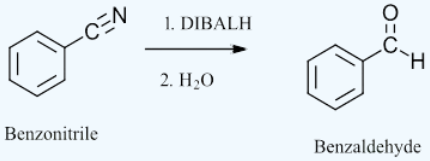
The use of DIBALH as a hydride source offers an efficient method for the synthesis of aldehydes. DIBALH only contains on hydride so the addition of one equivalent to a nitrile at low temperature (-78^{0}C) allows for the conversion to an aldehyde.



Predicting the Product of a Reaction with DIBALH

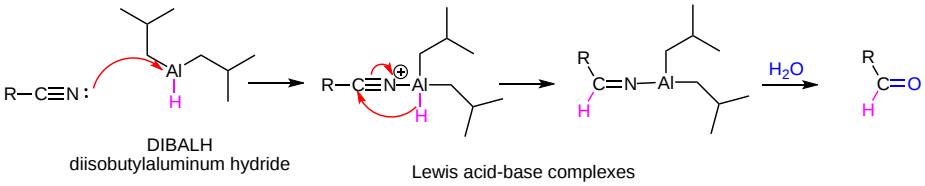


Example 6.6.1



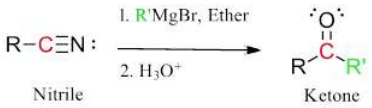
Mechanism of DIBALH Reduction of Nitriles

The mechanism starts with the formation of a Lewis acid-base complex which increases the electrophilic character of the nitrile's carbon. The nucleophilic addition of a hydride forms an imine anion which is also stabilized through formation of a Lewis acid-base aluminum complex. Unlike the reduction with $LiAlH_4$, DIBALH only has a single hydride so a second nucleophlic addition to the imine anion does not occur. Subsequently, the imine anion undergoes hydrolysis during acidic aqueous work-up to from an aldehyde. The mechanism of imine anion hydrolysis is the reverse of an imine formation previously discussed.



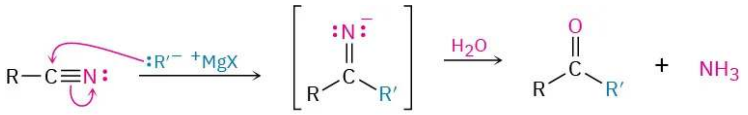
Conversion of Nitriles to Ketones with Organometallic Reagents

Some organometallic species, such as Grignard reagents or organolithium reagents, undergo a general Reaction



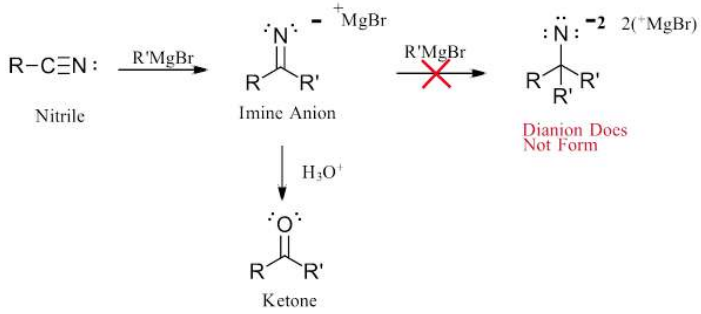
Grignard reactions

Grignard reagents add to a nitrile to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone. The mechanism of the hydrolysis is the exact reverse of imine formation.

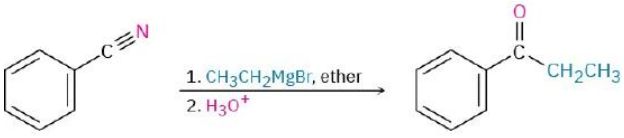


Nitrile **Imine anion** **Ketone**

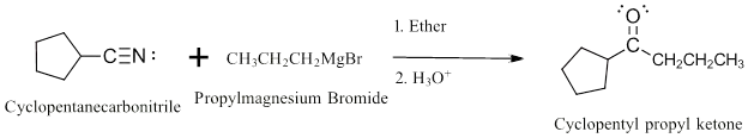
This reaction is similar to the reduction of a nitrile to an amine, except that only one nucleophilic addition occurs rather than two and the attacking nucleophile is a carbanion (R:⁻) rather than a hydride ion. Despite the presence of a pi bond, the negative charge of the imine anion prevents any further nucleophilic additions. During an aqueous work-up, the imine anion is hydrolyzed by water to form a ketone.



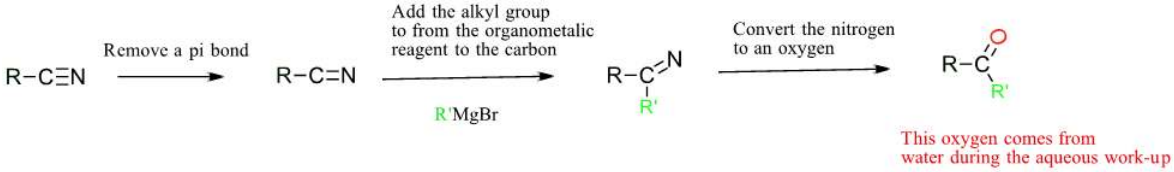
For example:



Benzonitrile **Propiophenone (89%)**



Predicting the Product of a Grignard Reaction

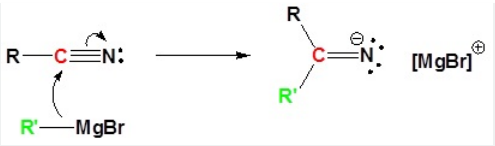


Just for your curiosity!

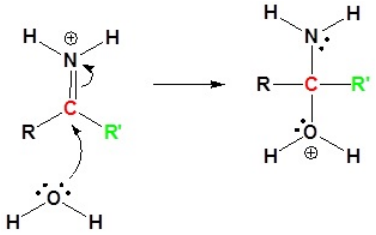
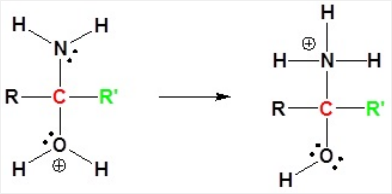
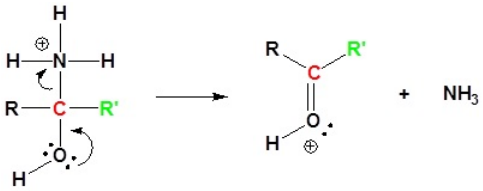
Mechanism of Organometallic Addition

The mechanism begins with the nucleophilic Grignard reagent reacting with the electrophilic carbon of the nitrile to form a salt of the imine anion. The imine salt is protonated to form an imine, which is then protonated to form a positively charged iminium ion. After nucleophilic attack by water and a proton transfer, the nitrogen from the nitrile is removed as a leaving group in the from of ammonia (NH_3). This step forms a protonated ketone called a ketonium ion which is subsequently deprotonated by ammonia to the neutral ketone and ammonium (NH_4^+).

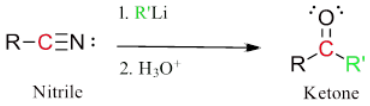
Step 1: Nucleophilic Attack by the Grignard Reagent to form an imine anion



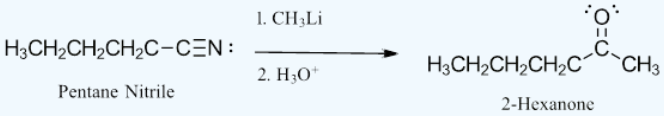
Step 2: Addition of H_3O^+ produces the protonation to form an imine followed by a second protonation to form an iminium ion.

Step 3: Nucleophilic attack by water to the minimum ion.	
Step 4: Proton Transfer from the protonated oxygen to a water molecule and from a water molecule to the amine. (Amines are more basic than water)	
Step 5: Removal of NH_3 as a leaving group to form a ketonium ion.	
Step 6: Deprotonation to form a ketone.	

Organolithium Reactions

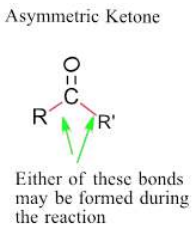


Examples

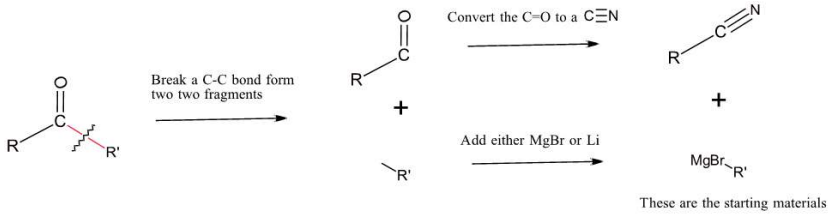


Planning the Synthesis of a Ketone from a Nitrile

These reactions can be employed to plan synthetic routes to desired molecules from nitriles. Because a C-C bond is formed, the reaction of an organometallic reagent with nitrile is an effective method for the synthesis of ketones. Also, asymmetrical ketones offer the possibility of two separate synthesis routes.

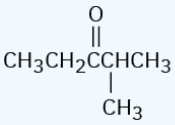


To plan a synthesis, we often think in reverse. Begin with the intended product (in this case the ketone). Break a C-C bond between the carbon in the carbonyl and an adjacent carbon. The fragment with the C=O becomes the nitrile starting material. The other fragment becomes either a Grignard or an organolithium reagent.



Worked Example 6.6.1: Synthesizing a Ketone from a Nitrile

How would you prepare 2-methyl-3-pentanone from a nitrile?



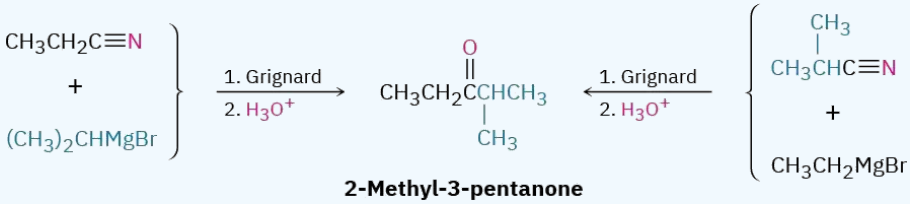
2-Methyl-3-pentanone

Strategy

A ketone results from the reaction between a Grignard reagent and a nitrile, with the C≡N carbon of the nitrile becoming the carbonyl carbon. Identify the two groups attached to the carbonyl carbon atom in the product. One will come from the Grignard reagent and the other will come from the nitrile.

Solution

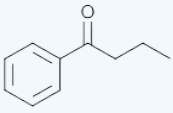
There are two possibilities.



2-Methyl-3-pentanone

Worked Example 6.6.1

Plan a synthesis of the following molecule using the reaction of a organometallic reagent and a nitrile.

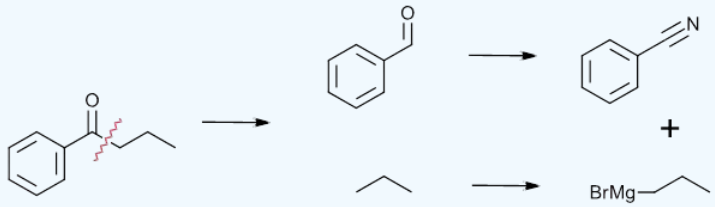


Solution

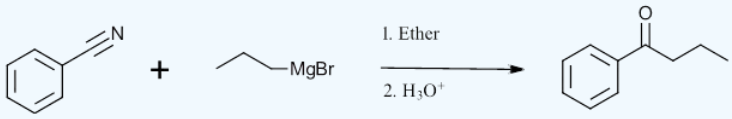
There are two possible pathways to synthesize this molecule.

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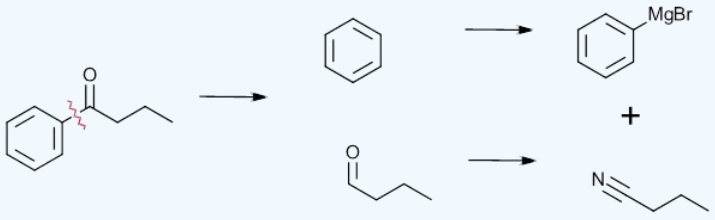
Solution 1



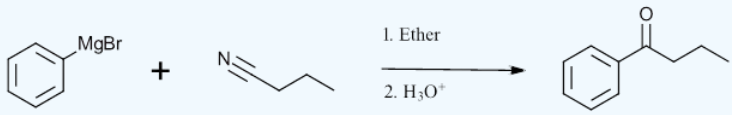
Pathway 1)



Solution 2

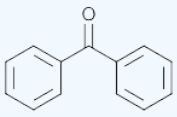
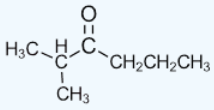


Pathway 2)



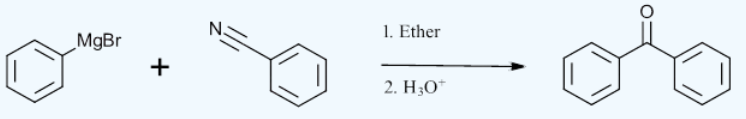
? Exercise 6.6.1

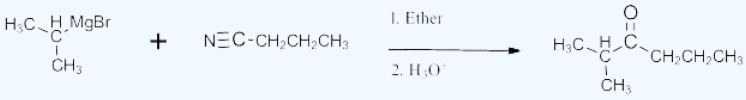
Show how the following compounds could be prepared from a nitrile:

a.  b. 

Answer

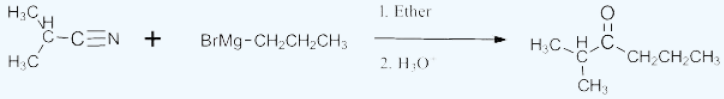
a.





Or

b.



Exercise 6.6.2

Show how the following transformations could be preformed:

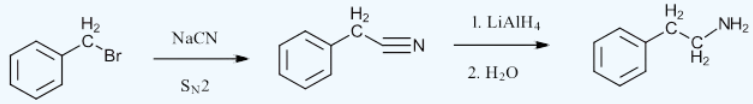
a.



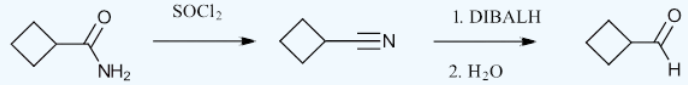
b.

Answer

a.

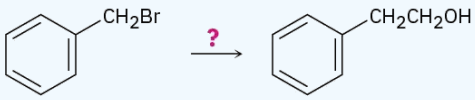


b.



Exercise 6.6.3

How might you prepare 2-phenylethanol from benzyl bromide? More than one step is needed.



Answer

1. NaCN; 2. H_3O^+; 3. $LiAlH_4$

Exercise 6.6.4

How might you carry out the following transformation? More than one step is needed.

Answer

1. PBr_3; 2. NaCN; 3. H_3O^+; 4. $LiAlH_4$

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6.7: Spectroscopy of Carboxylic Acids and Nitriles

Objectives

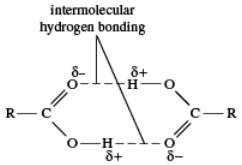
After completing this section, you should be able to

1. identify the two characteristic infrared absorptions displayed by all carboxylic acids.
2. state the approximate ^{1}H NMR absorption of a carboxylic acid proton.
3. use infrared and NMR spectroscopy data to assist in the identification of an unknown carboxylic acid, with or without the assistance of a table of characteristic absorptions.

Spectroscopy of Carboxylic Acids

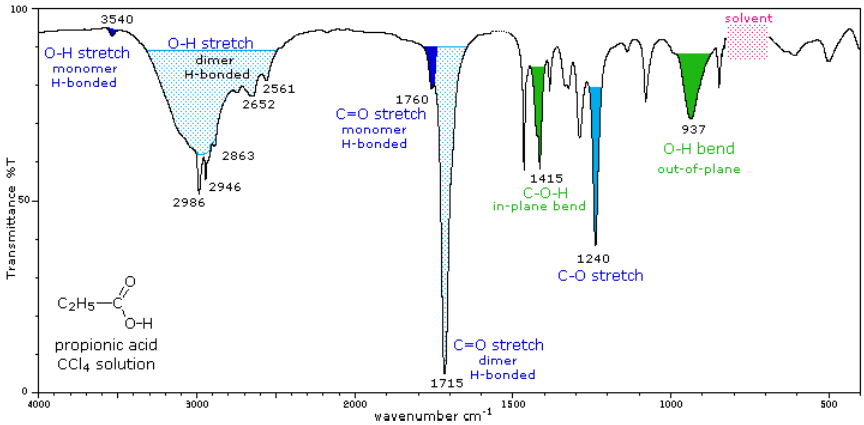
Infrared Spectroscopy

The carboxyl group is associated with two characteristic infrared stretching absorptions which change markedly with hydrogen bonding. The spectrum of propionic acid (propanoic acid) dissolved in CCl_4, shown below, is illustrative. Carboxylic acids exist predominantly as hydrogen bonded dimers in condensed phases.



The Hydrogen Bonding Dimer of Carboxylic Acids

The O-H stretching absorption for such dimers is very strong and broad, extending from 2500 to 3300 cm^{-1}. This absorption overlaps the sharper C-H stretching peaks, which may be seen extending beyond the O-H envelope at 2990, 2950 and 2870 cm^{-1}. The smaller peaks protruding near 2655 and 2560 cm^{-1} are characteristic of the dimer. In ether solvents a sharper hydrogen bonded monomer absorption near 3500 cm^{-1} is observed, due to competition of the ether oxygen as a hydrogen bond acceptor. The carbonyl stretching frequency of the dimer is found near 1710 cm^{-1}, but is increased by 25 cm^{-1} or more in the monomeric state. Other characteristic stretching and bending absorptions are marked in the spectrum.

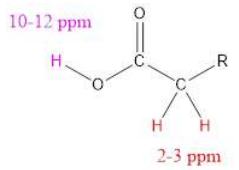


The Infrared Spectrum of Propanoic Acid

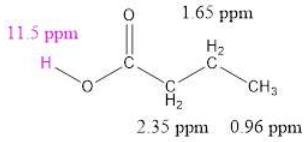
^{1}H Nuclear Magnetic Spectroscopy

The acidic O-H protons of carboxylic acids are highly deshielded due to the electronegativity of oxygen and anisotropy from the C=O carbonyl bond. They tend to be among the least shielded protons appearing far downfield in the 10–12 ppm region which is considered distinctive for carboxylic acids. Due to hydrogen bonding the proton of a carboxylic acid often appears as a broad

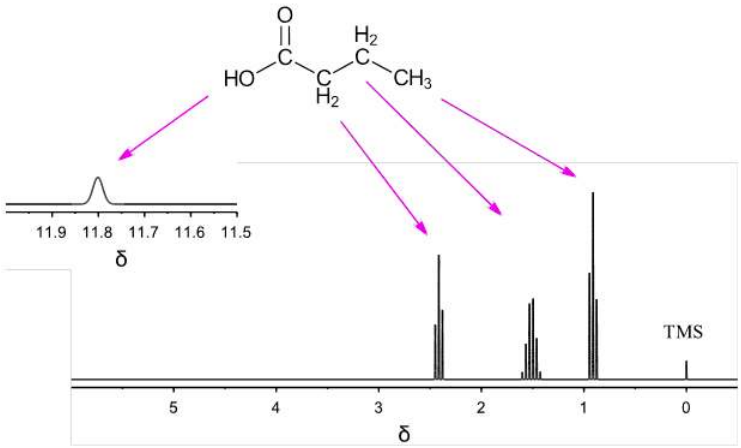
singlet and adding D_2O causes the signal to disappear due to hydrogen-deuterium exchange. Protons on carbons adjacent to a carboxylic acid absorb in the 2-3 ppm region. Some deshielding occurs due to the fact that the carbonyl oxygen is pulling electron density away from the carbonyl carbon which inductively pulls electron density away from the adjacent carbon.



The Typical ^{1}H Peaks for a Carboxylic Acid



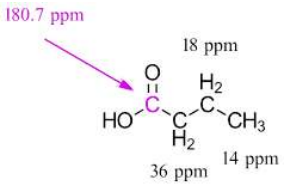
The ^{1}H Peaks for Butanoic Acid



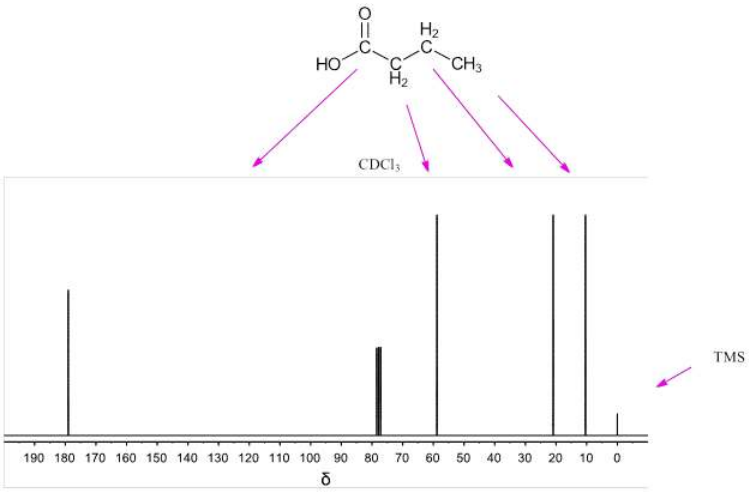
A ^{1}H NMR Spectra for Butanoic Acid

^{13}C Nuclear Magnetic Spectroscopy

The carbonyl carbon of a carboxylic acid is strongly deshielded (160-180 ppm) due to the presence of the highly electronegative oxygen. However, they are not as deshielded as the carbonyl carbon of an aldehyde or ketone (180-220 ppm).



The ^{13}C Peaks for Butanoic Acid



A ^{13}C NMR Spectra for Butanoic Acid

UV/Vis Spectroscopy

Without additional conjugation, carboxylic acids absorb at about 210 nm, which is too low to be useful.

Mass Spectrometry

The molecular ion of straight chain carboxylic acids is weak but usually present. For Larger acids, the McLafferty rearrangement results in a prominent peak and often accounts for the base peak. When the carboxylic acid does not contain any additional substituent in the alpha carbon, the McLafferty rearrangement results in the acetic acid enol radical cation with a characteristic m/z=60. Figure 1

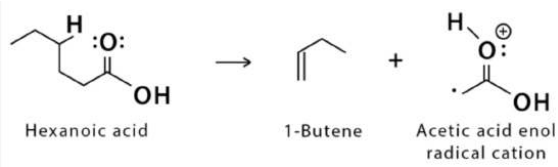


Figure **6.7.1**: The McLafferty rearrangement of hexanoic acid ($C_6H_{12}O_2$): m/z = 60.

Short chain carboxylic acids give prevalent peaks at [M – OH] and [M – CO_2H]. In large carboxylic acids, these peaks are less prevalent. Long chain carboxylic acids are better identified by the fragments from the cleavage between beta and gamma carbon. In the case of a linear carboxylic acid the fragment with m/z = 73 from [$C_3H_5O_2$] (Figure 2). There is also the presence of the hydrocarbon fragment from the cleavage between gamma and delta carbon (fragment with m/z = 86 from [$C_4H_7O_2$]; Figure 2)

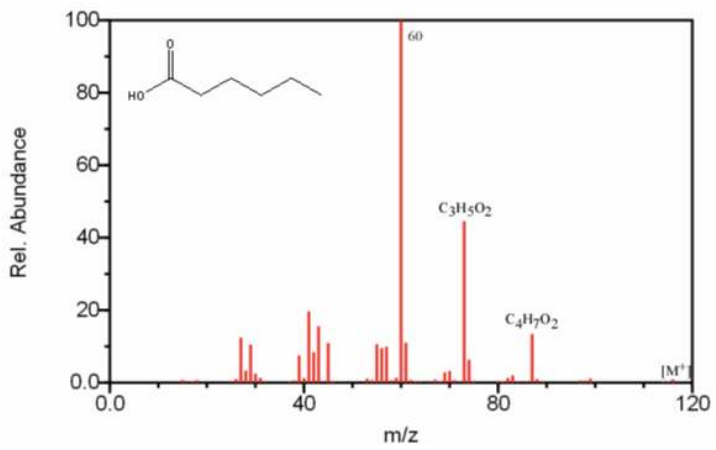


Figure **6.7.2**: The Fragmentation of hexanoic acid ($C_6H_{12}O_2$): MW = 116.16. Spectra from the NIST/EPA/NIH Mass Spectral Library.

Conjugated and Aromatic Carboxylic Acids

For conjugated acids, the molecular ion of straight chain carboxylic acids is more prominent than nonconjugated acids, based on the stabilization of the ion. In short chain acids, peaks due to the loss of OH (molecular ion less 17) and COOH (molecular ion less 45) are prominent due to alpha-cleavage (bonds next to C=O).

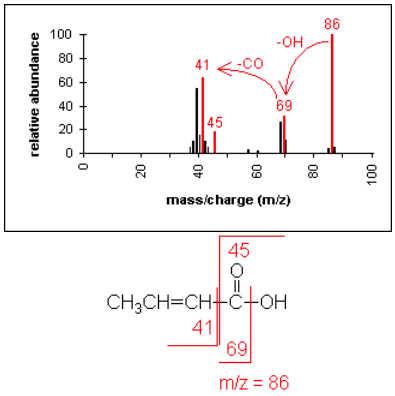


Figure **6.7.3**: The Fragmentation of 2-Butenoic acid ($C_4H_6O_2$): MW = 86.09.

Aromatic acids have a more prominent molecular ion peak but undergo similar fractionation to short chain hydrocarbons. They produce large peaks at [M – OH] and [M – CO_2H]. Aromatic acids can also lose water if an ortho group contains an abstractable hydrogen atom.

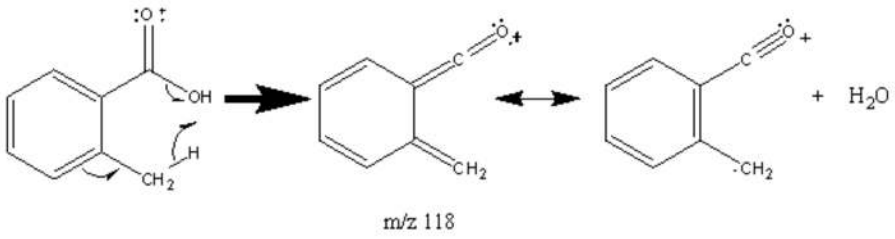
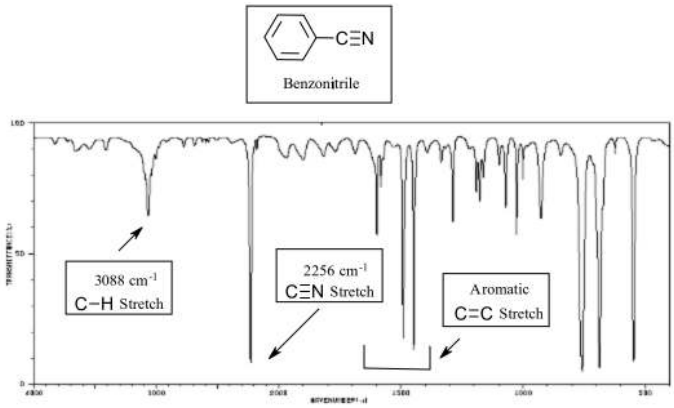


Figure **6.7.4**: The Dehydration Fragmentation of o-methylbenzoic acid ($C_8H_8O_2$) MW = 136; produce the peak [M – H_2O].

Spectroscopy of Nitriles

Infrared Spectroscopy

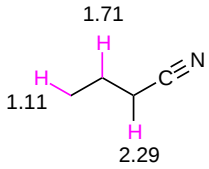
The CN triple bond stretch of nitriles appears in a distinctive region of an IR spectra, near 2250 cm^{-1}. One of the only other absorptions to appear in this region is the CC triple bond stretch of an alkyne (2100-2250 cm^{-1}).



Infrared Spectrum of Benzonitrile

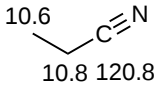
^{1}H Nuclear Magnetic Spectroscopy

Protons on carbons adjacent to a nitrile absorb in the 2-3 ppm region. Some deshielding occurs due to the fact that the sp hybridized nitrile carbon is more electronegative than the adjacent sp^3 hybridized carbon.



^{13}C Nuclear Magnetic Spectroscopy

The nitrile carbon absorbs in the 115–120 ppm region which not as far downfield as a typical carbonyl carbon (180-220 ppm).

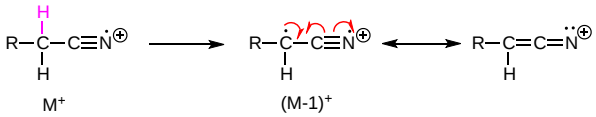


UV/Vis Spectroscopy

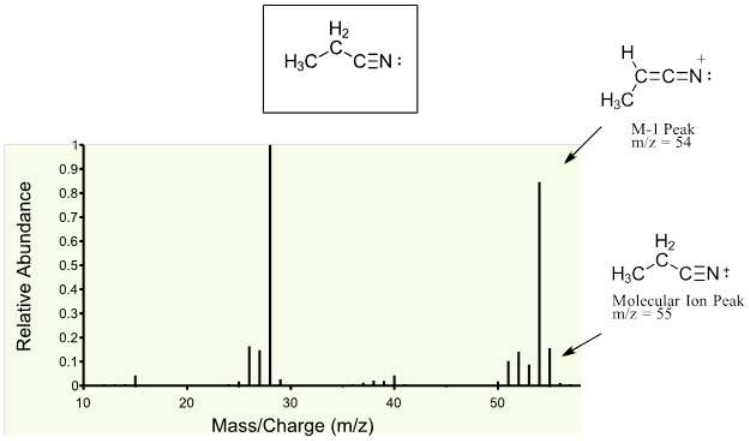
Most nitriles do not show absorption above 200 nm which does not make UV/Vis spectroscopy a useful tool to characterize them.

Mass Spectrometry

The molecular ion (M^+) peaks of simple nitriles are often weak or not present in a mass spectra. There is often a M-1 peak due to the loss of a -H.



Mechanism for the Formation of a M-1 Peak in Mass Spectra

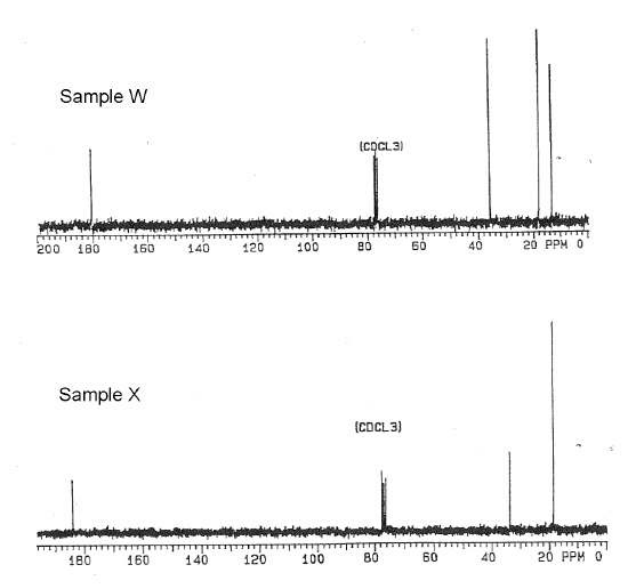


Mass Spectra of Propanenitrile

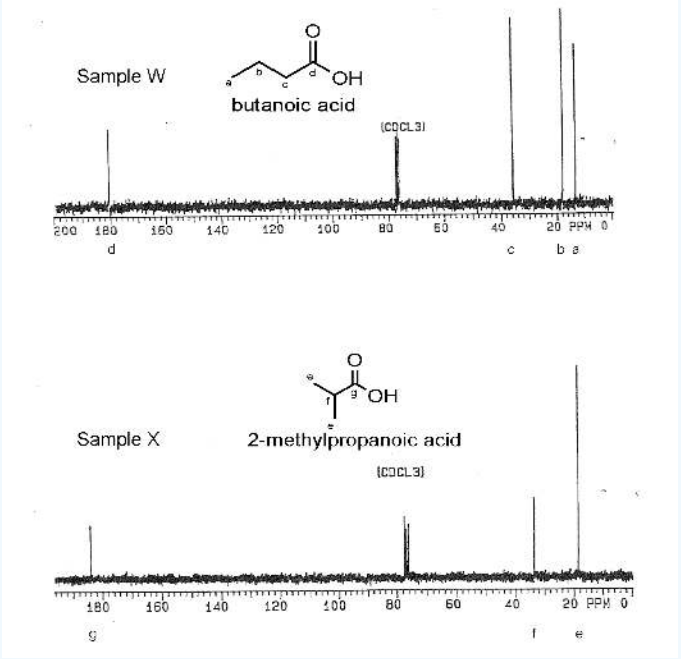
Exercise

Sample W is a reactant for a wide range of biochemical processes. Sample X was isolated from vanilla beans. Elemental analysis indicated the compounds are structural isomers with the composition: 54.52% C, 9.16% H and 36.32% O. The IR spectrum for each compound showed a broad absorption from 3500 - 2500 cm^{-1} and a strong band near 1710 cm^{-1}. The ^{1}H NMR is being serviced, so only the ^{13}C NMR spectra shown below were available.

Name and draw the bond-line structures for Samples W and X and correlate the ^{13}C NMR spectral signals to their respective compounds.



Answer



IR spectrum of benzonitrile. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

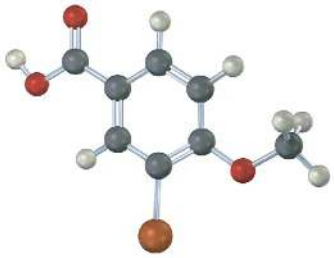
This page titled 6.7: Spectroscopy of Carboxylic Acids and Nitriles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Sol Parajon Puenzo (Cañada College) .

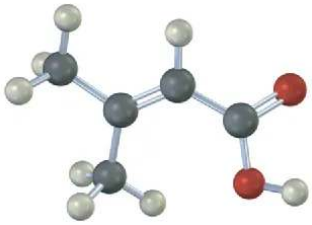
- **20.8: Spectroscopy of Carboxylic Acids and Nitriles** by Chris Schaller, Dietmar Kennepohl, Layne Morsch, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

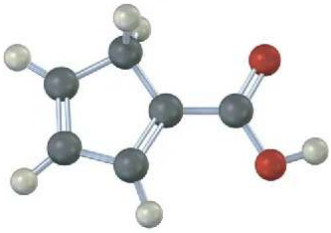
6.8: Additional Problems

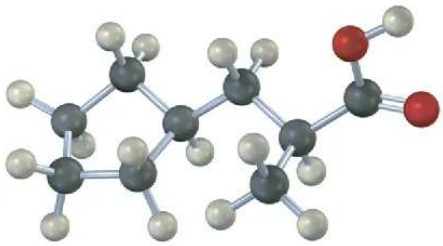
Visualizing Chemistry

PROBLEM 20-17 Give The IUPAC names for the following carboxylic acids (reddish brown = Br):

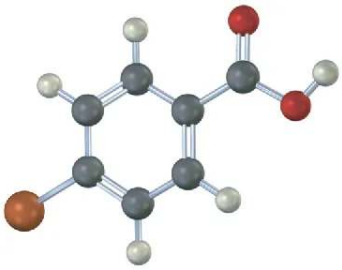
(a) 

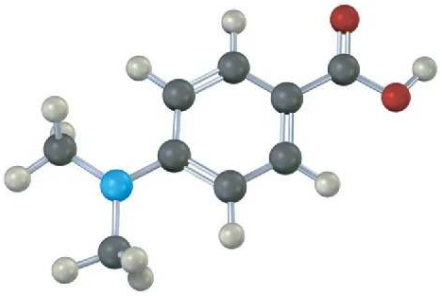
(b) 

(c) 

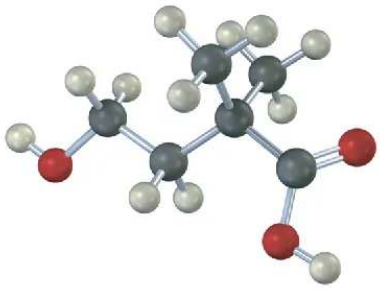
(d) 

PROBLEM 20-18 Would you expect the following carboxylic acids to be more acidic or less acidic than benzoic acid? Explain. (Reddish brown = Br.)

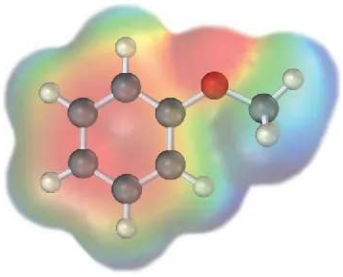
(a) 

(b) 

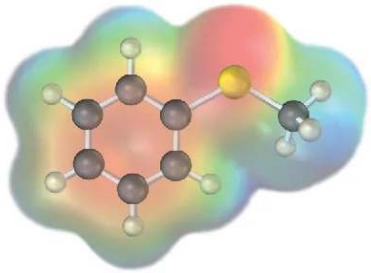
PROBLEM 20-19 The following carboxylic acid can't be prepared from an alkyl halide by either the nitrile hydrolysis route or the Grignard carboxylation route. Explain.



PROBLEM 20-20 Electrostatic potential maps of anisole and thioanisole are shown. Which do you think is the stronger acid, *p*-methoxybenzoic acid or *p*-(methylthio)benzoic acid? Explain.



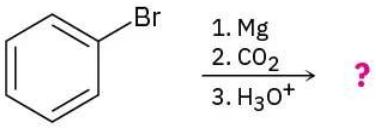
Anisole ($C_6H_5OCH_3$)

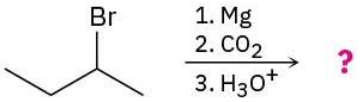


Thioanisole ($C_6H_5SCH_3$)

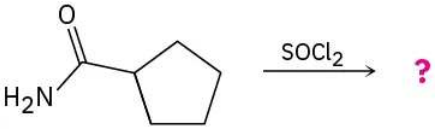
Mechanism Problems

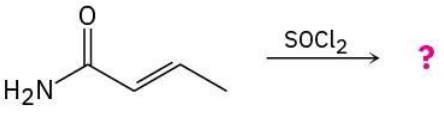
PROBLEM 20-21 Predict the product(s) and write the mechanism of each of the following reactions:

(a) 

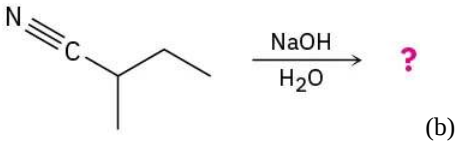
(b) 

Problem 20-22 Predict the product(s) and write the mechanism of each of the following reactions:

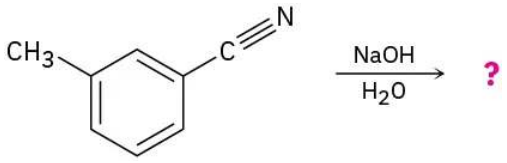
(a) 

(b) 

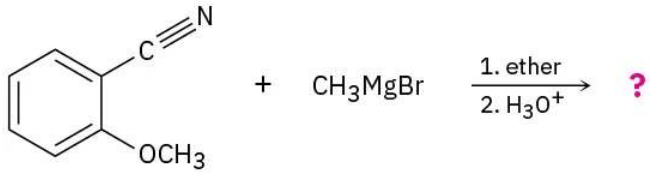
Problem 20-23 Predict the product(s) and write the mechanism of each of the following reactions:

(a) 

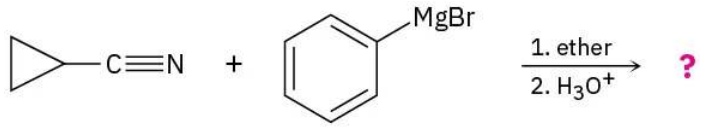
(b)

(b) 

Problem 20-24 Predict the product(s) and write the complete mechanism of each of the following reactions:

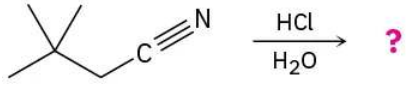
(a) 

(b)

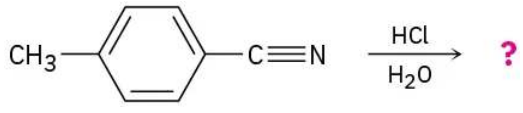


Problem 20-25 Acid-catalyzed hydrolysis of a nitrile to give a carboxylic acid occurs by initial protonation of the nitrogen atom, followed by nucleophilic addition of water. Review the mechanism of base-catalyzed nitrile hydrolysis in Section 20.7 and then predict the products for the following reactions. Write the steps involved in the acid-catalyzed reaction, using curved arrows.

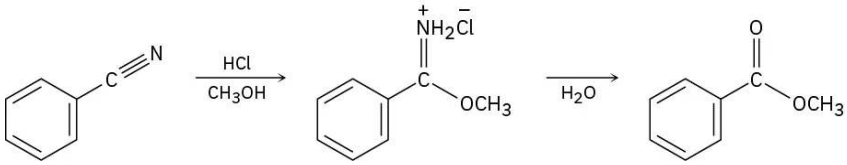
(a)



(b)



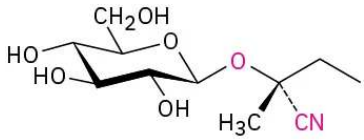
Problem 20-26 Nitriles can be converted directly to esters by the Pinner reaction, which first produces an iminoester salt that is isolated and then treated with water to give the final product. Propose a mechanism for the Pinner reaction using curved arrows to show the flow of electrons at each step.



Problem 20-27 Naturally occurring compounds called <i">cyanogenic glycosides, such as lotaustralin, release hydrogen cyanide, HCN, when treated with aqueous acid. The reaction occurs by hydrolysis of the acetal linkage to form a cyanohydrin, which then expels HCN and gives a carbonyl compound.

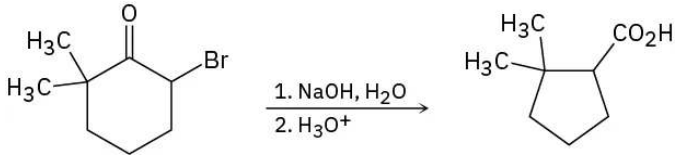
(a) Show the mechanism of the acetal hydrolysis and the structure of the cyanohydrin that results.

(b) Propose a mechanism for the loss of HCN, and show the structure of the carbonyl compound that forms.

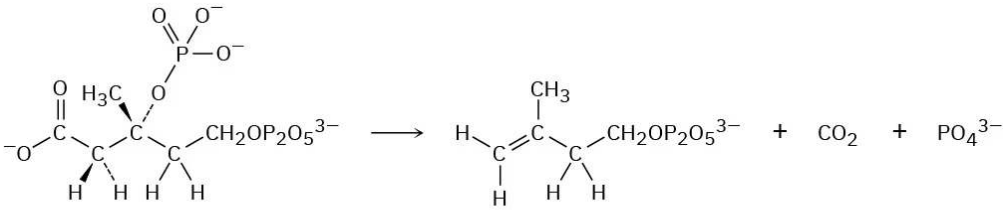


Lotaustralin

Problem 20-28 2-Bromo-6,6-dimethylcyclohexanone gives 2,2-dimethylcyclopentanecarboxylic acid on treatment with aqueous NaOH followed by acidification, a process called the Favorskii reaction. Propose a mechanism.

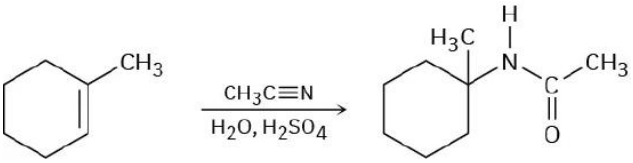


Problem 20-29 Naturally occurring compounds called *terpenoids*, which we'll discuss in **Section 27.5**, are biosynthesized by a pathway that involves loss of CO_2 from 3-phosphomevalonate 5-diphosphate to yield isopentenyl diphosphate. Use curved arrows to show the mechanism of this reaction.



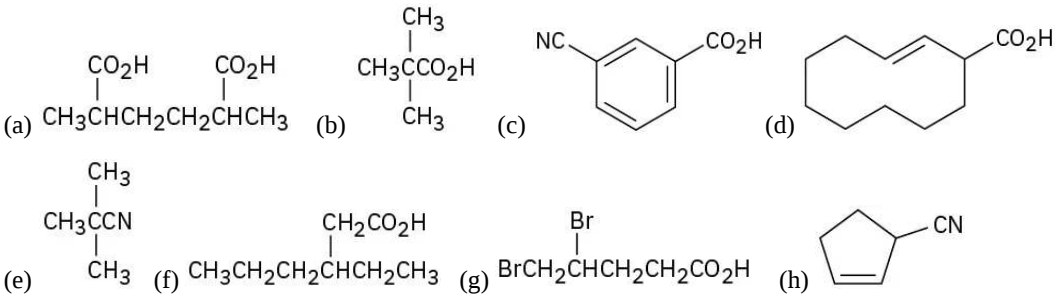
3-Phosphomevalonate 5-diphosphate **Isopentenyl diphosphate**

Problem 20-30 In the Ritter reaction, an alkene reacts with a nitrile in the presence of strong aqueous sulfuric acid to yield an amide. Propose a mechanism.



Naming Carboxylic Acids and Nitriles

Problem 20-31 Give the IUPAC names for the following compounds:



Problem 20-32 Draw structures corresponding to the following IUPAC names:

(a) *cis*-1,2-Cyclohexanedicarboxylic acid (b) Heptanedioic acid (c) 2-Hexen-4-ynoic acid (d) 4-Ethyl-2-propyloctanoic acid (e) 3-Chlorophthalic acid (f) Triphenylacetic acid (g) 2-Cyclobutenecarbonitrile (h) *m*-Benzoylbenzonitrile

Problem 20-33 Draw and name the following compounds:

(a) The eight carboxylic acids with the formula $C_6H_{12}O_2$

(b) Three nitriles with the formula C_5H_7N

Problem 20-34 Pregabalin, marketed as Lyrica, is an anticonvulsant drug that is also effective in treating chronic pain. The IUPAC name of pregabalin is (*S*)-3-(aminomethyl)-5-methylhexanoic acid. (An aminomethyl group is $–CH_2NH_2$.) Draw the structure of pregabalin.

Problem 20-35 Isocitric acid, an intermediate in the citric acid cycle of food metabolism, has the systematic name (2*R*,3*S*)-3-carboxy-2-hydroxypentanedioic acid. Draw the structure.

Acidity of Carboxylic Acids

Problem 20-36 Order the compounds in each of the following sets with respect to increasing acidity:

(a) Acetic acid, oxalic acid, formic acid

(b) *p*-Bromobenzoic acid, *p*-nitrobenzoic acid, 2,4-dinitrobenzoic acid

(c) Fluoroacetic acid, 3-fluoropropanoic acid, iodoacetic acid

Problem 20-37 Arrange the compounds in each of the following sets in order of increasing basicity:

(a) Magnesium acetate, magnesium hydroxide, methylmagnesium bromide

(b) Sodium benzoate, sodium *p*-nitrobenzoate, sodium acetylide

(c) Lithium hydroxide, lithium ethoxide, lithium formate

Problem 20-38 Calculate the pK_a's of the following acids:

(a) Lactic acid, $K_a = 8.4 \times 10^{-4}$

(b) Acrylic acid, $K_a = 5.6 \times 10^{-6}$

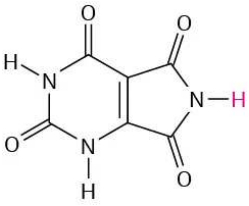
Problem 20-39 Calculate the K_a's of the following acids:

(a) Citric acid, $pK_a = 3.14$

(b) Tartaric acid, $pK_a = 2.98$

Problem 20-40 Thioglycolic acid, $HSCH_2CO_2H$, a substance used in depilatory agents (hair removers) has $pK_a = 3.42$. What is the percent dissociation of thioglycolic acid in a buffer solution at pH = 3.0?

Problem 20-41 In humans, the final product of purine degradation from DNA is uric acid, $pK_a = 5.61$, which is excreted in the urine. What is the percent dissociation of uric acid in urine at a typical pH = 6.0? Why do you think uric acid is acidic even though it does not have a CO_2H group?



Uric acid

Problem 20-42 Some pK_a data for simple dibasic acids are shown. How can you account for the fact that the difference between the first and second ionization constants decreases with increasing distance between the carboxyl groups?

Name/th>	Structure	pK_1	pK_2
Oxalic	HO_2CCO_2H	1.2	4.2
Succinic	$HO_2CCH_2CH_2CO_2H$	4.2	5.6
Adipic	$HO_2C(CH_2)_4CO_2H$	4.4	5.4

Reactions of Carboxylic Acids and Nitriles

Problem 20-43 How could you convert butanoic acid into the following compounds? Write each step showing the reagents needed.

(a) 1-Butanol (b) 1-Bromobutane (c) Pentanoic acid (d) 1-Butene (e) Octane

Problem 20-44 How could you convert each of the following compounds into butanoic acid? Write each step showing all reagents.

(a) 1-Butanol (b) 1-Bromobutane (c) 1-Butene (d) 1-Bromopropane (e) 4-Octene

Problem 20-45 How could you convert butanenitrile into the following compounds? Write each step showing the reagents needed.

(a) 1-Butanol (b) Butylamine (c) 2-Methyl-3-hexanone

Problem 20-46 How would you prepare the following compounds from benzene? More than one step is needed in each case.

(a) *m*-Chlorobenzoic acid (b) *p*-Bromobenzoic acid (c) Phenylacetic acid, $C_6H_5CH_2CO_2H$

Problem 20-47 Predict the product of the reaction of *p*-methylbenzoic acid with each of the following:

(a) $LiAlH_4$, then H_3O^+

(b) *N*-Bromosuccinimide in CCl_4

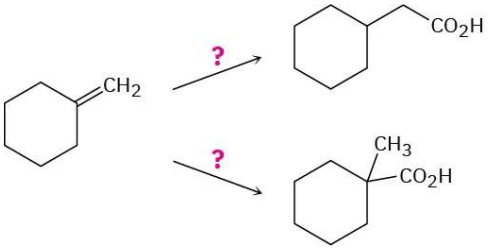
(c) CH_3MgBr in ether, then H_3O^+

(d) $KMnO_4$, H_3O^+

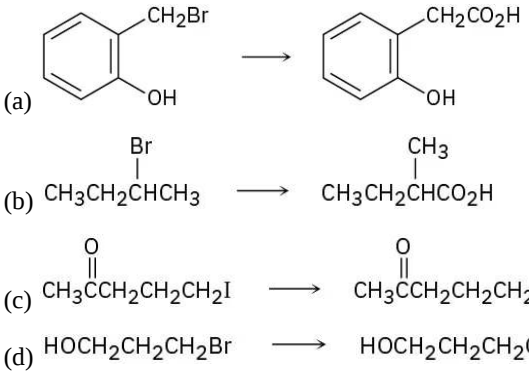
Problem 20-48 Using $^{13}CO_2$ as your only source of labeled carbon, along with any other compounds needed, how would you synthesize the following compounds?

(a) $CH_3CH_2{}^{13}CO_2H$ (b) PRODC$H_3{}^{13}CH_2CO_2H$

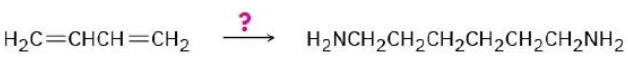
Problem 20-49 How would you carry out the following transformations?



Problem 20-50 Which method—Grignard carboxylation or nitrile hydrolysis—would you use for each of the following reactions? Explain.



Problem 20-51 1,6-Hexanediamine, a starting material needed for making nylon, can be made from 1,3-butadiene. How would you accomplish the synthesis?

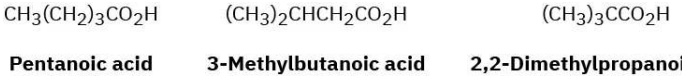


Problem 20-52 3-Methyl-2-hexenoic acid (mixture of *E* and *Z* isomers) has been identified as the substance responsible for the odor of human sweat. Synthesize the compound from starting materials having five or fewer carbons.

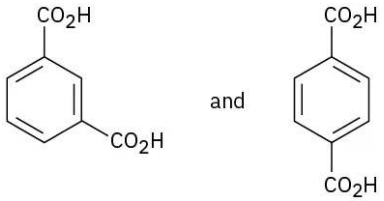
Spectroscopy

Problem 20-53 Propose a structure for a compound $C_6H_{12}O_2$ that dissolves in dilute NaOH and shows the following ^1H NMR spectrum: 1.08 δ (9 H, singlet), 2.2 δ (2 H, singlet), and 11.2 δ (1 H, singlet).

Problem 20-54 What spectroscopic method could you use to distinguish among the following three isomeric acids? Tell what characteristic features you would expect for each acid.

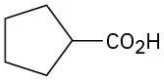


Problem 20-55 How would you use NMR (either ^{13}C or ^1H) to distinguish between the following pairs of isomers?

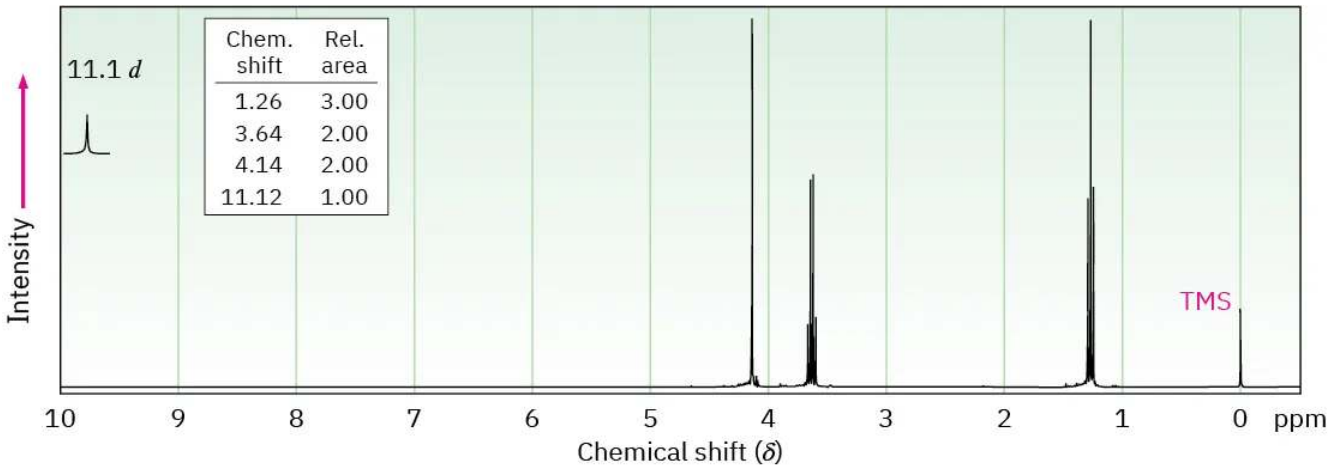
(a)  and

(b) $HO_2CCH_2CH_2CO_2H$ and $CH_3CH(CO_2H)_2$

(c) $CH_3CH_2CH_2CO_2H$ and $HOCH_2CH_2CH_2CHO$

(d) $(CH_3)_2C{=}CHCH_2CO_2H$ and 

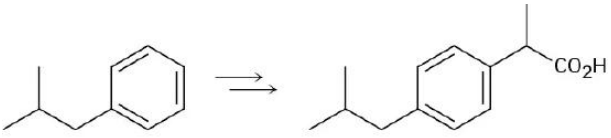
Problem 20-56 Compound **A**, $C_4H_8O_3$, has infrared absorptions at 1710 and 2500 to 3100 cm^{-1} and has the ^1H NMR spectrum shown. Propose a structure for **A**.



General Problems

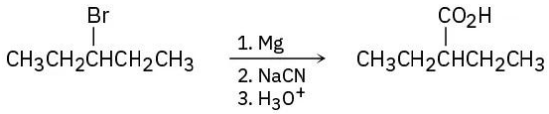
Problem 20-57 A chemist in need of 2,2-dimethylpentanoic acid decided to synthesize some by reaction of 2-chloro-2-methylpentane with NaCN, followed by hydrolysis of the product. After the reaction sequence was carried out, however, none of the desired product could be found. What do you suppose went wrong?

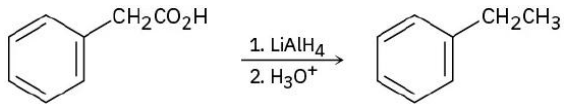
Problem 20-58 Show how you might prepare the anti-inflammatory agent ibuprofen starting from isobutylbenzene. More than one step is needed.

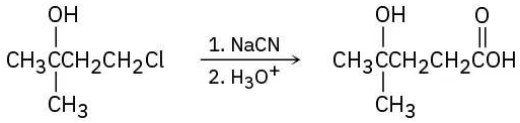


Isobutylbenzene **Ibuprofen**

Problem 20-59 The following synthetic schemes all have at least one flaw in them. What is wrong with each?

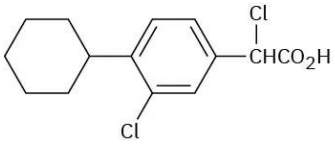
(a) 

(b) 

(c) 

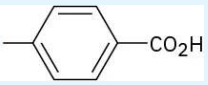
Problem 20-60 *p*-Aminobenzoic acid (PABA) was once widely used as a sunscreen agent. Propose a synthesis of PABA starting from toluene.

Problem 20-61 Propose a synthesis of the anti-inflammatory drug fenclorac from phenylcyclohexane.

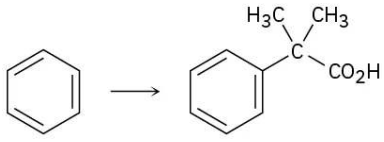


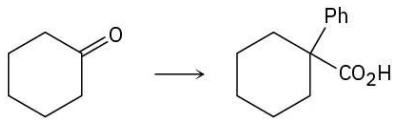
Fenclorac

Problem 20-62 The pK_a's of five *p*-substituted benzoic acids ($YC_6H_4CO_2H$) are listed below. Rank the corresponding substituted benzenes (YC_6H_5) in order of their increasing reactivity toward electrophilic aromatic substitution. If benzoic acid has pK_a = 4.19, which of the substituents are activators and which are deactivators?

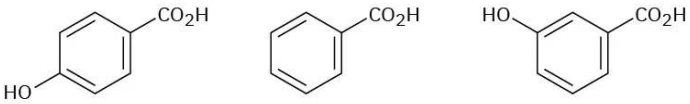
Substituent Y	**pK_a of** 
–Si(CH$_3$)$_3$	**4.27**
–CH=CHC≡N	**4.03**
–HgCH$_3$	**4.10**
–OSO$_2$CH$_3$	**3.84**
–PCl$_2$	**3.59**

Problem 20-63 How would you carry out the following transformations? More than one step is needed in each case.

(a) 

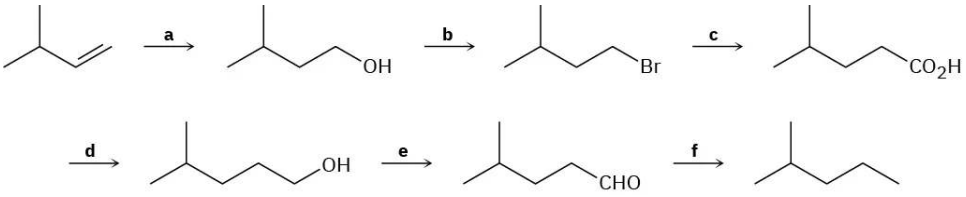
(b) 

Problem 20-64 The following pK_a values have been measured. Explain why a hydroxyl group in the para position decreases the acidity while a hydroxyl group in the meta position increases the acidity.

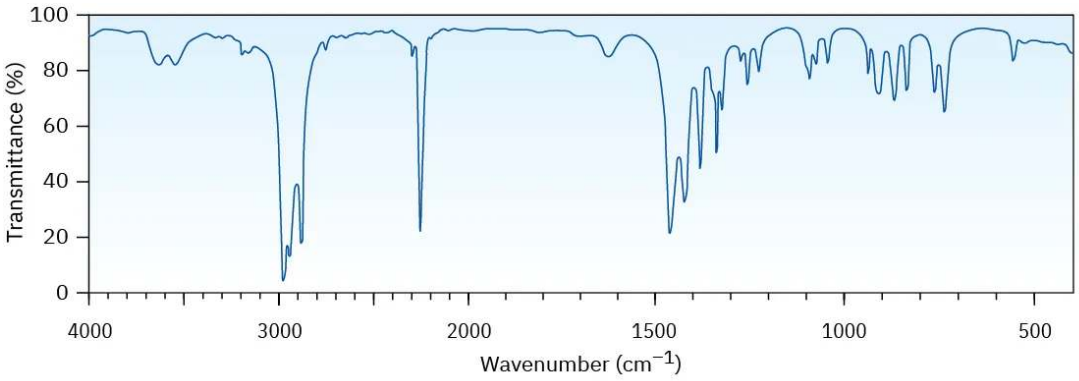


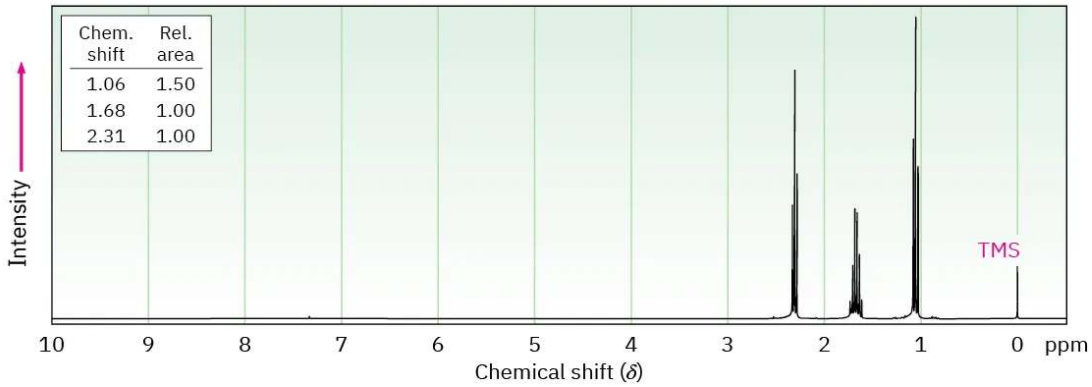
pK_a = 4.48 **pK_a = 4.19** **pK_a = 4.07**

Problem 20-65 Identify the missing reagents **a**–**f** in the following scheme:

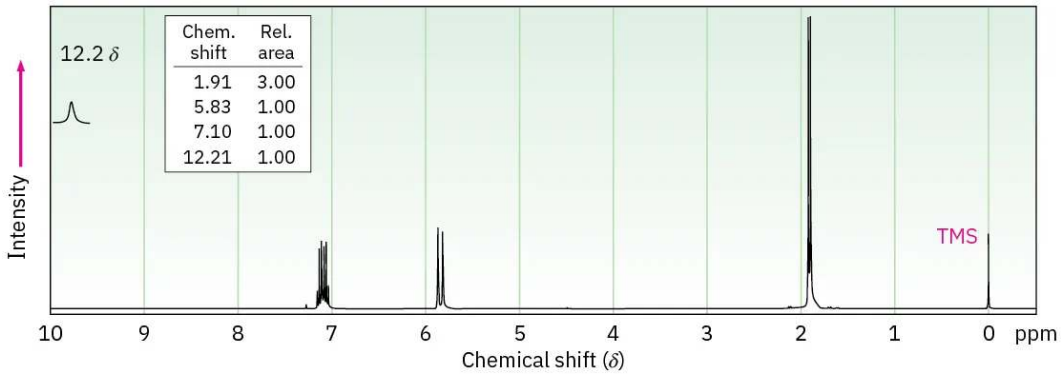


Problem 20-66 Propose a structure for a compound, C_4H_7N, that has the following IR and ^1H NMR spectra:

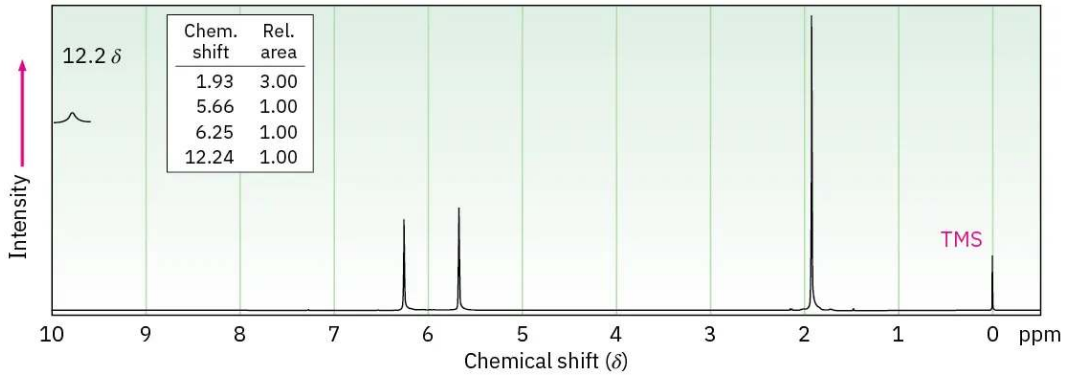




Problem 20-67 The two ^1H NMR spectra shown here belong to crotonic acid (*trans*-CH_3CH=Math input error$_2H$) and methacrylic acid [H_2C=$C(CH_3)CO_2H$]. Which spectrum corresponds to which acid? Explain.

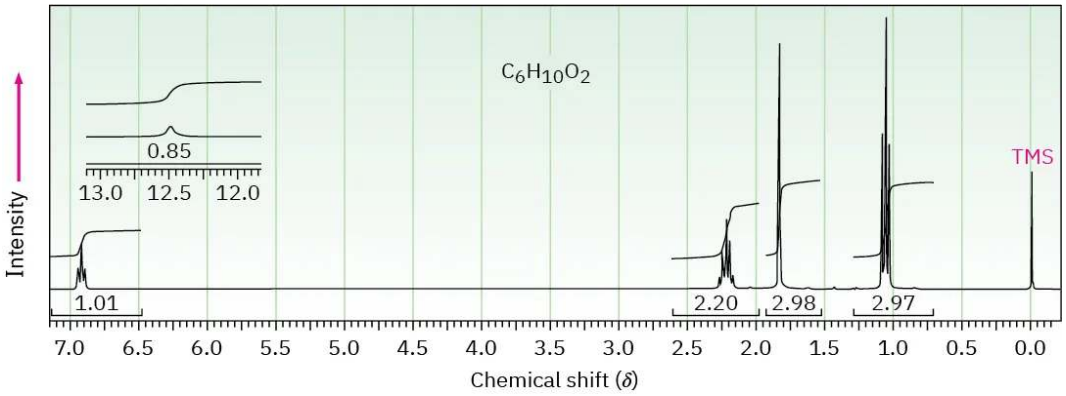


(a)

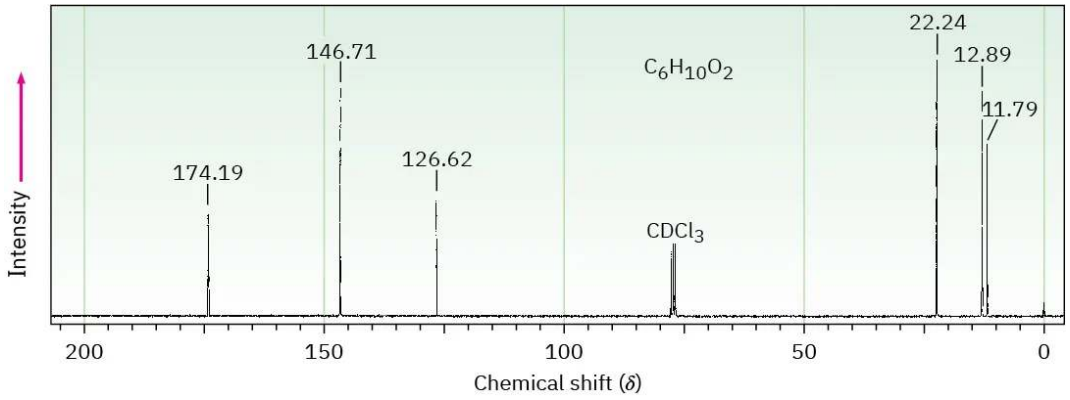


(b)

Problem 20-68 The ^{1}H and ^{13}C NMR spectra below belong to a compound with formula $C_6H_{10}O_2$. Propose a structure for this compound.



(a)



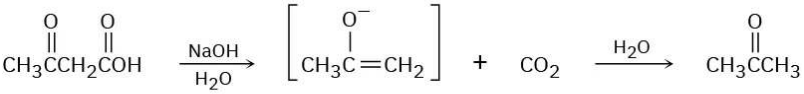
(b)

Problem 20-69 Propose structures for carboxylic acids that show the following peaks in their ^{13}C NMR spectra. Assume that the kinds of carbons (1°, 2°, 3°, or 4°) have been assigned by DEPT-NMR.

(a) $C_7H_{12}O_2$: 25.5 δ (2°), 25.9 δ (2°), 29.0 δ (2°), 43.1 δ (3°), 183.0 δ (4°)

(b) $C_8H_8O_2$: 21.4 δ (1°), 128.3 δ (4°), 129.0 δ (3°), 129.7 δ (3°), 143.1 δ (4°), 168.2 δ (4°)

Problem 20-70 Carboxylic acids having a second carbonyl group two atoms away lose CO_2 *(decarboxylate)* through an intermediate enolate ion when treated with base. Write the mechanism of this decarboxylation reaction using curved arrows to show the electron flow in each step.



An enolate ion

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6.S: Carboxylic Acids and Nitriles (Summary)

Concepts & Vocabulary

20.0 Chapter Objectives and Introduction to Carboxylic Acids

- Carboxylic acids are defined as molecules that have a hydroxyl group bonded to a carbonyl group (RCOOH).
- Fatty acids are naturally occurring carboxylic acids that are important components of lipids.
- Fatty acids can either be saturated (all carbon-carbon bonds are single bonds) and unsaturated (one or more carbon-carbon double bonds).
- Several other functional groups can be prepared from carboxylic acids and are considered derivatives (acyl halides, anhydrides, esters, amides and nitriles).

20.1 Naming Carboxylic Acids and Nitriles

- Carboxylic acids are named following IUPAC rules with ending -oic acid.
- When carboxylic acids are named as an attachment to a ring, add -carboxylic acid to the name of the cyclic compound.
- Nitriles are named following IUPAC rules with the ending -nitrile or -carbonitrile.

20.2 Structure and Properties of Carboxylic Acids

- Carboxylic acids have trigonal planar shape around the carbonyl carbon and due to resonance structures, all the atoms of the functional group are co-planar.
- Conjugation in carboxylic acids increases acidity of the hydroxyl hydrogen compared to alcohols. The conjugate base (carboxylate) is stabilized by resonance.
- Carboxylic acids form hydrogen bonded dimers yielding higher boiling points than for other molecules of similar size.
- Small carboxylic acids are often soluble in water due to hydrogen bonding. Larger carboxylic acids are often slightly soluble in water, though when converted to a carboxylate salt by treating with base, become water soluble.

20.3 Biological Acids and the Henderson-Hasselbalch Equation

- Carboxylic acids are fully protonated in acidic solutions.
- Carboxylic acids are fully dissociated in basic solutions.
- The Henderson-Hasselbalch equation can be used to relate pH, pKa and ratio of concentrations of acid and conjugate base.

20.4 Substituent Effects on Acidity

- Withdrawing groups (through inductive or resonance effects) can stabilize carboxylates, increasing acidity of carboxylic acids.
- Donating groups (through inductive or resonance effects) destabilize carboxylates, decreasing acidity of carboxylic acids.
- Nearly all substituents in ortho positions increase acid strength whether donating or withdrawing, this is called the *ortho*-effect.

20.5 Preparing Carboxylic Acids

- Carboxylic acids can be prepared through oxidation of several functional groups including: 1° alcohols, aldehydes, alkyl arene side chains, and alkenes.
- Carboxylic acids can also be prepared by carboxylation of Grignard reagents and hydrolysis of nitriles.

20.6 Reactions of Carboxylic Acids: An Overview

- There are four main categories of carboxylic acid reactions:
  - Acid/base reaction (salt formation)
  - Nucleophilic acyl substitution
  - Reduction
  - Substitution alpha to the carbonyl

20.7 Chemistry of Nitriles

- Nitriles have linear geometry due to the *sp* hybrid orbitals on carbon and nitrogen.
- Nitriles are less basic than amines.

- Nitriles can be prepared from aldehydes, ketones, or amides.
- Nitriles react similarly to carbonyl compounds where nucleophiles will attack the carbon end of the nitrile.
- Nitriles can be hydrolyzed to carboxylic acids under basic or acidic conditions.
- Nitriles can be reduced to amines by hydride reduction.
- Nitriles can be converted to aldehyde by reaction with DIBALH.
- Nitriles can be converted to ketones by reaction with organometallic compounds.

20.8 Spectroscopy of Carboxylic Acids and Nitriles

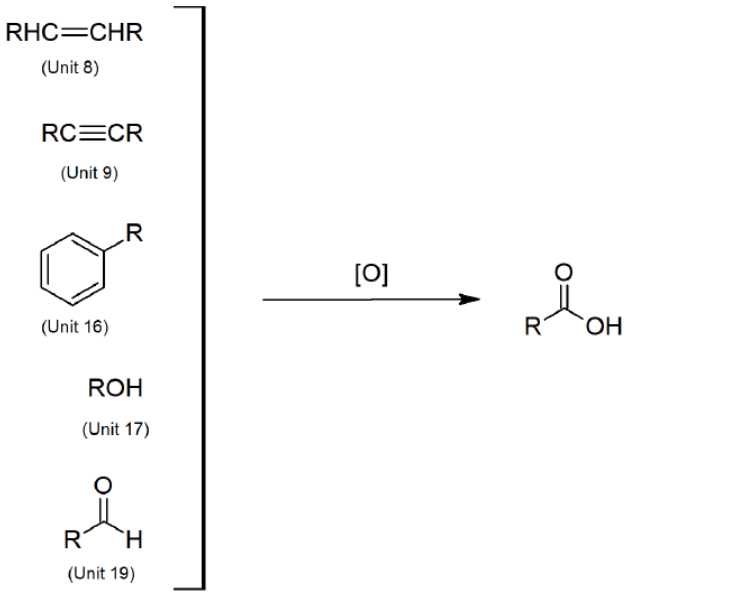
- IR of carboxylic acids typically show a very strong and broad OH stretch from about 2500 to 3300 cm^{-1} as well as a strong carbonyl stretch around 1710 cm^{-1}.
- ^{1}H NMR of carboxylic acids show the OH proton between 10-12 ppm as well as hydrogens on carbon adjacent to the carbonyl around 2-3 ppm.
- ^{13}C NMR of carboxylic acids show the carbonyl carbon at 160-180 ppm.
- Mass spectra of carboxylic acids often have fragments for OH (loss of 17) and COOH (loss of 45).
- The most identifying characteristic of IR of nitriles is the CN triple bond stretch which appears near 2250 cm^{-1}.
- ^{1}H NMR of nitriles show protons on the carbon next to the nitrile at around 2-3 ppm.
- ^{13}C NMR of nitriles show the nitrile carbon in the 115-120 ppm range.
- Mass spectra of nitriles will often not have a visible molecular ion, but instead exhibit a strong M-1 peak.

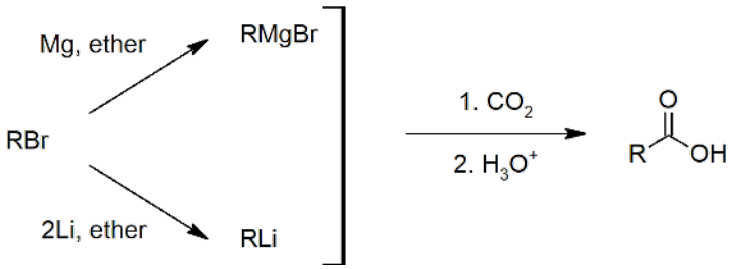
Skills to Master

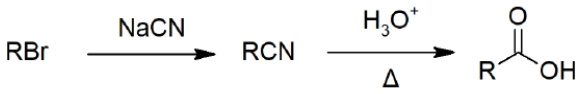
- Skill 20.1 Name carboxylic acids and nitriles using IUPAC rules.
- Skill 20.2 Draw the structure of carboxylic acids and nitriles from the IUPAC name.
- Skill 20.3 Describe the geometries and approximate bond angles of carboxylic acids and nitriles.
- Skill 20.4 Explain the acidity of carboxylic acids based on conjugate base stabilization.
- Skill 20.5 Explain physical properties of carboxylic acids.
- Skill 20.6 Describe the structure of carboxylic acids in buffered solutions.
- Skill 20.7 Use the Henderson-Hasselbach equation to relate pH, pK_a, and acid/conjugate base concentrations.
- Skill 20.8 Explain inductive effects on acidity.
- Skill 20.9 Explain relative acidity of aromatic acids.
- Skill 20.10 Draw mechanisms for preparing carboxylic acids including:
  - Oxidations
  - Carboxylation of Grignard reagents
  - Hydrolysis of Nitriles
- Skill 20.11 List the four categories of carboxylic acid reactions.
- Skill 20.12 Draw reactions for preparing nitriles including formation from:
  - aldehyde or ketone
  - 1° amide
- Skill 20.13 List general reactions of nitriles.
- Skill 20.14 Draw mechanisms for reactions of nitriles including:
  - Hydrolysis to acids (acidic and basic mechanisms)
  - Reduction to 1° amines
  - Conversion to aldehyde by reaction with DIBALH.
  - Conversion to ketones by reaction with organometallic compounds.
- Skill 20.15 Plan a synthesis of a ketone from a nitrile.
- Skill 20.16 Use IR, NMR and MS to identify carboxylic acids and nitriles.

Summary of Reactions

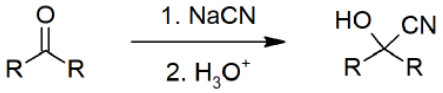
Carboxylic Acid Preparation

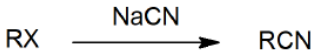


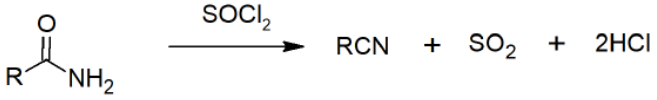




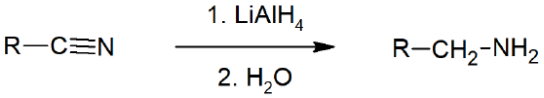
Nitrile Preparation

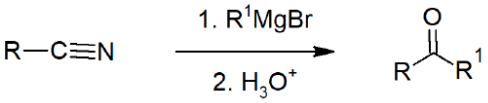






Reaction of Nitriles





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CHAPTER OVERVIEW

7: Carboxylic Acid Derivatives - Nucleophilic Acyl Substitution Reactions

The compounds discussed in this chapter are all considered to be derived from carboxylic acids, and include acid halides, acid anhydrides, esters and amides (thioesters and acyl phosphates are also briefly mentioned). As you proceed through the chapter, you should be looking for similarities in behaviour among the various classes of compounds. These similarities can be readily understood once you appreciate the fact that, in most of their reactions, carboxylic acid derivatives react via the nucleophilic acyl substitution mechanism.

In this chapter, we describe the nomenclature of the various types of carboxylic acid derivatives, and explain the relative reactivity of these compounds in terms of resonance contributions to the ground state of each type of compound.

We describe the reactions of carboxylic acids, acid halides, acid anhydrides, esters, amides, polyamides and polyesters in detail, and discuss the biological importance of thiol esters briefly. The chapter concludes with a look at how infrared spectroscopy and NMR spectroscopy can be used in the identification of unknown carboxylic acid derivatives.

7.0: Chapter Objectives and Introduction to Carboxylic Acid Derivatives
7.1: Naming Carboxylic Acid Derivatives
7.2: Nucleophilic Acyl Substitution Reactions
7.3: Nucleophilic Acyl Substitution Reactions of Carboxylic Acids
7.4: Chemistry of Acid Halides
7.5: Chemistry of Acid Anhydrides
7.6: Chemistry of Esters
7.7: Chemistry of Amides
7.8: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives
7.9: Polyamides and Polyesters - Step-Growth Polymers
7.10: Spectroscopy of Carboxylic Acid Derivatives
7.11: Additional Problems
7.S: Carboxylic Acid Derivatives (Summary)

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7.0: Chapter Objectives and Introduction to Carboxylic Acid Derivatives

Objectives

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this chapter are used in conjunction with any of the reactions described in previous chapters.
3. solve road-map problems that require a knowledge of the chemistry of carboxylic acid derivatives.
4. define, and use in context, any of the key terms introduced in this chapter.

After completing this section, you should be able to

1. identify, and give an example of an acid halide, an acid anhydride, an ester, and an amide.
2. write the general form of a nucleophilic acyl substitution reaction.

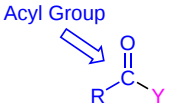
Key Terms

Make certain that you can define, and use in context, the key terms below.

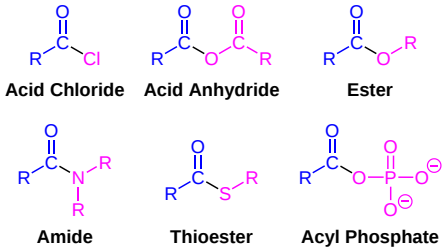
- acyl derivative
- nucleophilic acyl substitution reaction

Carboxylic Acid Derivatives

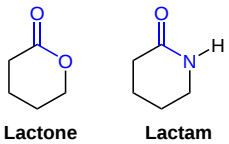
Carboxylic acid derivatives are formed when the hydroxyl group of a carboxylic acid is replaced by some other group, Y. These compounds are also called the **acyl derivatives** of a carboxylic acid because they usually contain an acyl group bonded to a substituent which can act as a leaving group in a nucleophilic acyl substitution reaction.



Although many types of carboxylic acid derivatives are known, this chapter focuses on six: acid halides (acyl halides), anhydrides, esters, amides, thioesters, and acylphosphates.



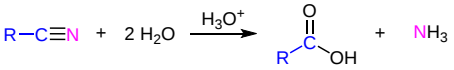
Cyclic esters and amides are referred to as **lactones** and **lactams**, respectively.



Carboxylic acid derivatives can be hydrolyzed back to the acid.



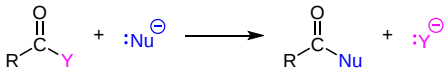
Nitriles, $\mathrm{RC \equiv N}$, discussed in the last chapter, are often are considered to be carboxylic acid derivatives, even though the acyl group is not present, because hydrolysis of nitriles leads to carboxylic acids.



Nitrile **Carboylic Acid**

Nucleophilic Acyl Substitution Reaction

The main type of reaction for carboxylic acid derivatives is called nucleophilic acyl substitution. This reaction involves the replacement of the Y group by attack of a nucleophile $\mathrm{Nu^{\ominus}}$ at the carbonyl carbon with subsequent cleavage of the $\mathrm{C-Y}$ bond.



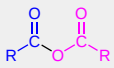
Y = Leaving Group

Physical Properties of Carboxylic Acid Derivatives

The intermolecular forces of the respective acyl group combine with the size and structure of the Y-group to determine the physical

properties of the the carboxylic acid derivatives as shown in the summary below.

Name	Structure	Intermolecular Forces
Acid Chloride		Polar, No H-Bonding

Ester		Polar, No H-Bonding	1 Volatile Liquids
Acid Anhydride		Polar, No H-Bonding	1 Acid Anhydrides
Ni		Among the most polar compounds without H-Bonding	C H

Nitrile		
Amide		Complex H-Bonding

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7.1: Naming Carboxylic Acid Derivatives

Objectives

After completing this section, you should be able to

1. provide a satisfactory name of given structures for acid halides, acid anhydrides, esters, amides, thioesters, and acyl phosphates.
2. draw the condensed or shorthand structure of acid halides, acid anhydrides, esters, amides, thioesters, and acyl phosphates, given either its commonly used or IUPAC name.

Nomenclature of Acid Halides, RCOX

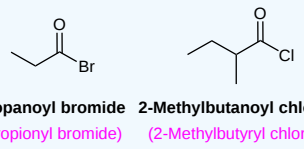
The nomenclature of acid halides starts with the name of the corresponding carboxylic acid. If the corresponding carboxylic acid has an **–oic acid** or **–ic acid** ending it is removed and replaced with the ending **-oyl** followed by the first syllable of the name of the halogen along with an **–ide** ending.

However, there are a number of specific exceptions where IUPAC allows the ending **-yl** to be used instead. Examples are formic ⇒ formyl, acetic ⇒acetyl, propionic ⇒propionyl, butyric ⇒butyryl, oxalic ⇒ oxalyl, and succinic ⇒ succinyl.

When the corresponding acid includes a **-carboxylic acid** ending, it is removed and replaced with the ending **-carbonyl.** This is followed by the first syllable of the name of the halogen along with an **–ide** ending

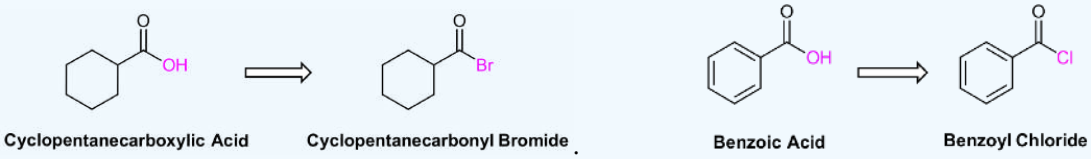
The carbonyl carbon is given the #1 location number. The acid halide functional group is assumed to be on the end of the parent chain, so it is not necessary to include the functional group location number in the name.

Acid Halides Examples 7.1.1



Propanoyl bromide (Propionyl bromide)

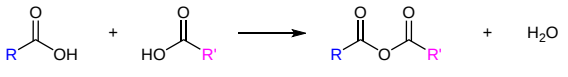
2-Methylbutanoyl chloride (2-Methylbutyryl chloride)



Cyclopentanecarboxylic Acid **Cyclopentanecarbonyl Bromide** **Benzoic Acid** **Benzoyl Chloride**

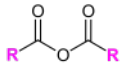
Nomenclature of Anhydrides, RCO_2COR'

An anhydride functional group results when two carboxylic acids combine and lose water (anhydride = without water). The names of anhydrides come from the names of the two combined carboxylic acids. The carbonyl carbon is given the #1 location number on both chains. The anhydride functional group is assumed to be on the end of the each parent chain, so it is not necessary to include the functional group location number in the name.



Carboxylic Acids **Anhydride** **Water**

Symmetrical anhydrides made from unsubstituted carboxylic acids and cyclic anhydrides made from dicarboxylic acids are named based on their corresponding carboxylic acid. The ending **-acid** is replaced with **-anhydride**. This is true for both the IUPAC and common nomenclature. An anhydride is symmetrical when it is acyclic and the acyl R groups are the same. Example 7.1.2

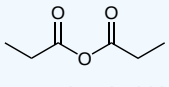


Symmetrical Anhydride

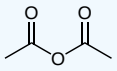
An unsymmetrical anhydride is created from two different carboxylic acids. For unsymmetrical anhydrides, name both acids *alphabetically* with a space between them. Then add the end word **anhydride**. Example 7.1.2

Anhydrides Examples 7.1.2

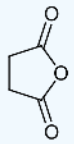
Symmetrical Anhydride:



Propanoic anhydride
(Propionic anhydride)

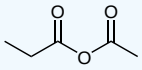


Ethanoic anhydride
(Acetic anhydride)

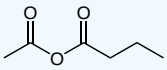


Succinic Anhydride

Unsymmetrical Anhydride:



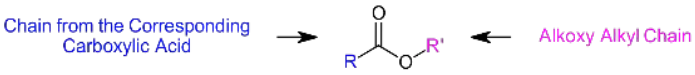
Ethanoic propanoic anhydride
(Acetic propionic anhydride)



Butanoic ethanoic anhydride
(Acetic butyic anhydride)

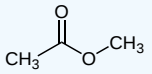
Nomenclature of Esters, RCO_2R'

Esters consist of two distinctly different carbon chains which need to be named separately. One carbon chain is from the corresponding carboxylic acid and the other chain, attached to the singly bonded oxygen, is called the alkoxy alkyl chain.

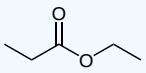


Esters are named as if the alkoxy alkyl chain is a substituent **(Prefix + yl)**. This is followed by the name of the corresponding carboxylic acid part of the ester with **-ic acid** or **-oic acid** replaced with the ending **–ate**. The carbonyl carbon is given the #1 location number. The carbonyl functional group is assumed to be on the end of the parent chain, so it is not necessary to include the functional group location number in the name.

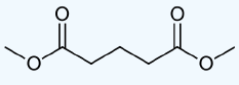
Esters Examples 7.1.3*a*



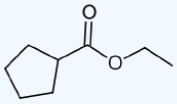
Methyl ethanoate



Ethyl propanoate



Dimethyl glutarate

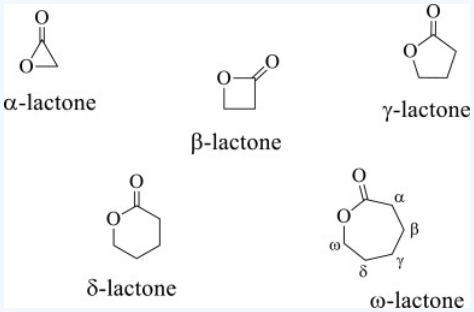


Ethyl cyclopentanecarboxylate

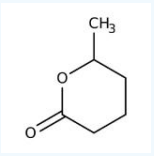
Cyclic esters are called lactones. In simple lactones, a Greek letter identifies the position of the alkyl oxygen relative to the carboxyl carbonyl group. Other names can be used; for example, gamma-lactone can be called Tetrahydrofuran-2-one or butano-4-lactone. But this nomenclature is not enough for substituted lactones. Example: delta-Hexanolactone (widely used in butter, cream, milk, nut, fruit flavors, and in cosmetic flavor).

Esters Examples 7.1.3

Simple Lactones:

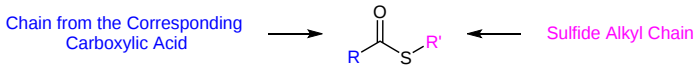


Substituted Lactones:



Nomenclature of Thioesters, RCOSR'

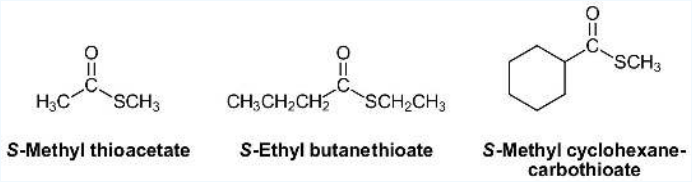
Thioesters have two distinctly different carbon chains. One carbon chain is from the corresponding carboxylic acid and the other chain, attached to the sulfur, is called the sulfide alkyl chain.



Thioesters are named as if the sulfide alkyl chain is a substituent with the letter *S* preceding **(*S*-Prefix + yl)**. This is followed by the parent chain of the corresponding carboxylic acid, named as an alkane with the ending **–thioate** added. For thioesters attached to a carbon ring the ending **-carboxylic acid** is replaced with **-carbothioate**. When using the common names of the carboxylic acid the **-ic acid** ending is replaced **-ate** and the prefix **thio-** is added.

The carbonyl carbon is given the #1 location number. The carbonyl functional group is assumed to be on the end of the parent chain, so it is not necessary to include the functional group location number in the name.

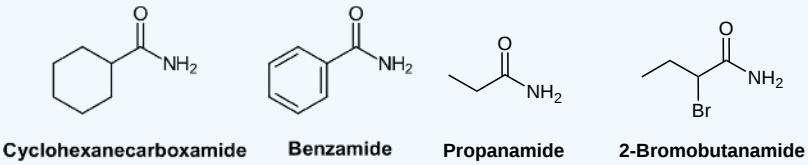
Thioesters Examples 7.1.4



Nomenclature of Amides, $RCONH_2$, RCONHR', RCONR'R''

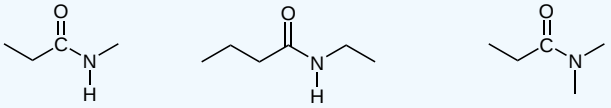
Primary amides ($RCONH_2$) are named by changing the name of the corresponding acid by removing the **-oic acid** or **-ic acid** endings and adding **-amide**. Amides derived from a cyclic carboxylic acid have the **-carboxylic acid** ending replaced with **-carboxamide**. The carbonyl carbon is given the #1 location number. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

Primary Amides Examples 7.1.5



Secondary (RCONHR') and tertiary (RCONR'R'') amides are named by using an upper case N to designate that the alkyl groups are attached to the nitrogen atom. These alkyl groups are named as substituents **(Prefix + yl)**.

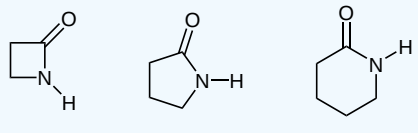
Secondary and Tertiary Amides Examples 7.1.6



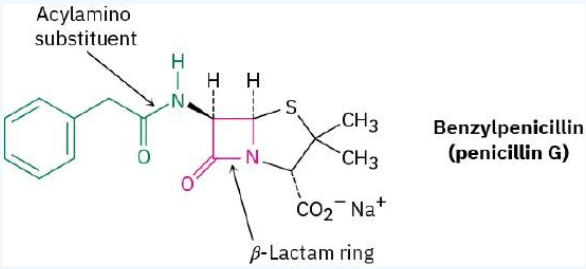
N-Methylpropanamide **N-Ethylbutanamide** **N,N-Dimethylpropanamide**

Cyclic amides are called lactams. A Greek letter identifies the location of the nitrogen on the alkyl chain relative to the carboxyl carbonyl group.

Cyclic Amides Examples 7.1.7



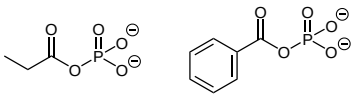
b-Lactam **g-Lactam** **d-Lactam**



Benzylpenicillin (penicillin G)

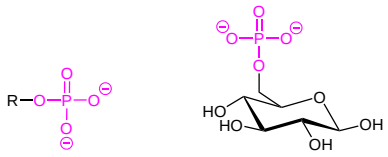
Nomenclature of Acyl Phosphates, $RCOOPO_3^{2-}$

Acyl phosphates are named following the rules as acid halides except name of the halogen is replaced with the word **phosphate**. If there is an alkyl group attached to one of the phosphate oxygens, it is named as a substituent **(parent + yl)** and listed before the end word phosphate.



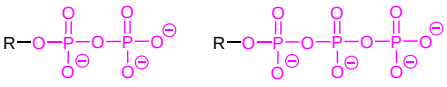
Propanoyl Phospate **Benzoyl Phosphate**

When a phosphate ion is attached to a carbon atom on an organic molecule, the chemical linkage is referred to as a phosphate ester, and the whole species is called an organic monophosphate. Glucose-6-phosphate is an example.

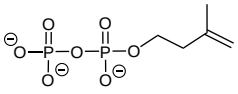


Organic monophosphate **Glucose-6-phosphate**

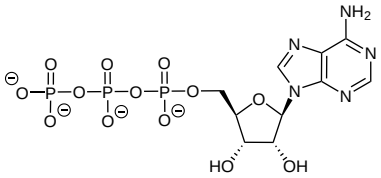
If an organic molecule is linked to two or three phosphate groups, the resulting species are called organic diphosphates and organic triphosphates. Isopententyl diphosphate and adenosine triphosphate (ATP) are good examples:



Organic diphosphate (ROPP) **Organic triphosphate (ROPPP)**

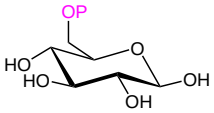


Isopentenyl diphosphate

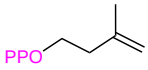


ATP

Phosphate groups on organic structures are sometimes abbreviated simply as 'P', a convention that we will use throughout this text. For example, glucose-6-phosphate and isopentenyl diphosphate are often depicted as shown below. Notice that the 'P' abbreviation includes the oxygen atoms and negative charges associated with the phosphate groups.

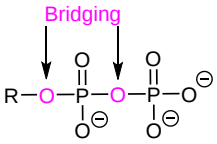


Glucose-6-phosphate



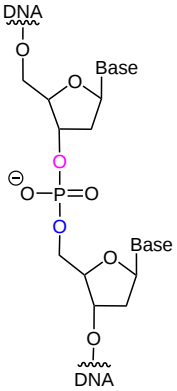
Isopentenyl diphosphate

Oxygen atoms in phosphate groups are referred to either 'bridging' and 'non-bridging', depending on their position. An organic diphosphate has two bridging and five non-bridging oxygens.



When a single phosphate is linked to two organic groups, the term 'phosphate diester' is used. The backbone of DNA is composed of phosphate diesters.

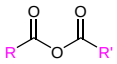
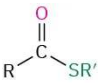
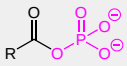
Phosphate diester



The term 'phosphoryl group' is a general way to refer to all of the phosphate-based groups mentioned above.

Functional-Group's Priority in Nomenclature

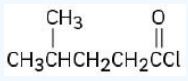
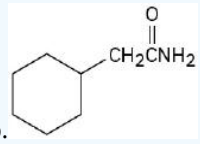
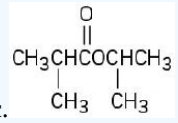
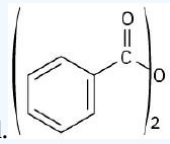
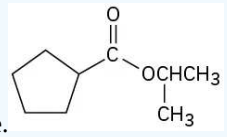
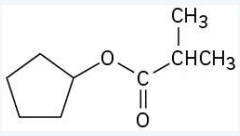
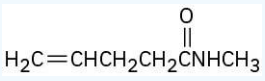
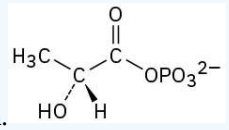
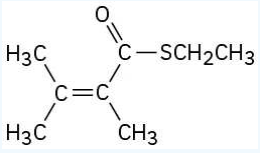
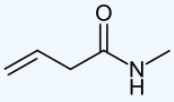
Nomenclature of Carboxylic Acids and Carboxylic Acid Derivatives

Functional Group	Structure	Suffix Name	Suffix (directly attached to the parent chain)	Prefix
Carboxylate		-oate	-carboxylate	
Carboxylic acid		-oic acid	-carboxylic acid	carboxy
Anhydride		-oic anhydride		
Ester		(R') ...-oate	(R') ...-carboxylate	(R')oxycarbonyl
Thioester		-thioate	-carbothioate	
Acyl Phosphate		-oyl phosphate	-carbonyl phosphate	
Acyl halide		-oyl halide	-carbonyl halide	halocarbonyl
Amide		-amide	-carboxamide	carbamoyl
Nitrile		-nitrile	-carbonitrile	cyano

Exercises

? Exercise 7.1.1

Give IUPAC names for the following substances:

a. 
b. 
c. 
d. 
e. 
f. 
g. 
h. 
i. 
j. 

Answer

a. 4-Methylpentanoyl chloride b. Cyclohexylacetamide c. Isopropyl 2-methylpropanoate d. Benzoic anhydride

e. Isopropyl cyclopentanecarboxylate f. Cyclopentyl 2-methylpropanoate g. N-Methyl-4-pentenamide

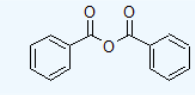
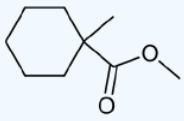
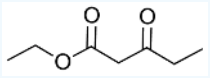
h. (R)-2-Hydroxypropanoyl phosphate i. Ethyl 2,3-dimethyl-2-butenethioate j. N-methyl-3-butenamide

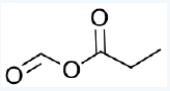
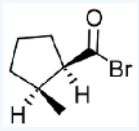
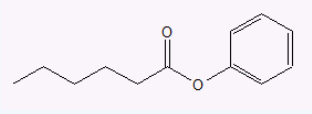
Exercise 7.1.2

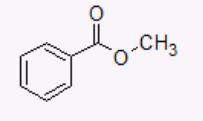
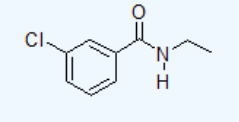
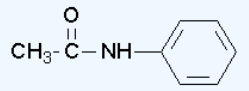
Draw structures corresponding to the following names:

a. Phenyl benzoate
b. benzoic anhydride
c. N-Ethyl-N-methylbutanamide
d. 2,4-Dimethylpentanoyl chloride
e. Methyl 1-methylcyclohexanecarboxylate
f. Ethyl 3-oxopentanoate
g. Methyl p-bromobenzenethioate
h. Formic propanoic anhydride
i. cis-2-Methylcyclopentanecarbonyl bromide
j. *S*-Methyl *p*-bromothiobenzoate
k. phenyl hexanoate
l. methyl benzoate
m. 3-chloro-N-ethylbenzamide
n. N-phenylethanamide

Answer

b.  e.  f. 

h.  i.  k. 

l.  m.  n. 

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7.2: Nucleophilic Acyl Substitution Reactions

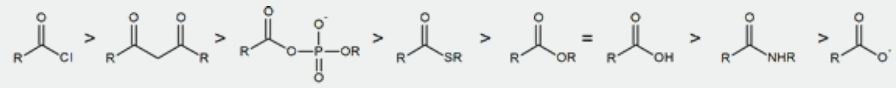
Objectives

After completing this section, you should be able to

1. compare the reactions of carboxylic acid derivatives with nucleophiles to the reactions of aldehydes and ketones with nucleophiles.
2. arrange a given list of carboxylic acid derivatives in order of increasing or decreasing reactivity towards nucleophiles.
3. explain the difference in reactivity towards nucleophiles of two or more given carboxylic acid derivatives.
4. explain why esters and amides are commonly found in nature, but acid halides and acid anhydrides are not.

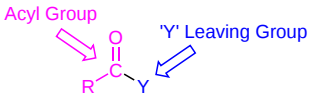
Study Notes

The reading describes the relative reactivities of "biologically relevant acyl groups." Both acid anhydrides and acid halides readily react with water and cannot exist for any length of time in living organisms. The following scheme illustrates the relative reactivities of most carboxylic acid derivatives considering the R group to be the same for all of them.



Carboxylic acid derivatives and acyl groups

Carboxylic acid derivatives can be distinguished from aldehydes and ketones by the presence of a group containing an electronegative heteroatom - usually oxygen, nitrogen, sulfur or phosphorus – bonded directly to the carbonyl carbon and represented by the symbol **Y**. The rest of the carboxylic acid derivative is called the **acyl group, which comprises** the carbonyl group and the attached alkyl group (R).



Being electronegative, the Y group has the potential of receiving electrons from the alkoxide intermediate created during a nucleophilic acyl substitution and acting as a leaving group. Eliminating a leaving group allows carbonyl bond reformation and C-Y bond cleavage to complete a substitution reaction.

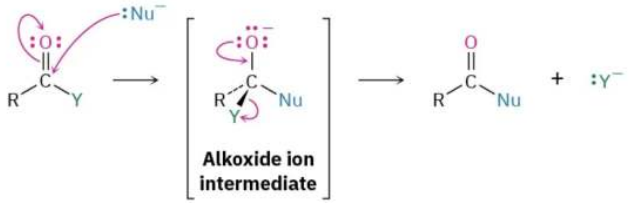
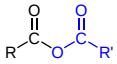


Figure 7.2.1: The general mechanisms of nucleophilic acyl substitution reactions. The reaction begins with addition of a nucleophile to a polar C═O bond to give a tetrahedral, alkoxide ion intermediate. This intermediate expels a leaving group to give a new carbonyl compound.

The stability of a negative charge on a Y group can be gauged by the pK_a of its corresponding conjugate acid (HY). A low conjugate acid pK_a implies that the Y leaving group is a weak base with a stable negative charge and thus would make an efficient leaving group. Likewise, a high conjugate acid pK_a means the Y group would likely make a poor leaving group. As shown in the table below, the conjugate acids of the possible carbide ($R:^-$) and hydride ($H:^-$) leaving groups of aldehydes and ketones have a relatively high pK_a, while those of the Y leaving groups of carboxylic acid derivatives are much lower. In fact, the stability of the leaving groups is an important factor in determining the reactivity of different carboxylic acid derivatives toward nucleophilic acyl

substitutions. Based on the pK_a data we can deduce that amides will most likely be the least reactive of the carboxylic acid derivatives.

Carbonyl Compounds and their Leaving Groups

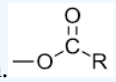
Name	Carbonyl Compound	Leaving Group	Conjugate Acid of the Leaving Group	pK_a
Acid Chloride		Cl^-	H-Cl	-7
Acid Anhydride				3-5
Ester		$^-OR'$	H-OR'	15-16
Carboxylic Acid		^-OH	H-OH	15.7
Amide		$^-NH_2$	$H-NH_2$	36
Ketone		$^-R'$	H-R'	50
Aldehyde		^-H	H-H	Very Large

Exercise 7.2.1

What is the 'Y' group in:

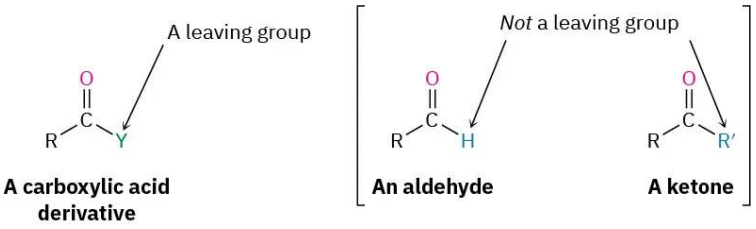
a. an acid anhydride? b. a carboxylic acid?

Answer

a.  b. 

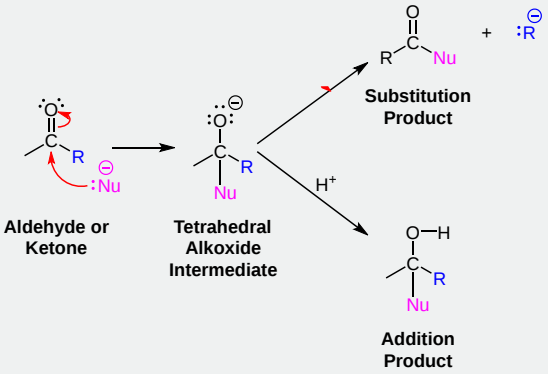
The Mechanism of Nucleophilic Acyl Substitution

Aldehydes and ketones, along with carboxylic acid derivatives all have the C=O carbonyl bond in common. Thus, the electrophilic character of the carbonyl carbon plays an important part in the reactivity of all of these compounds. Because the carbonyl carbons of aldehydes and ketones do not contain suitable leaving groups, their primary reaction is fundamentally different than carboxylic acid derivatives.

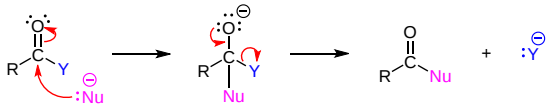


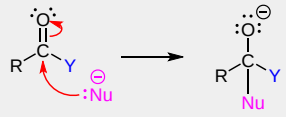
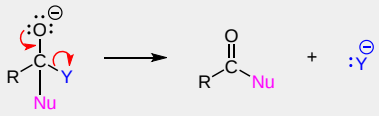
Note

Remember that aldehydes and ketones tend to undergo nucleophilic addition to form a tetrahedral alkoxide intermediate. Once formed, the negative charge of the alkoxide intermediate cannot be transferred to other substituents because the potential carbide ($R:^-$) and hydride ($H:^-$) leaving groups are too unstable. Instead the negative charge is held by the alkoxide until protonation converts it into an alcohol.



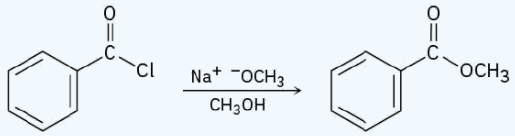
Carboxylic acid derivatives tend to undergo a reaction called nucleophilic acyl substitution. Similarly to nucleophilic addition, this mechanism starts with a nucleophilic attack on an electrophilic carbonyl carbon, forming a tetrahedral alkoxide intermediate. The alkoxide negative charge can gain stability by being transferred to the Y leaving group. Elimination of the Y leaving group in the second mechanistic step, allows the C=O carbonyl bond to reform thus creating a new acyl compound. The reaction is considered a substitution due to the Y group of the carboxylic acid derivative being exchanged with an incoming nucleophile.



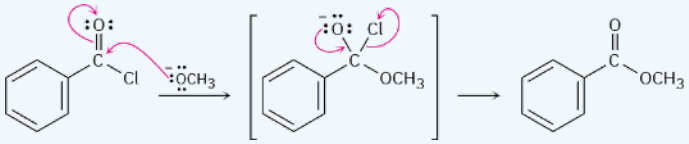
Step 1) Nucleophilic Addition	Step 2) Leaving Group Removal
	
Carboxylic Acid Derivative → Tetrahedral alkoxide Intermediate	Tetrahedral alkoxide Intermediate → New Acyl Compound + Leaving Group

Exercise 7.2.2

Show the mechanism of the following nucleophilic acyl substitution reaction, using curved arrows to indicate the electron flow in each step:



Answer



The Relative Reactivity of Carboxylic Acid Derivatives

The relative reactivity of carboxylic acid derivatives is an important concept for entering into a detailed examination of nucleophilic acyl substitutions. There are two main concepts directly relating to the mechanism, which when combined lead to an overall explanation of the differences in reactivity: **the stability of the carbonyl** and **the Y leaving group**.

Carbonyl Stability

Both the initial addition step and the subsequent elimination step can affect the overall rate of a nucleophilic acyl substitution reaction, but the addition is usually the rate-limiting step. Thus, any factor that makes the carbonyl group more reactive toward nucleophiles favors the substitution process.

Steric and electronic factors are both important in determining reactivity. Sterically, we find within a series of similar acid derivatives that unhindered, accessible carbonyl groups react with nucleophiles more readily than do sterically hindered carbonyl groups. The reactivity order is

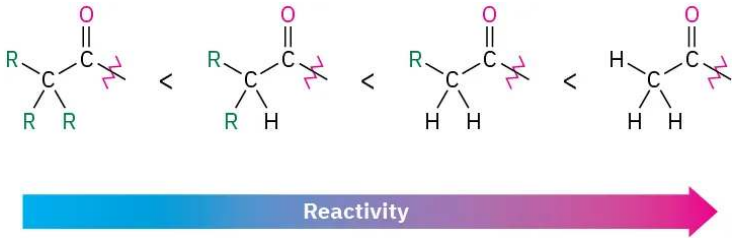
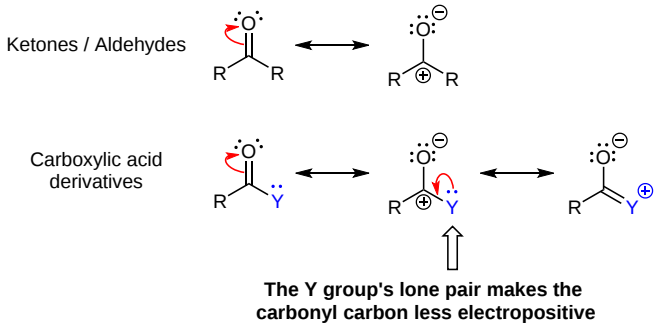


Figure 7.2.2: Reactivity order based on sterically accessible carbonyl groups.

Electronically, any stabilization of the carbonyl moiety reduces the electrophilic character of the carbonyl carbon by reducing its partial positive charge, reducing the rate of this step of the mechanism. The ability of substituents attached to the carbonyl carbon to donate or withdraw electron density is the primary factor determining carbonyl stabilization. As previously discussed, the presence of two electron donating alkyl substituents reduces the partial positive charge on ketones' carbonyl carbon, making them less reactive to nucleophilic attack than aldehydes.

Additionally, the Y group heteroatom's ability to stabilize a carbonyl by donating electrons through resonance makes most carboxylic acid derivatives even less reactive. Thus, amides are the least reactive because the pair of electrons on the nitrogen atom provides electrons to the carbonyl carbon. Overall, delocalization of the carbonyl carbon's partial positive charge onto the adjacent Y group heteroatom reduces the electrophilic character of the carbonyl. The electronegativity of the Y group heteroatom generally determines extent of this stabilization. The less electronegative the Y group heteroatom, the better it is able to stabilize the resonance structure with the delocalized positive charge, reducing the carbonyl's electrophilicity.



As contrast, strongly polarized acyl compounds react more readily than less polar ones. Thus, acid chlorides are the most reactive because the electronegative chlorine atom withdraws electrons from the carbonyl carbon. Although subtle, electrostatic potential maps of various carboxylic acid derivatives indicate these differences by the relative blueness on the C═O carbons. Acyl phosphates are hard to place on this scale because they are not often used in the laboratory, but in biological systems they appear to be somewhat more reactive than thioesters.

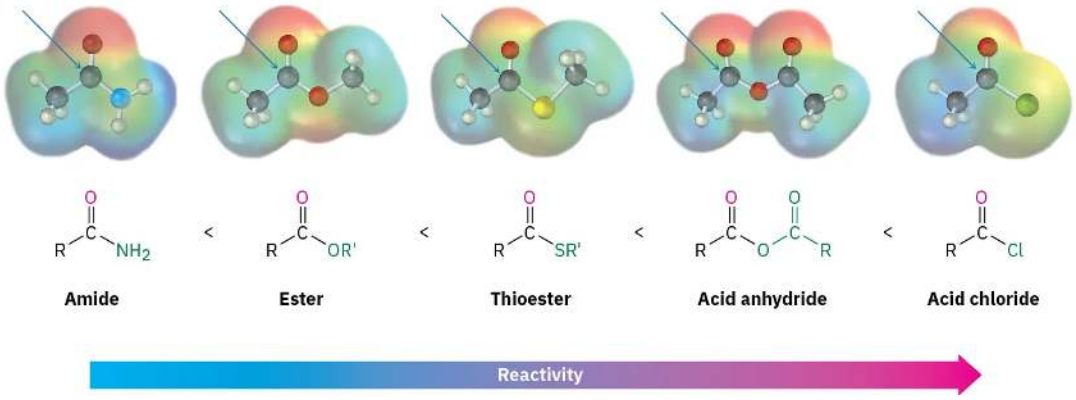
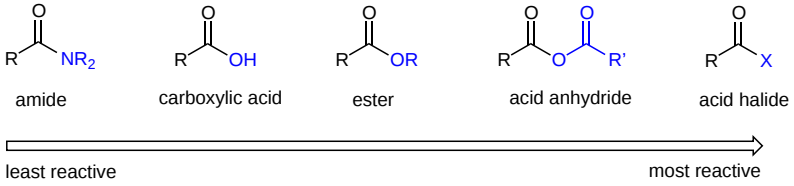


Figure 7.2.3: Reactivity order based on electronically stabilized carbonyl groups, by induction and by conjugation.

Leaving Group Ability

The leaving group ability of the Y group is the most important factor in determining the rate of the second mechanistic step of nucleophilic acyl substitution. As discussed above, the effectiveness of a leaving group is related to its ability to stabilize a negative charge particularly through having a relatively high electronegativity or having the ability to delocalize the negative charge through resonance. The Y group structural features which allow for the stabilization of a negative charge also allow for the stabilization of the transition state of the second step of the mechanism. Overall, the better the leaving group ability of the Y group, the higher the rate of second step of the mechanism.

These two effects, carbonyl stability and leaving group ability, when combined predict the relative reactivity of carboxylic acid derivatives. Fortunately, the effects tend to work synergistically. Y groups that are effective leaving groups also tend to poorly stabilize carbonyls through resonance making reaction rates of nucleophilic acyl substitution higher. Likewise, poor leaving groups tend to stabilize carbonyls through resonance and reduce reaction rates effectively. In fact, depending on the carbonyl structure, either step one or step two of the mechanism can be the rate-determining step. For Y groups with a poor leaving group ability, the second step of the mechanism is rate determining because of the weakly stabilized transition state. The first step of the mechanism is rate determining for Y groups with good leaving group ability because they tend to stabilize the starting material's carbonyl, increasing the energy distance to the first transition state.



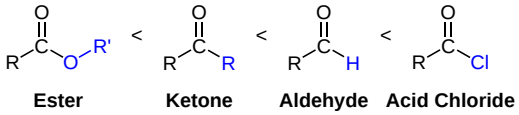
How the two effects actually combine to produce the overall reactivity for each carboxylic acid derivative is slightly different. As comparison of one of the more reactive carboxylic acid derivatives, acid chlorides, and one of the least reactive, amides, will be used as a discussion.

In amides, the nitrogen atom is a powerful electron donating group by resonance. Nitrogen is less electronegative than oxygen and can therefore better stabilize the resonance structure of the delocalized positive charge than most other acid derivatives. This lowers the energy of the starting material which increases the overall energy barrier. Likewise, $-NH_2$ is a relatively poor leaving group (since it is the conjugate base of a very weak acid RNH_2) which increases the transition state energy of the second step of the mechanism also increasing the overall energy barrier. The two effects combine to increase the overall energy barrier which must be overcome during the reaction, causing reaction rates to decrease and making amides very unreactive toward nucleophilic acyl substitution.

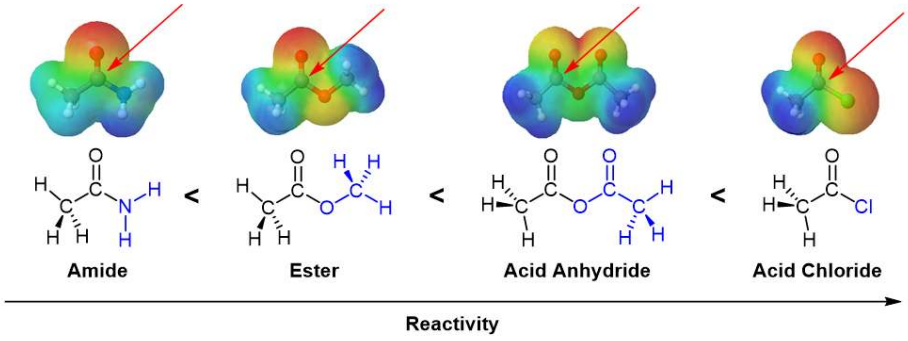
In acid chlorides the -Cl is a very effective leaving group making the energy barrier of the second step relatively small. However, this does not have a significant effect since the first step of the mechanism is rate determining. The resonance stabilization offered

by the chlorine atom is ineffective due to the poor overlap between the chlorine 3p orbital and the carbon 2p orbital. The poor overlap means that acid chlorides are much less stabilized by resonance than amides. In addition, since chlorine is more electronegative than nitrogen was in the amide example, the inductive electron-withdrawing effects of chlorine become important. This destabilizes the carbonyl and increases the electrophilic character of the carbonyl carbon. The energy barrier of the first step of the mechanism is small due to the lack of stabilization in the acid chloride starting material. Therefore the overall rate of reaction for acid chlorides is high making them very reactive towards nucleophilic acyl substitutions.

As a general rule, stabilizing effects from the Y heteroatom tends to make carboxylic acid derivatives less reactive toward the initial nucleophilic attack than aldehydes and ketone. One notable exception is acid chlorides, where the destabilizing inductive electron-withdrawing properties of the chlorine outweigh the resonance stabilizing effects making them more reactive towards nucleophilic attack. This point will become important later in the chapter where it will be used to explain the outcome of certain reactions.



The reactivity of a carboxylic acid derivative can be visualized by using an electrostatic potential map to look at the electron density around the carbonyl carbon. A blue/green color represents the amount of positive charge present. The carbonyl carbons of the amide and ester have a relatively small amount of positive charge making them among the least reactive toward nucleophilic attack. The acid chloride's and anhydride's carbonyl carbon has more of a blue/color color indicating a higher positive charge and making them more reactive than the amide and ester.



? Exercise 7.2.3

Rank the compounds in each of the following sets in order of their expected reactivity toward nucleophilic acyl substitution:

a. CH_3CCl, CH_3COCH_3, CH_3CNH_2

b. $CH_3COCH_2CH_3$, $CH_3COCH_2CCl_3$, $CH_3COCH(CF_3)_2$

Answer

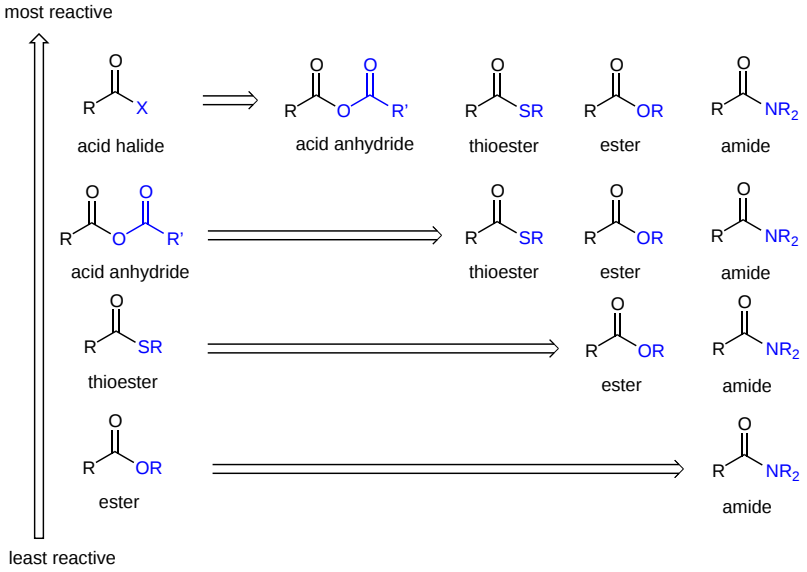
a. Acetyl chloride > Methyl acetate > Acetamide

b. Hexafluoroisopropyl acetate > 2,2,2-Trichloroethyl acetate > Ethyl acetate

Acid Derivative Interconversion

From this understanding of reactivity, multiple step synthesis strategies can be developed. Typically more reactive carboxylic acid derivatives can be used to synthesize less reactive derivatives as illustrated in the diagram below. As will be shown later in this chapter, highly reactive acid chlorides, when combined with the appropriate nucleophile, can be directly converting into acid

anhydrides, thioester, esters, and amides. However, the less reactive amides cannot be directly converted into ester, thioester, anhydrides, or acid chlorides. It is possible to make these conversions with an amide but multiple reaction steps are required.



The nucleophiles required to make the conversion from one carboxylic acid derivative to another are common and have been discussed multiple times in this text. Because the same nucleophile is typically used to convert to a specific carboxylic acid derivative conversion, the reactions are given generic names. (Figure 7.2.3).

- **Hydrolysis:** A reaction with water as a nucleophile to create a carboxylic acid.
- **Alcoholysis:** A reaction with an alcohol nucleophile to create an ester.
- **Aminolysis:** A reaction with ammonia or an amine nucleophile to create an amide.
- **Reduction:** A reaction with a hydride nucleophile to create an aldehyde or 1° alcohol.
- **Organometallic (Grignard reaction):** A reaction with a carbanion nucleophile from an organometallic reagent to create a ketone or a 3° alcohol.

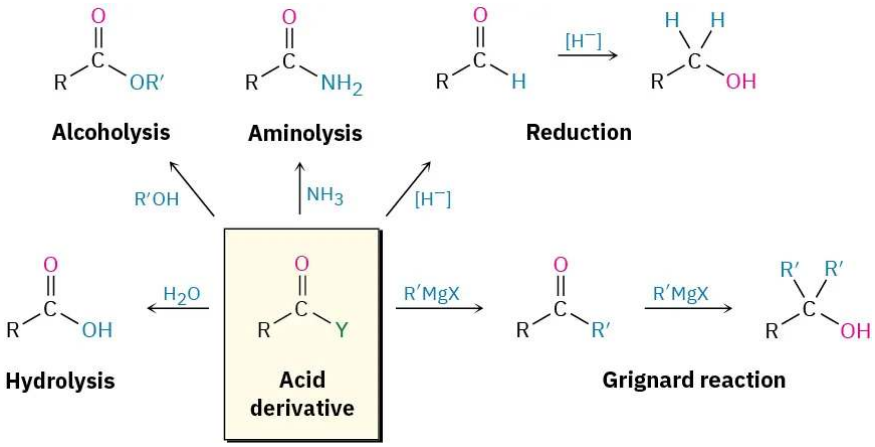
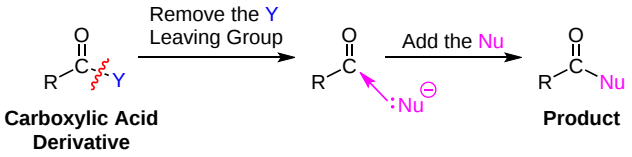


Figure 7.2.4: Some general reactions of carboxylic acid derivatives.

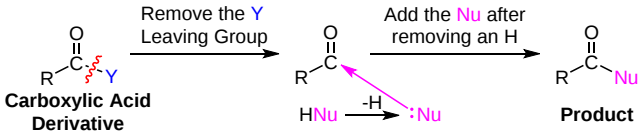
Predicting the Product of a Nucleophilic Acyl Substitution Reaction

There are two major pieces of a nucleophilic acyl substitution reaction which need to be identified in order to predict the product: the leaving group of the carboxylic acid derivative (Y) and the nucleophile. It is important to identify if the nucleophile is neutral (i.e. water, alcohols, ammonia, amines) or negatively charged (i.e. hydroxide, alkoxides, hydrides, carbanions). Also, it is important to note that certain hydride and organometallic reagents are capable of a double addition to carboxylic acid derivatives where the first step is a nucleophilic acyl substitution and the second is a nucleophilic addition.

Negatively Charged Nucleophiles

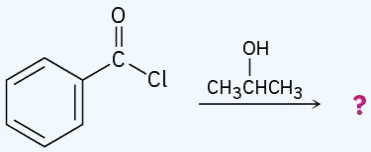


Neutral Nucleophiles



Worked Example 7.2.1: Predicting the Product of a Nucleophilic Acyl Substitution Reaction

Predict the product of the following nucleophilic acyl substitution reaction of benzoyl chloride with 2-propanol:

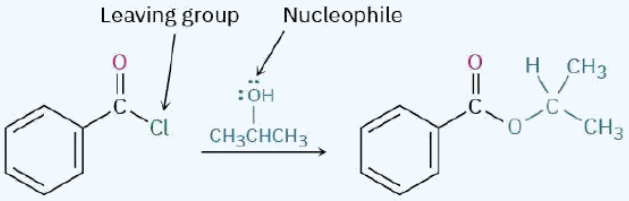


Benzoyl chloride

Strategy

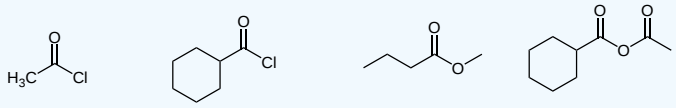
A nucleophilic acyl substitution reaction involves the substitution of a nucleophile for a leaving group in a carboxylic acid derivative. Identify the leaving group (Cl^- in the case of an acid chloride) and the nucleophile (an alcohol in this case), and replace one by the other. The product is isopropyl benzoate.

Solution



Exercise 7.2.4

Which of the following compounds would be expected to be the most reactive towards nucleophilic acyl substitution? Briefly explain your answer.



a) A B b) A B

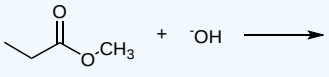
Answer

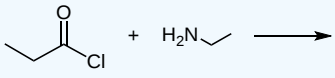
a) Compound A would be expected to be the more reactive. For two compounds with the same carboxylic acid derivative group, the one with the least steric crowding on the acyl side is typically the most reactive.

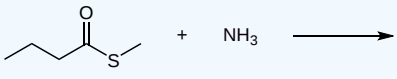
b) Compound B would be expected to be the more reactive. In general, acid anhydrides are more reactive than esters.

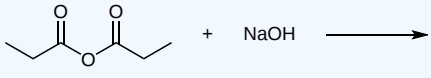
Exercise 7.2.5

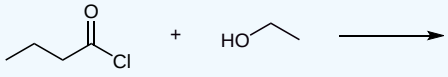
Predict the products of the following nucleophilic acyl substitution reactions:

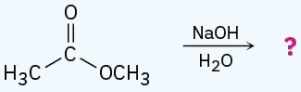
a. 

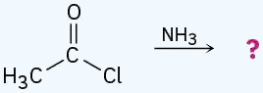
b. 

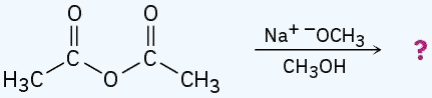
c. 

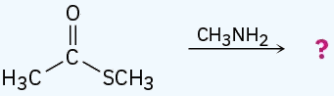
d. 

e. 

f. 

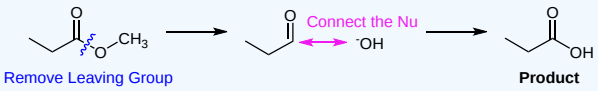
g. 

h. 

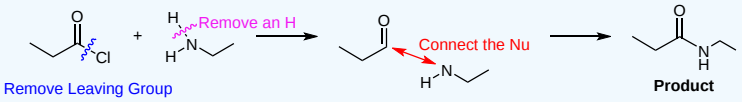
i. 

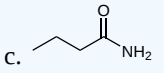
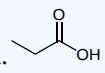
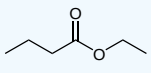
Answer

a. The nucleophile is negatively charged, it will use the pair of electrons to make the attack, and the leaving group will leave with the negative charge, leaving the final molecule neutral.



b. The nucleophile is neutral, it uses the non-bonded pair of electrons to make the initial attack. Then, the leaving group will leave with the negative charge, for the final molecule to be neutral, a proton needs to be removed.

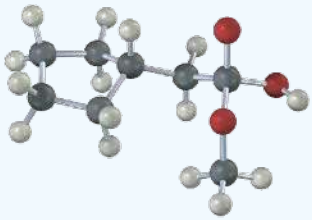


c.  d.  e. 

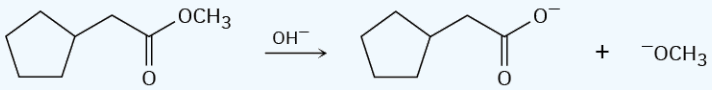
f. $CH_3CO_2^-\ Na^+$ g. CH_3CONH_2 h. $CH_3CO_2CH_3 + CH_3CO_2^-\ Na^+$ i. $CH_3CONHCH_3$

Exercise 7.2.6

The following structure represents a tetrahedral alkoxide ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product.



Answer



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7.3: Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

Objectives

After completing this section, you should be able to

1. write an equation to describe the formation of
   a. an acid chloride from a carboxylic acid.
   b. an ester from a carboxylic acid.
   c. an amide from a carboxylic acid.
   d. an alcohol from carboxylic acid.
2. write an equation to represent the formation of a cyclic anhydride from a dicarboxylic acid.
3. write the detailed mechanism for the reaction of a carboxylic acid with thionyl chloride.
4. identify the reagents necessary to convert a given carboxylic acid to a given acid chloride, ester, amide or alcohol.
5. identify the carboxylic acid required for a direct synthesis of a given acid chloride, amide, ester or alcohol.
6. write an equation to describe the formation of an ester through the nucleophilic attack of a carboxylate anion on an alkyl halide.
7. write a detailed mechanism for the Fischer esterification reaction.
8. describe the evidence from isotopic labelling experiments that is commonly cited to support the generally accepted mechanism of the Fischer esterification reaction.
9. explain why the direct conversion of a carboxylic acid to an amide can only be achieved with difficulty and at a high temperature.

Key Terms

Make certain that you can define, and use in context, the key term below.

- Fischer esterfication reaction

Study Notes

If necessary, review the S_N2 reaction between a carboxylate anion and a primary alkyl halide (Sections 11.2 and 11.3).

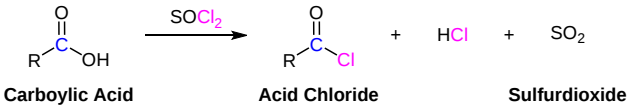
You should recall that the oxygen-18 isotope, ^{18}O, has a nucleus containing eight protons and ten neutrons. Because it is non-radioactive, ^{18}O can be safely employed in the investigation of reaction mechanisms.

The poor leaving group ability of -OH makes carboxylic acids relatively unreactive towards nucleophilic acyl substitutions. The addition of a strong acid protonates the carbonyl oxygen making the carbonyl carbon more electrophilic and circumventing this problem. Also, the substitution reaction can be promoted by converting -OH into a better leaving group. Despite the lack of reactivity, under the right conditions carboxylic acids can be successfully converted into acid chlorides, acid anhydrides, esters, and amides through nucleophilic acyl substitution.

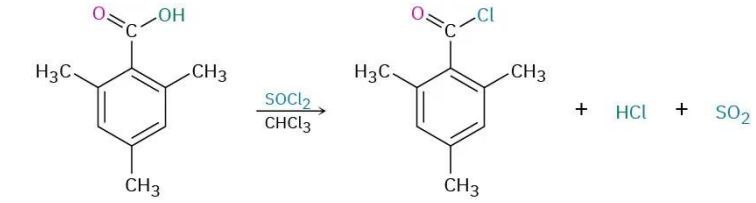
Conversion of Carboxylic acids to Acid Chlorides

Carboxylic acids can be converted to acid chlorides by reaction with thionyl chloride ($SOCl_2$). During the reaction with thionyl chloride, the hydroxyl group of the carboxylic acid is converted to an acyl chlorosulfite moiety which is a better leaving group. During the reaction a nucleophilic chloride anion is produced which reacts with the acyl chlorosulfite intermediate through nucleophilic acyl substitution to produce an acid halide.

General Reaction

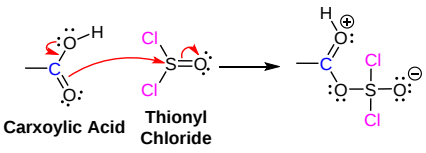
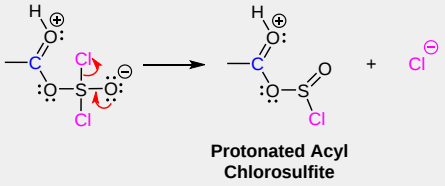
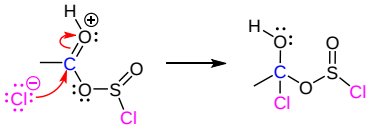
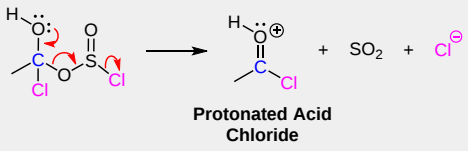
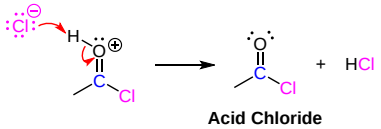


Example



Mechanism

The O=S-Cl bonds of thionyl chloride are analogous to the O=C-Cl bonds of an acid halide in that they can undergo a type of nuleophilicy acyl substitution. During the first step of the mechanism, the carboxylic acid reactant acts as a nucleophile and attacks the electrophilic sulfur of thionyl chloride, pushing the pi electrons of the S=O bond onto oxygen. Reforming the S=O bond and eliminating a cloride anion (Cl^-) as a leaving group creates a protonated acyl chlorosulfite. The chlorosulfite group represents an excellent leaving group due to its ability to stabilize a negative charge. The carbonyl of the protonated acyl chlorosulfite intermediate is activated to nucleophilic attack, and promptly reacts with the nucleophilic chloride anion created during the second step of the mechanism to produce a tetrahedral alkoide intermediate. Subsequent reforming of the protonated carbonyl bond eliminates the chlorosulfite group as sulfurdioxide (SO_2) and a chloride anion. Lastly, the chloride anion deprotonates the carbonyl to form the acid chloride product.

1) Nucleophilic attack on S=O bond	
2) Removal of Cl leaving group	
3) Nucleophilic attack on the carbonyl	
4) Leaving group removal	
5) Deprotonation	

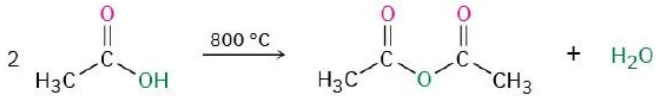
Conversion of Carboxylic Acids into Acid Anhydrides

An acid anhydride (or just anhydride) is the product of condensation of two carboxylic acid molecules with the release of a water molecule. The most common anhydride in organic chemistry is acetic anhydride, due to the high temperatures needed to remove water.

General Reaction



Example



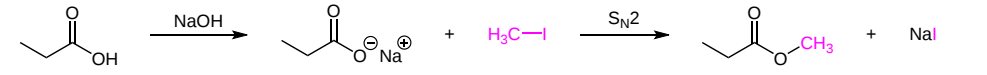
Acetic acid **Acetic anhydride**

Conversion of Carboxylic Acids into Esters

Nucleophilic Alkylation

Carboxylic acids can be easily converted into their conjugate bases through deprotonation with a base, such as sodium hydroxide. The resulting carboxylate can be alkylated using by an S_N2 reaction with either a methyl or primary halide. If a methyl ester is required, methyl iodide (CH_3I) is a commonly used reagent.

Example

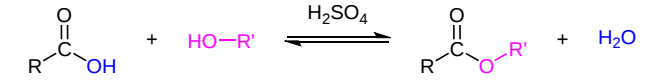


Propanoic Acid **Sodium Propanoate** **Methyl Iodide** **Methyl Propanoate** **Sodium Iodide**

The Fischer Esterification

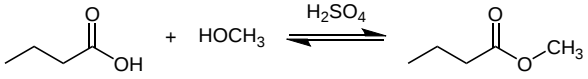
Alcohols can be used as nucleophiles to convert carboxylic acids to esters. Due to the poor leaving group ability of -OH in carboxylic acids, an acid catalyst is required to speed up the reaction. Usually the alcohol starting material is used as the reaction solvent so that it can be present in a large excess. This helps to increase the reaction's yield by pushing reaction equilibrium to the right which can be understood via Le Chatelier's principle.

General Reaction



Carxoylic Acid **Alcohol** **Ester** **Water**

Example

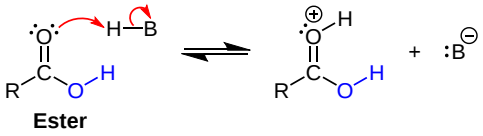
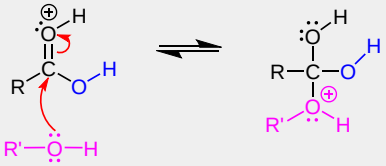
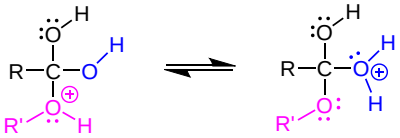
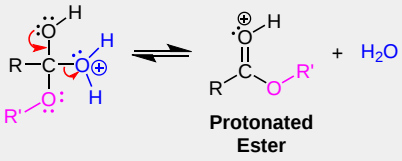
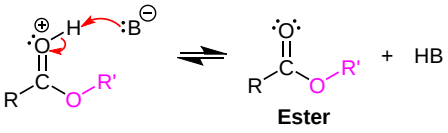


Butanoic Acid **Methyl Butanoate**

Mechanism

The mechanism begins with protonation of the carbonyl to increase its electrophilic character. A tetrahedral alkoxide intermediate is formed when the alcohol nucleophile adds to the protonated carbonyl, pushing the carbonyl pi electrons onto the oxygen. A different tetrahedral alkoxide intermediate is created when a proton is then transferred to one of the hydroxides (OH), turning it into

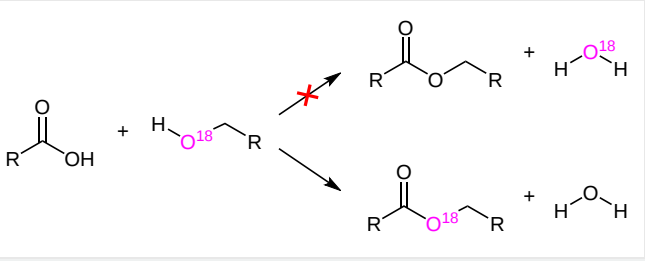
a good leaving group. Reforming the protonated carbonyl bond then eliminates water as a leaving group. Finally, deprotonation of the carbonyl by water creates the ester product and regenerates the acid catalyst. All the steps of the mechanism are reversible

Step 1: Protonation of the carbonyl	
Step 2: Nucleophilic attack on the carbonyl	
Step 3: Proton transfer	
Step 4: Removal of water as a leaving group	
Step 5: Deprotonation	

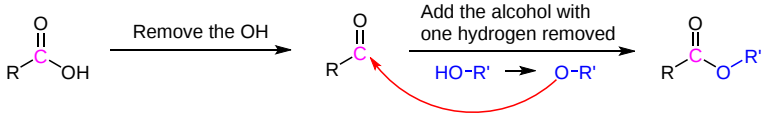
Note

Isotopic Labeling

Evidence to support the Fischer esterification mechanism comes from isotopic labeling experiments with oxygen-18. If the reaction is carried out with an oxygen-18 labeled alcohol, the isotope is found exclusively in the ester and not the water generated. This shows that the C-OH bond of the carboxylic acid and the H-OR bond of the alcohol that is broken during the reaction.

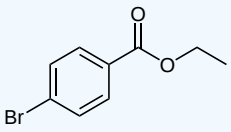


Predicting the Products of a Fischer Esterification

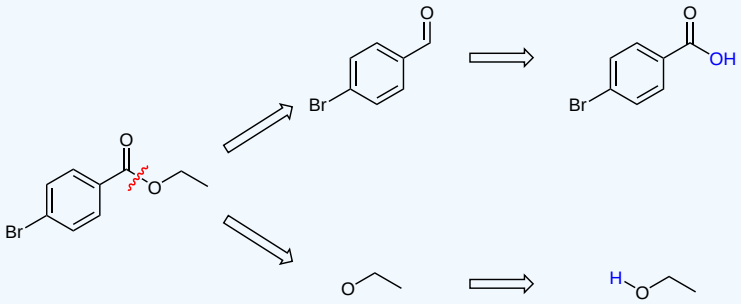


Worked Example 7.3.1: Planning a Synthesis Using a Fischer Esterification

How could the following molecule be made using a Fischer Esterification?

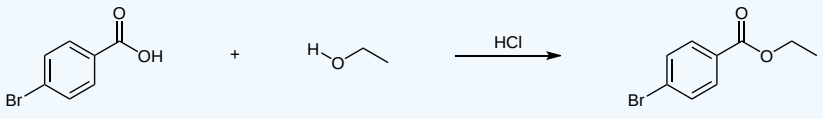


Analysis



The key bond formed during a Fischer Esterification is the C-O sigma bond. The target molecule can be separated into the two required starting materials by breaking this bond. The carbonyl carbon fragment gains an –OH to become a carboxylic acid and the oxygen fragment gains an H to become an alcohol. The carboxylic acid and the alcohol are reacted using a strong acid catalyst.

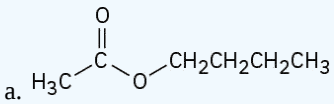
Solution

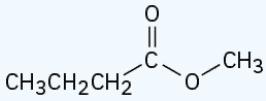


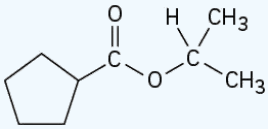
***p*-Bromo Benzoic Acid** + **Ethanol** → **Ethyl *p*-Bromo Benzoate**

Exercise 7.3.1

How might you prepare the following esters from the corresponding acids?

a. 

b. 

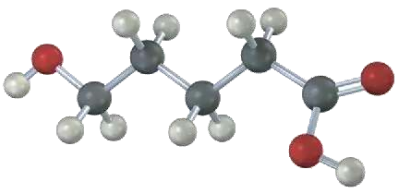
c. 

Answer

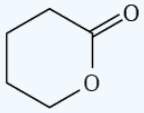
a. Acetic acid + 1-butanol
b. Butanoic acid + methanol
c. Cyclopentanecarboxylic acid + isopropyl alcohol

Exercise 7.3.2

If the following molecule is treated with acid catalyst, an intramolecular esterification reaction occurs. What is the structure of the product? (*Intramolecular* means within the same molecule.)



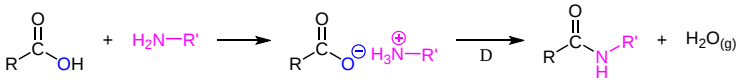
Answer



Direct Conversion of Carboxylic Acids to Amides

The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a stable carboxylate salt. However when the ammonium carboxylate salt is heated to a temperature above 100 ^{o}C, water is driven off and an amide is formed. Due to the extreme conditions, this reaction is rarely used. When converting to an amide it is preferred to convert the carboxylic acid to a more reactive form such as an acid chloride first and then convert this molecule to an amide.

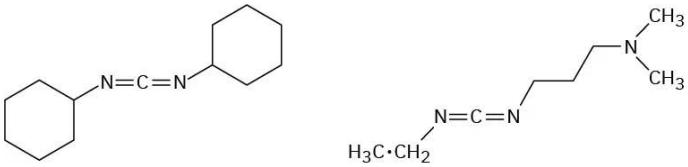
General Reaction



Ammonium Carboxylate Salt

Conversion of Carboxylic Acids to Amides using DCC

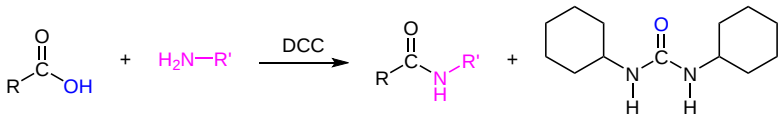
The formation of amides from carboxylic acids and amines is a reaction of great importance in biochemistry. Proteins are formed through the creating of amide bonds between amino acid residues, so a great deal of research has been performed to find efficient methods. The direct conversion of a carboxylic acids to amides is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. One solution to this problem is through the use of dialkylcarbodiimides (R-N=C=N-R) coupling reagents, such as dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropylcarbodiimide (EDEC).



Dicyclohexylcarbodiimide **1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide**

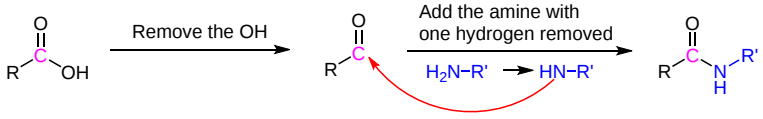
During a DCC amide coupling, the OH of a carboxylic acid is made into a good leaving group which can then be replaced by an amine during nucleophilic acyl substitution. Using DCC as a coupling reagent, 1° and 2° amines can be used to create 2° and 3° amides respectfully.

Basic reaction

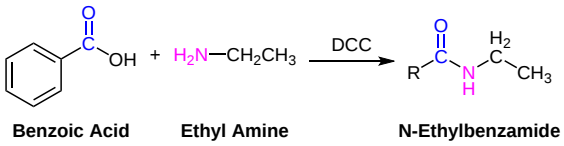


Carboxylic Acid **Amine** **Amide** **N,N'-Dicyclohexylurea**

Predicting the products of DCC Coupling

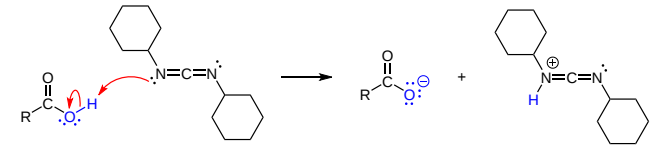
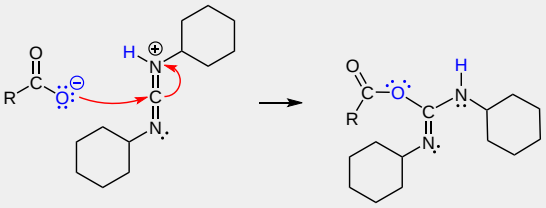
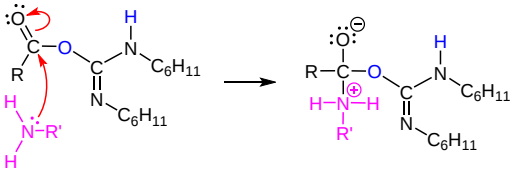
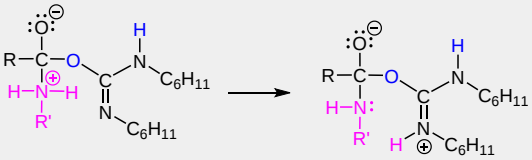
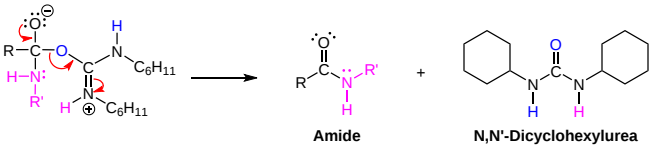


Example



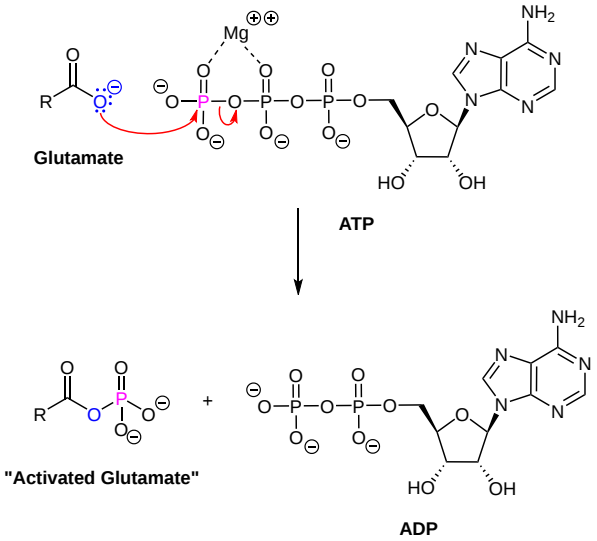
Mechanism

DCC deprotonates the carboxylic acid to form a carboxylate, which is a better nucleophile. The corresponding protonation of DCC increases the electrophilic character of its C=N imide bond. The caboxylate nucleophile then adds to the imide bond and pushes the C=N pi electrons onto the nitrogen. The amine nucleophile can now add itself to the carbonyl bond as part of a nuleophilic acyl substitution. The DCC coupled oxygen is eliminated as dicyclohexylurea, a good leaving group, to create the amide product.

Step 1: Deprotonation	
Step 2: Nucleophilic attack by the carboxylate	
Step 3: Nucleophilic attack by the amine	
step 4: Proton transfer	
Step 5: Leaving group removal	

Biologic Conversion of Carboxylic Acids

In biological chemistry direct conversion of a carboxylic acid to an acyl derivative by nucleophilic acyl substitution does not occur. Rather, the first conversion is from a carboxylate (the *least* reactive acyl transfer substrate) to an acyl phosphate (the *most* reactive acyl transfer substrate). This transformation requires a reaction that we are familiar with: phosphorylation of a carboxylate oxygen with ATP as the phosphate donor.

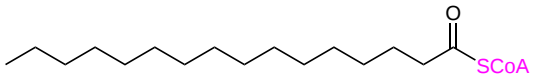


Note that this is just one of the many ways that ATP is used as a energy storage unit: in order to make a high energy acyl phosphate molecule from a low energy carboxylate, the cell must 'spend' the energy of one ATP molecule.

Biosynthesis of Fats

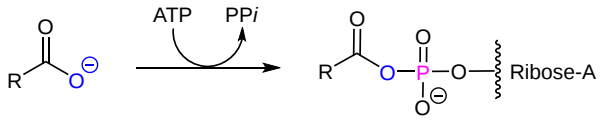
In the biosynthesis of fats, for example, a long-chain carboxylic acid reacts with ATP to give an acyl adenylate, followed by subsequent nucleophilic acyl substitution of a thiol group in coenzyme A to give the corresponding acyl CoA (Figure 7.3.3). This activation is often accomplished in living organisms by reaction of the acid with adenosine triphosphate (ATP) to give an acyl adenosyl phosphate, or *acyl adenylate*, a mixed anhydride combining a carboxylic acid and adenosine monophosphate (AMP, also known as adenylic acid).

In the biologically active form of fatty acids, the carboxylate groups have been converted to thioesters using coenzyme A. For example, the activated form of the C_{16} fatty acid palmitate is:



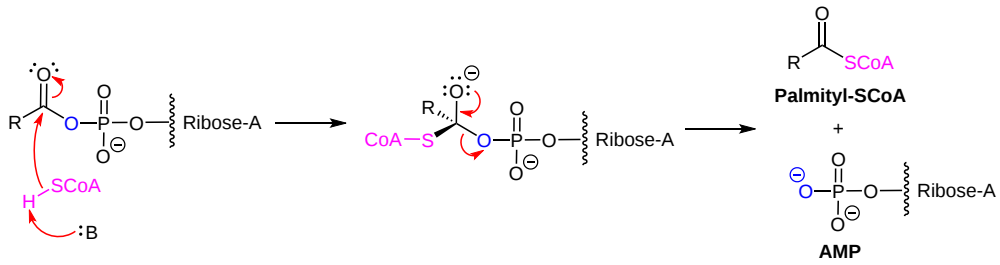
Palmityl-SCoA

Let's take a look at how this activation takes place, in a reaction catalyzed by an enzyme called acyl CoA synthetase. You already know that carboxylates are not themselves good substrates for acyl substitution reactions, and must be activated. Thus, you might predict that the first step of this reaction requires ATP to make a high-energy acyl phosphate intermediate. In fact, the activated carboxylate in this case is an acyl-AMP, formed in the same way as the acyl-AMP intermediate in the asparagine synthetase reaction:



Palmitate **Palmityl-AMP**

The activated acyl-AMP intermediate is then attacked by the thiol sulfur of coenzyme A, and the AMP group is expelled to form the fatty acyl CoA.



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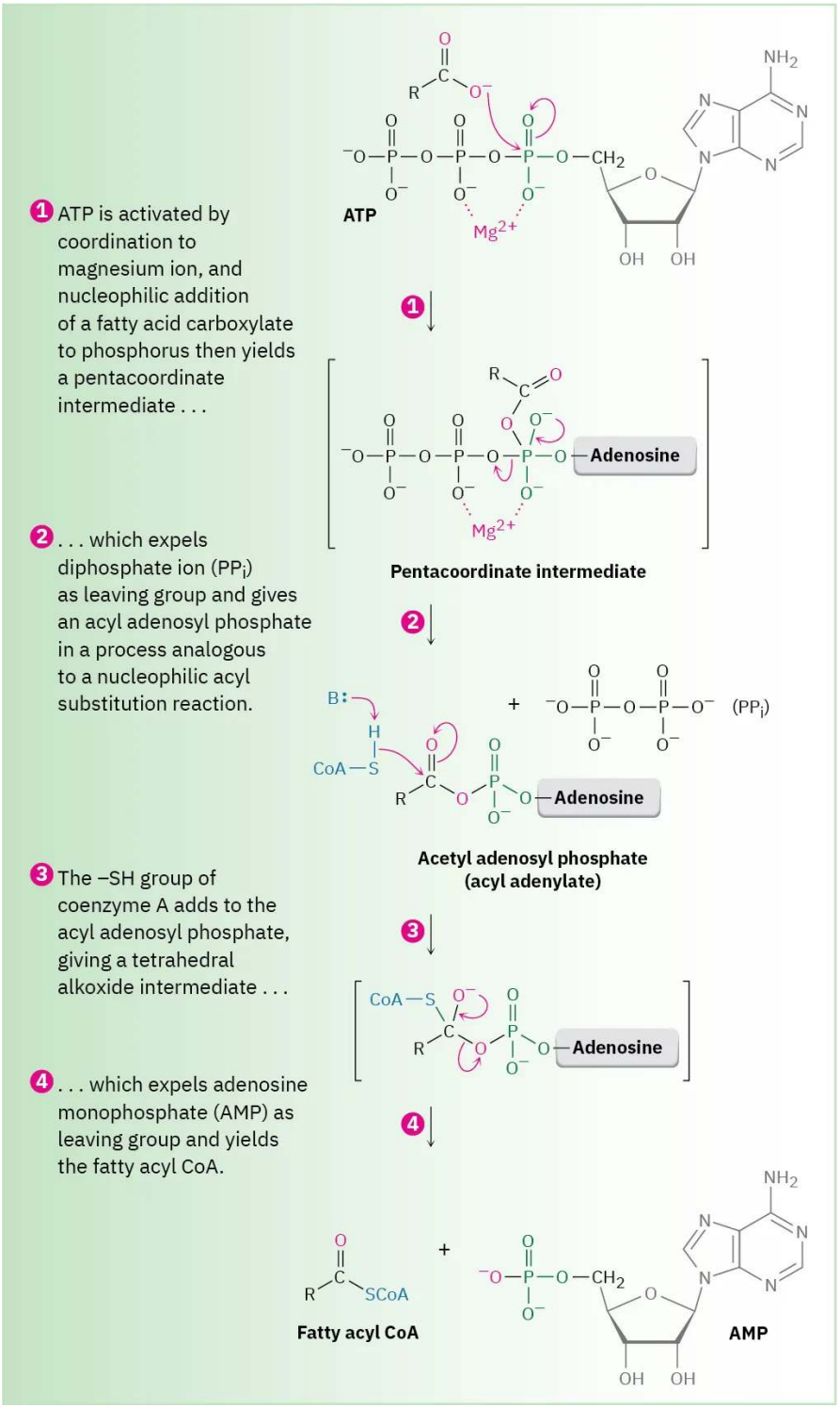


Figure 7.3.3: In fatty-acid biosynthesis, a carboxylic acid is activated by reaction with ATP to give an acyl adenylate, which undergoes nucleophilic acyl substitution with the –SH group on coenzyme A. (ATP = adenosine triphosphate; AMP = adenosine monophosphate.)

Note that the first step in Figure 7.3.3—reaction of the carboxylate with ATP to give an acyl adenylate—is itself a nucleophilic acyl substitution *on phosphorus*. The carboxylate first adds to a P=O double bond, giving a five-coordinate phosphorus intermediate that expels diphosphate ion as a leaving group.

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7.4: Chemistry of Acid Halides

Objectives

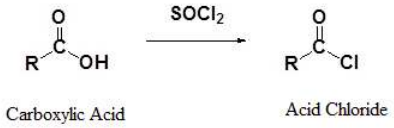
After completing this section, you should be able to

1. identify the reagent normally used to convert a carboxylic acid to an acid bromide.
2. write equations to show how an acid halide may be converted into each of the following: a carboxylic acid, an ester, an amide.
3. write a detailed mechanisms for the reaction of an acid halide with each of the following: water, an alcohol, ammonia, a primary or secondary amine.
4. identify the product formed when a given acid halide reacts with any of the following reagents: water, an alcohol, a primary or secondary amine.
5. identify the acid halide, the reagents, or both, needed to prepare a given carboxylic acid, ester or amide.
6. identify the product formed when a given acid halide reacts with water, a given alcohol, ammonia, or a given primary or secondary amine.
7. identify lithium aluminum hydride as a reagent for reducing acid halides to primary alcohols, and explain the limited practical value of this reaction.
8. identify the partial reduction of an acid halide using lithium tri-*tert*-butoxyaluminum to form an aldehyde.
9. write an equation to describe the formation of a tertiary alcohol by the reaction of an acid halide with a Grignard reagent.
10. write a detailed mechanism for the reaction of an acid halide with a Grignard reagent.
11. identify the product formed from the reaction of a given acid halide with a given Grignard reagent.
12. identify the acid halide, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
13. write an equation to illustrate the reaction of an acid halide with a lithium diorganocopper reagent.
14. identify the product formed from the reaction of a given acid halide with a given lithium diorganocopper reagent.
15. identify the acid halide, the lithium diorganocopper reagent, or both, that must be used to prepare a given ketone.

Acid halides are highly reactive carboxylic acid derivatives. As such they are able to be used to synthesize many other carboxylic acid derivatives.

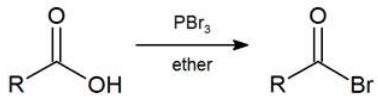
Formation of Acid Halides

Carboxylic acids react with thionyl chloride ($SOCl_2$) to form acid chlorides. A nucleophilic acyl substitution allows for the replacement of the carboxylic acid –OH with a chloride atom.



Carboxylic Acid Acid Chloride

Earlier (Section 10.5), we saw that primary and secondary alcohols react with phosphorous tribromide (PBr_3) to afford the corresponding alkyl bromide. In a similar fashion, acid bromides can be formed from the corresponding carboxylic acid by reaction with PBr_3.

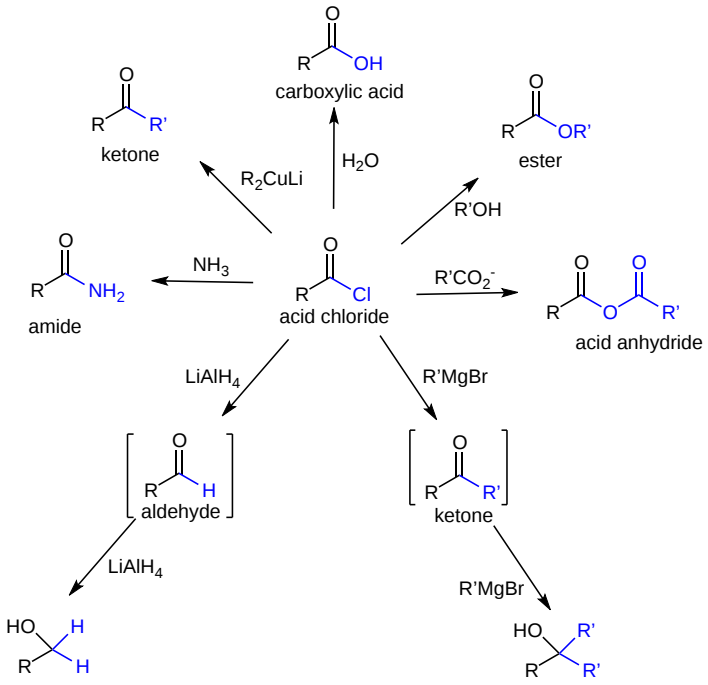


Carboxylic Acid Acid Bromide

https://chem.libretexts.org/@go/page/500435

Reactions of Acid Halides

The high reactivity of acid halides allows them to be easily converted into other acyl compound through nucleophilic acyl substitution. Depending on the nucleophilic reagent applied, acid halides can be used to create carboxylic acids, anhydrides, esters, amides, or ketones. Also, acid halides undergo a double nucleophilic addition with LiAlH4 to produce primary alcohols and Grignard reagents to produce tertiary alcohols. Although this section will only represent reactions with acid chlorides, other acid halides undergo similar reactions.



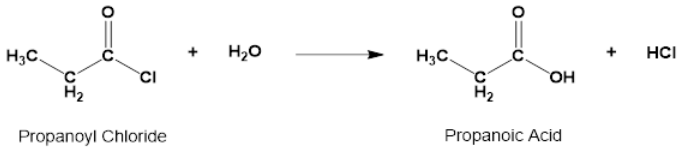
Conversion of Acid Chlorides to Carboxylic Acids: Hydrolysis

Acid chlorides are converted into carboxylic acids through a nucleophic acyl substitution with water. This reaction follows the typical mechanism where a water nucleophile attacks the electrophilic carbonyl carbon to form a tetrahedral alkoxide intermediate. The carbonyl bond is reformed and Cl- is eliminated as a leaving group. Because water is a neutral nucleophile, an oxonium intermediate in produced. The oxonium intermediate is deprotonated by the chloride anion to produce a neutral carboxylic acid and HCl. The HCl is commonly removed from the reaction mixture by a basic work-up.

General reaction

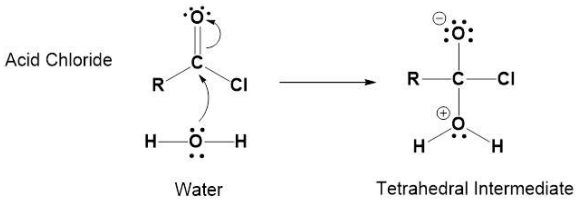


Example

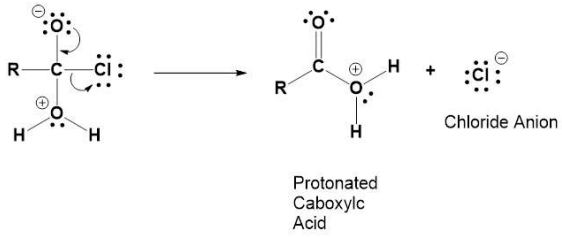


Mechanism

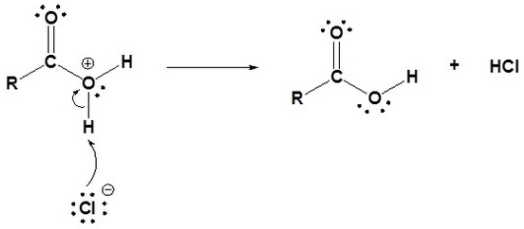
1) Nucleophilic attack by water



2) Leaving group is removed



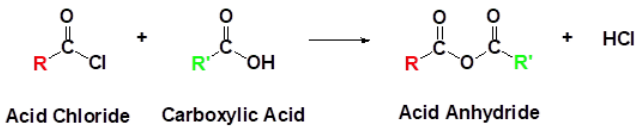
3) Deprotonation



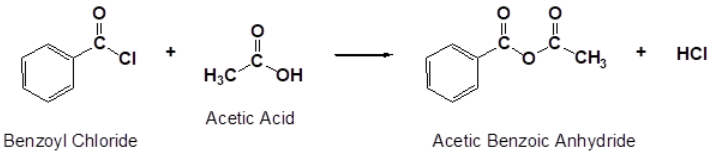
Conversion of Acid Chlorides to Anhydrides

Acid chlorides react with carboxylic acids to form anhydrides through a nucleophilic acyl substitution. Because the carboxylic acid nucleophile is neutral, HCl is produced as a side-product during the reaction and is typically removed as part of a basic work-up. Both symmetrical and asymmetrical anhydrides can be created using this reaction. Carboxylates can also be used to form anhydrides in a similar reaction under basic conditions.

General Reaction

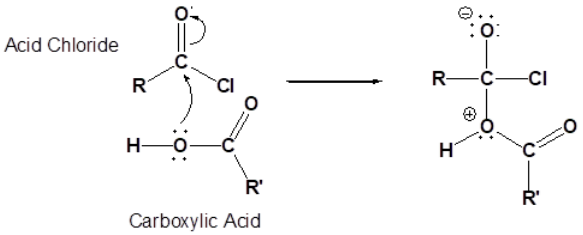


Example

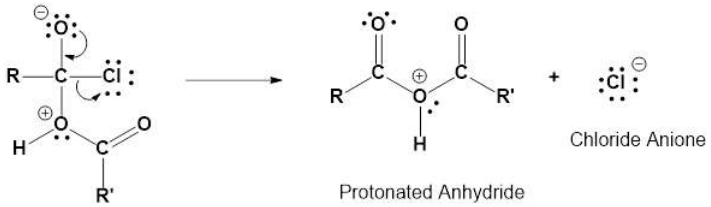


Mechanism

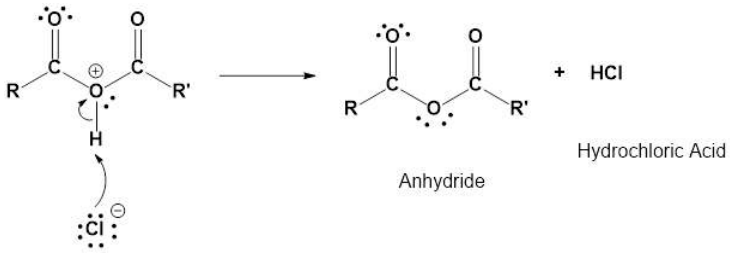
1) Nucleophilic attack by a carboxylic acid



2) Leaving group removal



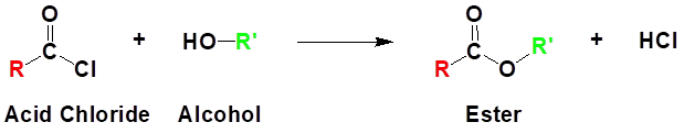
3) Deprotonation



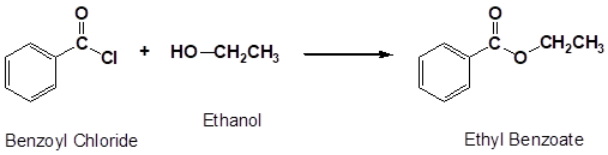
Conversion of Acid Chlorides to Esters: Alcoholysis

Acid chlorides react with alcohol nucleophiles to produce esters. This reaction is the preferred method for preparing esters. Pryidine is often added to the reaction mixture to remove the HCl produced.

General Reaction

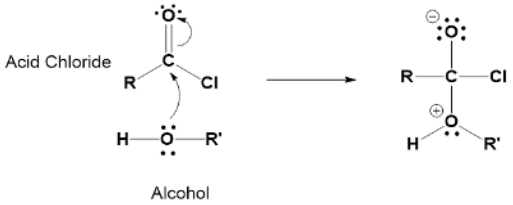


Example

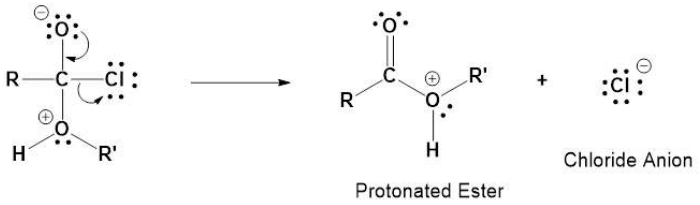


Mechanism

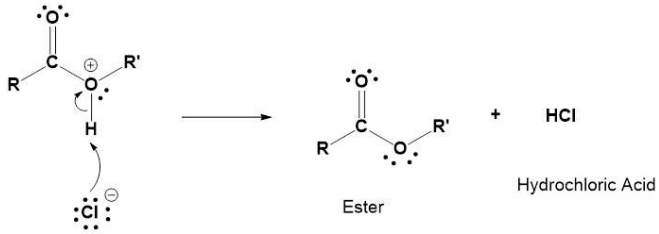
1) Nucleophilic attack by an alcohol



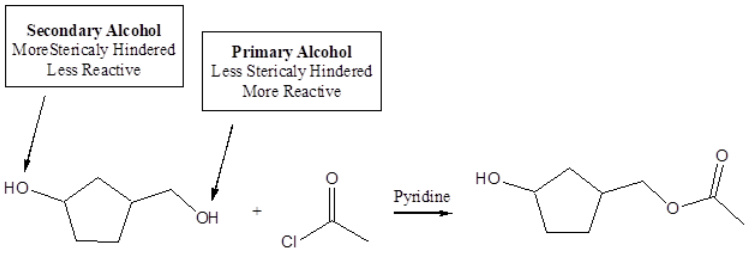
2) Leaving group removal



3) Deprotonation

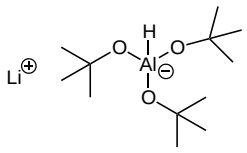


This reaction is particularly affected by steric hindrance so bulky alkyl groups on either the acid chloride or the alcohol significantly decrease the rate. For a given acid chloride there is a reactivity order among alcohols of primary > secondary > tertiary. If a compound has multiple alcohols the less hindered one will be selectively esterified.

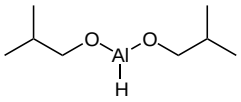


Conversion of Acid Chlorides to Aldehydes: Reduction

Acid chlorides can be converted to aldehydes using a hindered reducing agent such as lithium tri-tert-butoxyaluminum hydride $LiAlH(Ot\text{-}Bu)_3$ or diisobutylaluminum hydride (DIBALH). These hydride sources are weaker reducing agents than lithium aluminum hydride in part because they are sterically hindered. Also, they have only one equivalent of hydride which makes stoichiometric control of hydride addition much easier.



lithium tri-tert-butoxyaluminum hydride

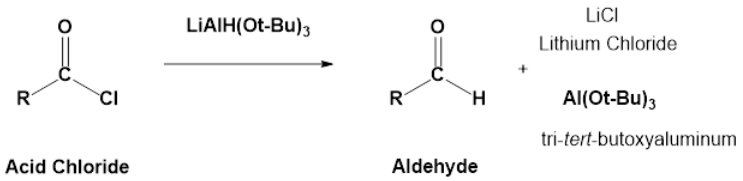


diisobutylaluminum hydride

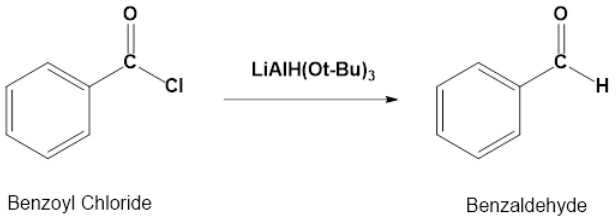
The mechanism of this reaction is analogous to the hydride reduction of carboxylic acids. We have previously seen that $LiAlH_4$ will reduce carboxylic acids to 1° alcohols thorough an aldehyde intermediate. In that case, the aldehyde intermediate was actually more reactive to hydride reduction than the carboxylic starting material. This prevented the isolation of the aldehyde intermediate because of it quick conversion to the 1° alcohol. $LiAlH_4$ would also convert acid chlorides to 1° alcohols but this reaction would be inefficient because it would be easier to perform the reaction on the corresponding carboxylic acid.

Because acid chlorides are highly activated, they will still react with the weaker hydride sources, to form an aldehyde. Once formed, the aldehyde competes with the remaining acid chloride for the remaining hydride reagent. However, acid chlorides are more reactive towards nucleophilic attack than aldehydes. The acid chloride starting material is quickly consumed by hydride reduction before the aldehyde has a chance to react allowing for isolation of the resulting aldehyde. Using a reaction temperature of -78 °C also helps to isolate the aldehyde as the product by further slowing the aldehyde reduction reaction.

General Reaction



Example

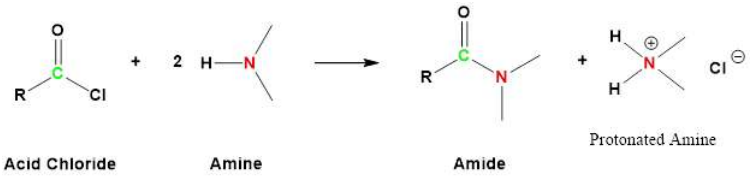


Conversion of Acid chlorides to Amides: Aminolysis

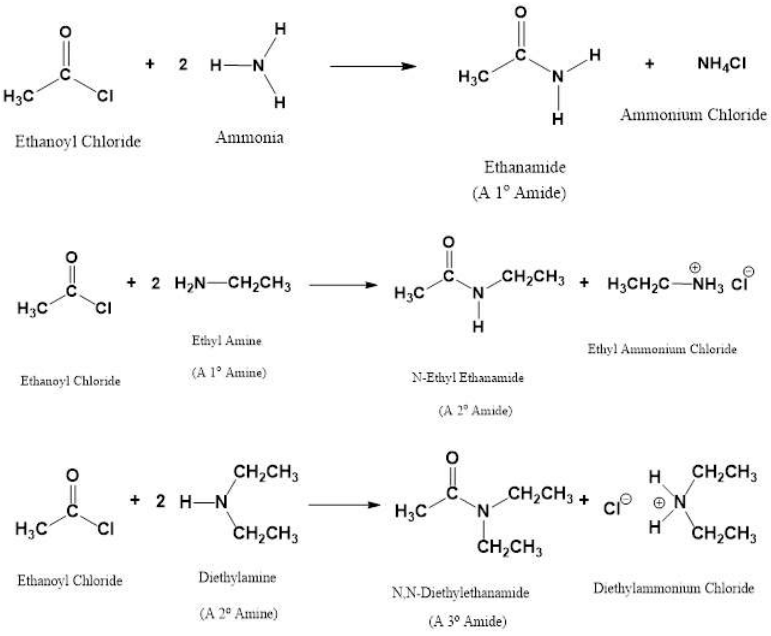
Ammonia, 1° amines, and 2° amines react with acid chlorides to form 1°, 2°, and 3° amides respectively. These reactions typically take place rapidly at room temperature and provides high reaction yields.

The reaction is commonly run with an excess of the amine starting material. Without the excess the amine reactant would eventually become protonated by the HCl produced by the reaction to form a non-nucleophilic ammonium compound. If the amine is not readily available, the reaction is usually run with a base, such as NaOH or pyridine, to neutralize the HCl produced.

General Reaction



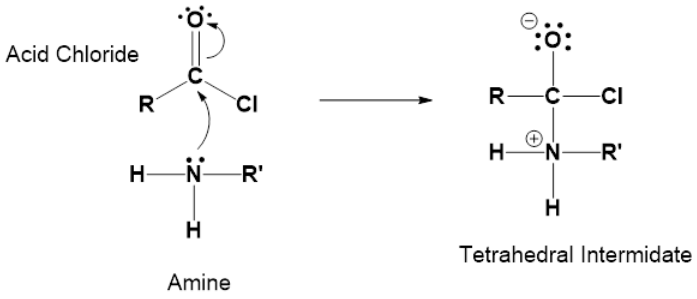
Examples



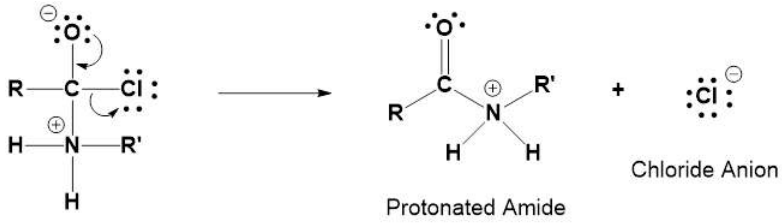
Mechanism

The mechanism of aminolysis follows a typical nucleophilic acyl substitution. The amine nucleophile attacks the carbonyl carbon of the acid chloride forming an alkoxide tetrahedral intermediate. The -Cl leaving group is eliminated, allowing the carbonyl bond to be reformed. Because amines are neutral nuleophiles a protonated amide is produced after this step. In the last step of the mechanism, a second amine acts as a base, removing a proton, and allowing for the amide product to be formed.

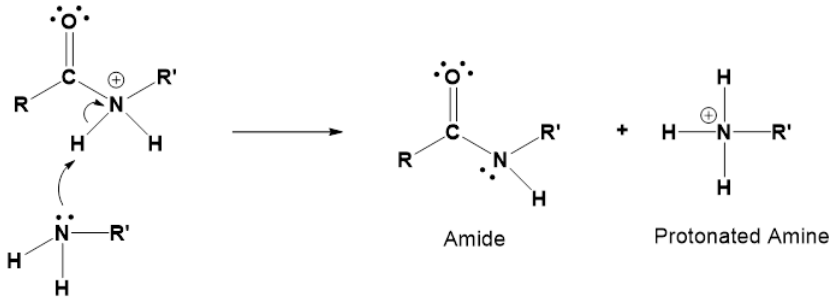
1) Nucleophilic attack by an amine



2) Leaving group removal

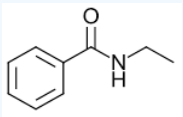


3) Deprotonation



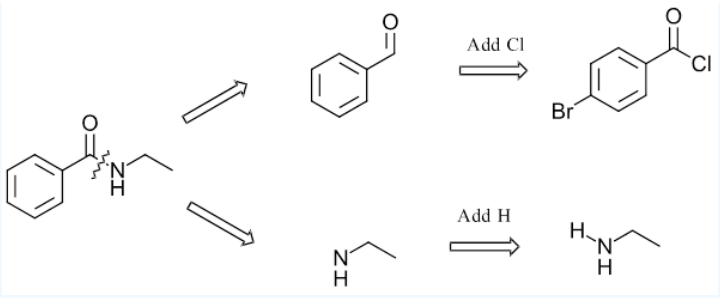
Example 7.4.1

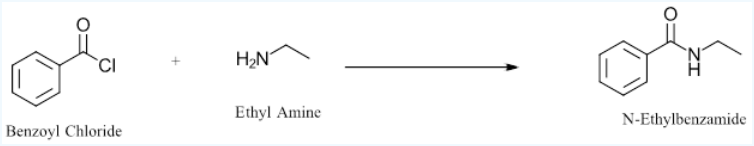
How could the following molecule be synthsized using an aminolysis of an acid chloride?



Solution

The key bond formed during this reaction is the C-N sigma bond between the carbonyl carbon and the nitrogen. Breaking this bond separated the target molecule into the two required starting materials. The carbonyl carbon gains an –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1º amine. The acid chloride and the 1º amine can then be joined to form the product.

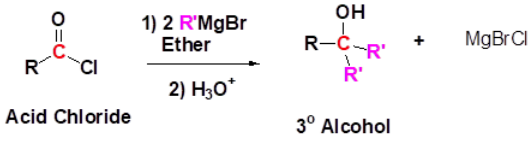




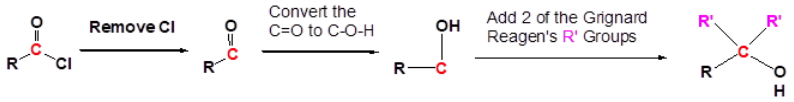
Conversion of Acid Chlorides to 3º Alcohols: Grignard Reagents

Addition of Grignard reagents converts acid halides to 3º alcohols while forming two C-C bonds. The Grignard reagent adds to the carbonyl carbon twice during this reaction. First, as part of a nucleophilic acyl substitution to form a ketone intermediate. Then as part of a nucleophilic addition to the ketone to form a 3º alcohol.

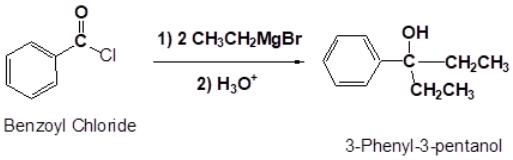
General Reaction



Predicting the Product of a Grignard Reaction

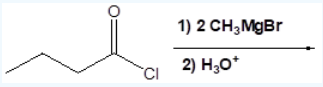


Example



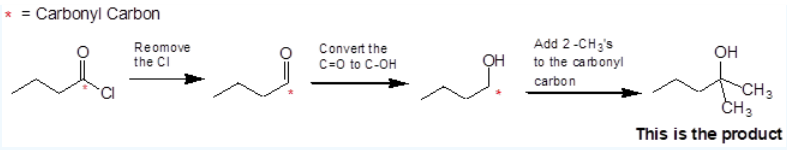
Example 7.4.2

Draw the products of the following reaction.



Solution

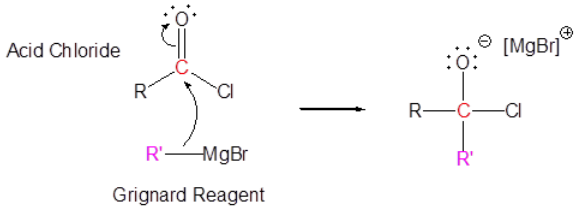
The carbanion nucleophile from the Grignard reagent is added to the carbonyl carbon twice. Once as part of a nucleophilic acyl substitution which eliminates the Cl leaving group. Then again as part of a nucleophilic addition which converts the carbonyl C=O into an alcohol OH. These steps are combined to form a 3º alcohol.



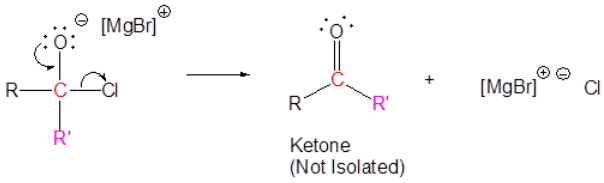
Mechanism

The mechanism starts with the Grignard reagent's carbanion nucleophile adding to the acid halide carbonyl to form a tetrahedral alkoxide intermediate. The chloride leaving group is then eliminated, reforming the carbonyl to create a ketone intermediate. Once formed, the ketone is in competition with the acid chloride for the Grignard reagent remaining. Although acid chlorides are more reactive toward nucleophilic addition than ketones, the high reactivity of Grignard reagents makes isolating the ketone intermediate difficult. The reaction mechanism continues with the addition of a second carbanion nucleophile to the ketone to form another tetrahedral alkoxide intermediate. Protonation of the alkoxide as part of an acidic work-up creates the 3° alcohol product.

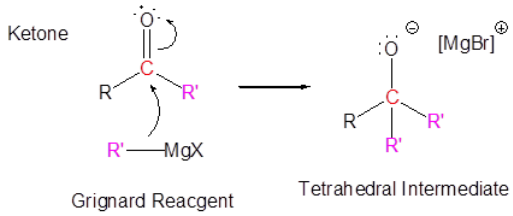
1) Nucleophilic attack



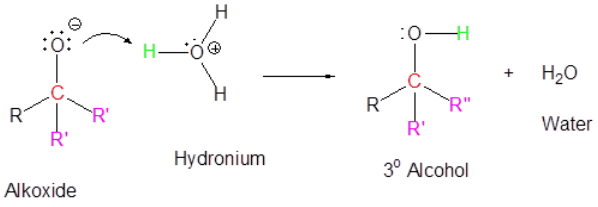
2) Leaving group removal



3) Nucleophilic attack



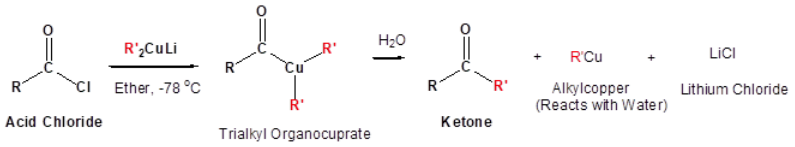
4) Protonation



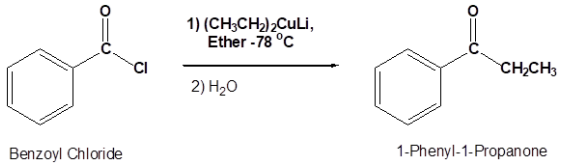
Conversion of Acid Chlorides to Ketones: Gilman Reagents

When acid chlorides are reacted with Grignard reagents the ketone intermediate is difficult to isolate because the addition of a second equivalent of the highly reactive Grignard reagent rapidly occurs. Organocuprates however are significantly less reactive than organolithium and organomagnesium reagents and when an acid chloride is reacted with a diorganocuprate (Gillman) reagent (R_2CuLi), a ketone product is produced in excellent yields.

General Reaction



Example

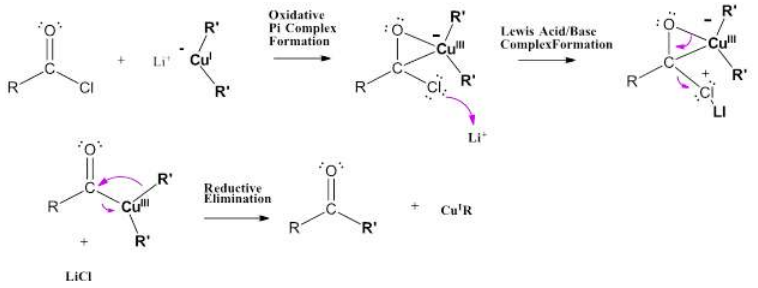


Mechanism

The copper atom in organocuprate reagents radically changes the reaction mechanism for their nucleophilic addition to acid chlorides. Computational studies suggest that the reaction mechanism is more complicated than the typical "addition-elimination" sequence seen in nucleophilic acyl substitutions but rather involves multiple mechanistic steps involving complexation with copper and lithium.

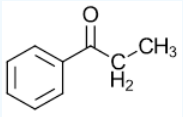
The mechanism starts with an oxidative pi-complex formation between the Cu atom in Gilman reagents and the C=O carbonyl bond in acid chlorides. Next, the chloride atom is activated toward elimination through formation of a Lewis Acid/Base complex with a lithium cation. The subsequent elimination of the –Cl leaving cleaves the C-Cl bond and forms a Cu-C bond creating a triorganocopper(III) intermediate. A ketone product is formed when reductive elimination breaks the Cu^{III}-C bond of the intermediate and forms a C-C bond between the carbonyl carbon and an alkyl group from the organocuprate reagent. During the reduction step, copper gains two electrons forming an alkylcopper (CuR) compound as a side product.

This mechanism, in part, explains the selectivity of organocuprates for acid chlorides. Acid chlorides are promoted for this reaction due to the strong electrostatic interaction between chlorine and the lithium cation present. Most other carbonyls compounds, such as ketones, carboxylic acids, esters, acid anhydrides, or amides lack this Cl-Li interaction and react with organocuprate reagents either very slowly or not at all. Because ketones do not react with organocuprate reagents, they are not subject to further nucleophilic additions and are easily isolated as the product of this reaction.



Example 7.4.3

How could the following molecule be synthesized using a Gilman reagent and an acid chloride?

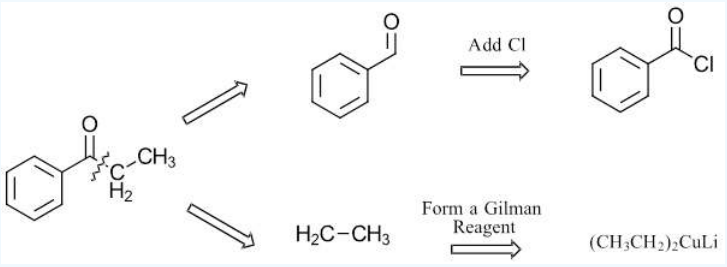


Solution

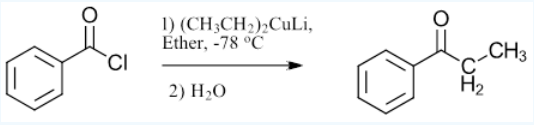
The key bond formed during this reaction is the C-C sigma bond between the carbonyl carbon and an alpha carbon. Breaking this bond separated the target molecule into two possible two starting materials. The carbonyl carbon gains an –Cl to become

an acid chloride and the alkyl fragment becomes part of a Gilman Reagent R_2CuLi. The required alkyl fragment becomes the R group in the Gilman reagent. Remember that the Gilman reagent has contains two of the alkyl fragment. Because ketones have two alpha carbons there should be two possible acid chloride/Gilman reagent combinations to make this molecule.

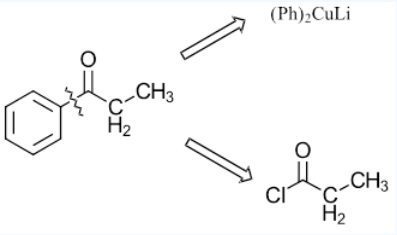
Pathway 1



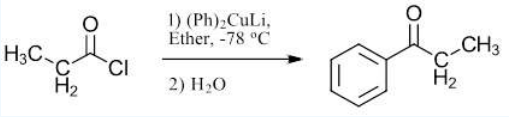
Solution 1



Pathway 2



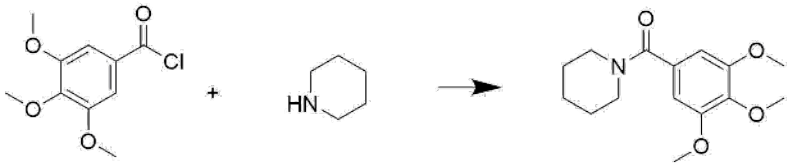
Solution 2



Exercises

Q21.4.1

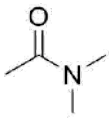
Draw the mechanism for the following reaction

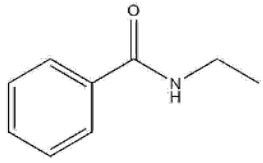


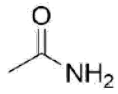
Q21.4.2

Propose a synthesis of the following molecules from an acid chloride and an amide.

(a)

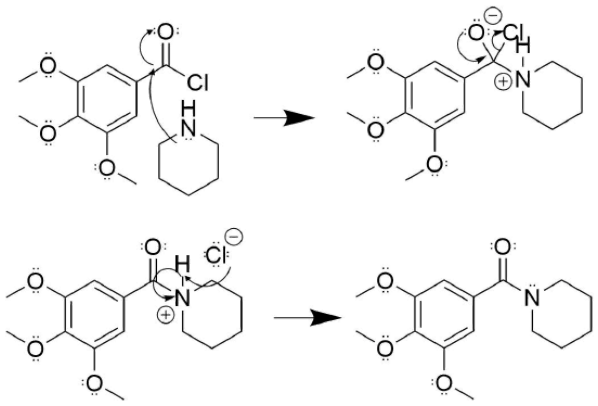


(b) 

(c) 

Solutions

S21.4.1



S21.4.2

a. Acetyl chloride and dimethylamine
b. Benzoyl chloride and ethylamine
c. Acetyl chloride and ammonia

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7.5: Chemistry of Acid Anhydrides

Objectives

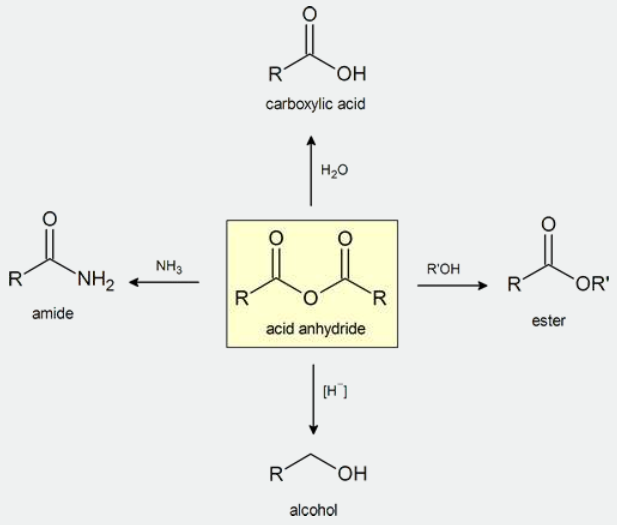
After completing this section, you should be able to

1. write an equation to illustrate the preparation of an acid anhydride from an acid halide and the sodium salt of a carboxylic acid.
2. identify the product formed from the reaction of a given acid halide with the sodium salt of a given carboxylic acid.
3. identify the acid halide, carboxylate salt, or both, required to prepare a given acid anhydride.
4. write an equation to describe the reaction of an acid anhydride with each of the following: water, alcohol, ammonia, a primary or secondary amine, lithium aluminum hydride.
5. identify the product formed when a given acid anhydride is reacted with any of the reagents listed in Objective 4, above.
6. write a detailed mechanism for the reaction of an acid anhydride with any of the reagents listed in Objective 4, above.
7. identify the acid anhydride, the nucleophilic reagent, or both, needed to prepare a specified carboxylic acid, ester, amide, or primary alcohol.

Study Notes

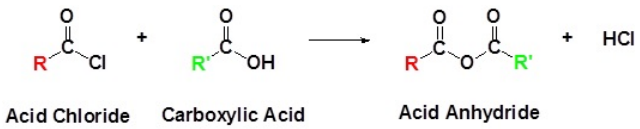
The reactions described in this section are, in principle, identical to those discussed in Section 21.4. Once you have understood the mechanism of nucleophilic acyl substitution, these reactions should not present you with any great difficulty, and memorization can be kept to a minimum.

This figure provides a convenient general summary of a few of the reactions described in Section 21.5. Note that from a synthetic perspective the ester- and amide-forming reactions are the most common, so they are the focus of this section.



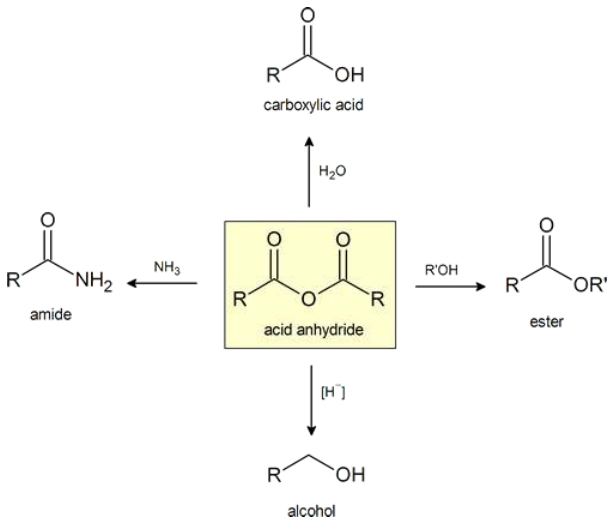
Preparation of Acid Anhydrides

As show in Section 21.4, acid anhydrides are generally made using a nucleophilic acyl substitution reaction of an acid chloride with a carboxylic acid or a carboxylate anion.

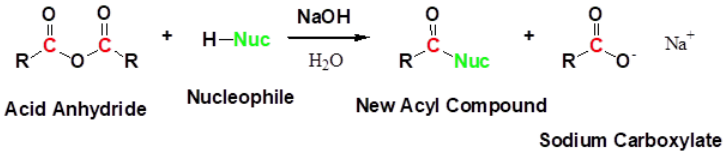


Chemistry of Anhydrides

Anhydrides are highly reactive to nucleophilic attack and undergo many of the same reactions as acid chlorides that were explored in section 21.4. Although slower reacting than acid chlorides, anhydrides react with water to form carboxylic acids, with alcohols to form esters, and with amines to form amides. Anhydrides can also be reduced to 1º alcohols by hydride reduction. Because many anhydrides are made from the coupling of two carboxylic acids, reactions using anyhydrides waste one equivalent of the carboxylic acid as a leaving group. As a consequence, reactions are only commonly performed with inexpensive, readily available anhydrides, such as acetic anhydride or benzoic anhydride. Anydrides have the advantage of being easier to work with than acid chlorides.



Generic Reaction with an Anhydride

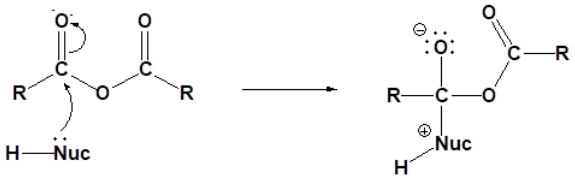


H—NUC = H_2O, NH_3, H_2NR, HNR_2 HOR

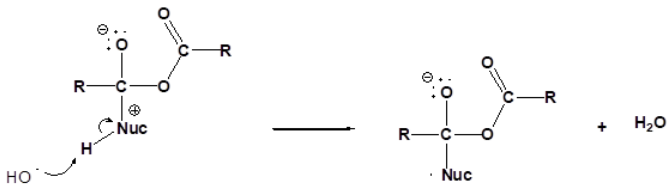
Generic Mechanism of Nucleophilic Acyl Substitution using an Anhydride

The following nucleophilic acyl substitution reactions are all similar and can be represented by one generic mechanism. The nuceophile (water, ammonia, amine, or alcohol) adds to one of the carbonyl carbons in the anhydride forming a tetrahedral alkoxide intermediate. The reforming of the carbonyl C=O bond eliminates a carboxylate leaving group. Because the nucleophile is neutral, a protonated intermediate is formed. A base deprotonates the intermediate to form the neutral carboxylic acid derivative product (carboxylic acid, ester, amide).

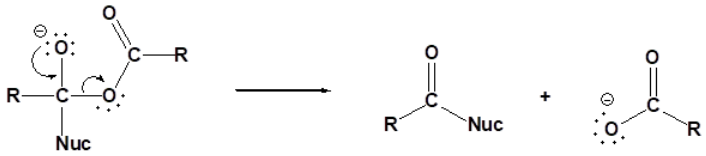
1) Nucleophilic attack



2) Deprotonation

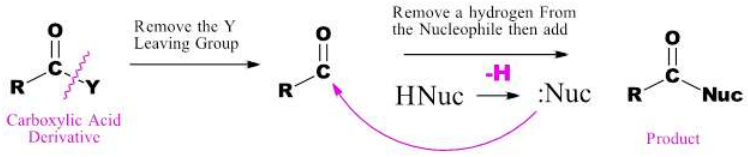


3) Leaving group removal



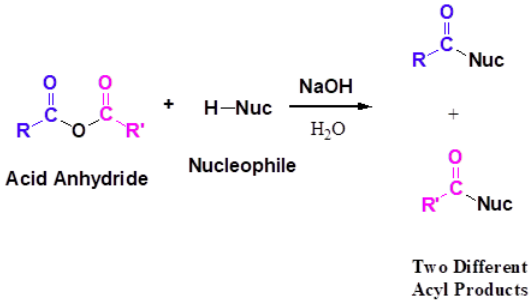
Predicting the Products of an Anhydride Reaction

An anhydride and a neutral nucleophile react to form a new acyl compound through nucleophilic acyl substitution. During this reaction there are three changes in bonding. The leaving group is removed from the anhydride. The neutral nucleophile loses a hydrogen. A C-Nuc bond is formed between the nucleophile and the anhydride's electrophilic carbonyl carbon.



Reactions with Asymmetrical Anhydrides

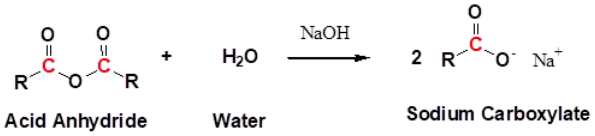
Asymmetrical anhydrides are typically not used in the formation of esters and amides because they have the possibility of forming two different products. This is not the case when symmetrical anhydrides are used.



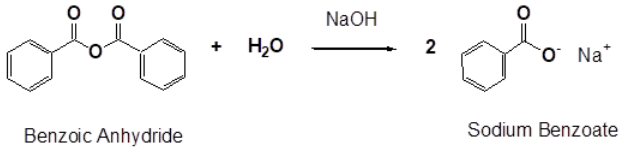
Conversion of Acid Anhydrides to Carboxylic Acids: Hydrolysis

Anhydrides react rapidly with water to form two carboxylic acids compounds. Because anhydrides are often prepared from carboxylic acids this reaction serves little synthetic value. However, this reaction serves as a reminder to prevent the exposure of anhydrides to moisture because they will become contaminated with the corresponding carboxylic acids.

General Reaction



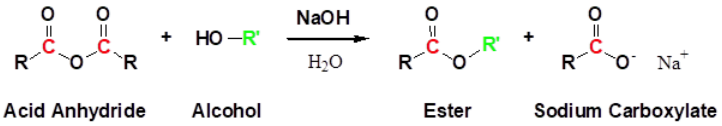
Example



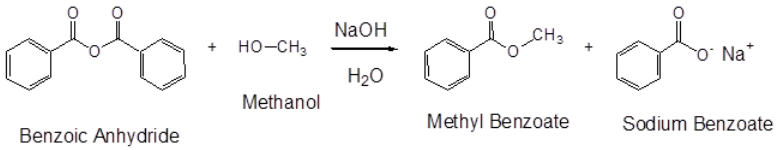
Conversion of Acid Anhydrides to Esters: Alcoholysis

Anhydrides react with alcohols to form esters as the main product and a carboxylate as a side product. The reaction is typically run with a base, such as NaOH or pyridine, to remove any acid produced. Notice that one acyl group from the anhydride is incorporated into the ester and the other acyl group forms a carboxylate.

General Reaction

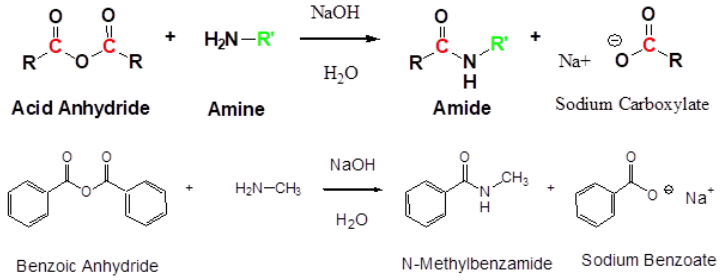


Example



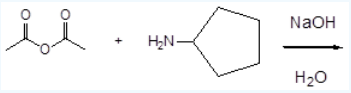
Conversion of Acid Anhydrides to Amides: Aminolysis

Acid anhydrides react with ammonia, 1°, or 2° amines to form the corresponding amides. Two molar equivalents of amine are required. It is important to run this reaction with a base to neutralize the acid produced otherwise the amine reactant would be become protonated to form a non-nucleophilic ammonium compound. During the reaction, one acyl group from the anhydride becomes part of the amide while the other acyl group becomes a carboxylate.



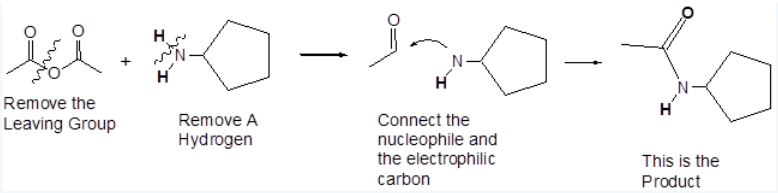
✔ Example 7.5.1

Draw the products of the following reaction:



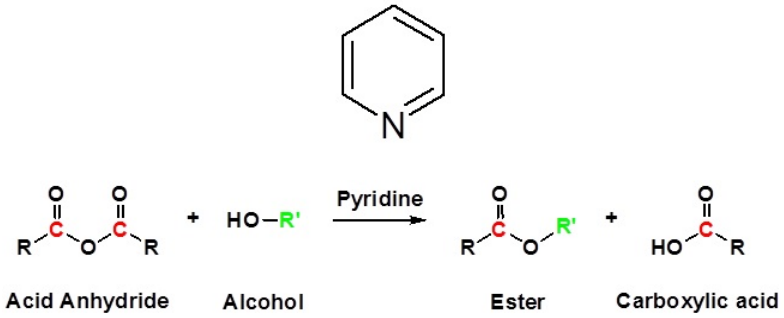
Solution

The reaction of an anhydride and an amine form an amide through nucleophilic acyl substitution. During this reaction three changes in bonding occur. The leaving group is removed from the anhydride. The amine loses a hydrogen. A C-N bond is formed between the amine and the electrophilic carbonyl carbon.

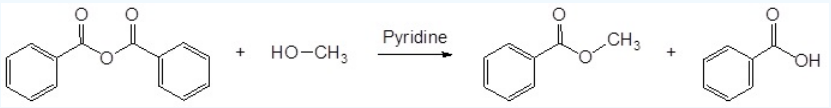


Acid Anhydrides react with alcohols to form esters

Reactions of anhydrides use Pyridine as a solvent

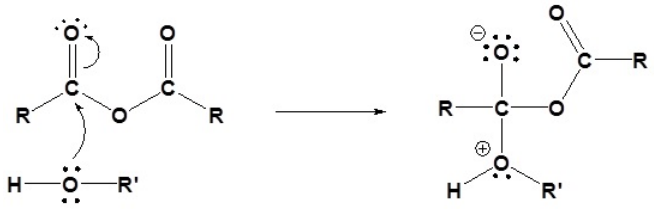


Example 21.5.1

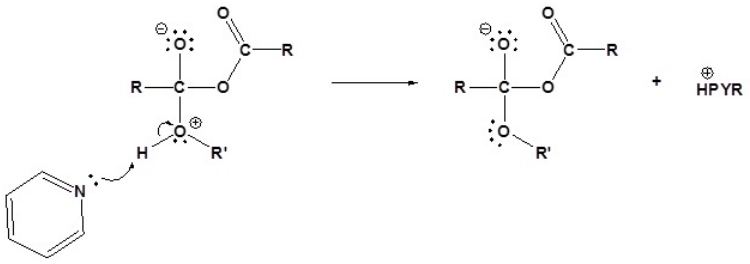


Mechanism

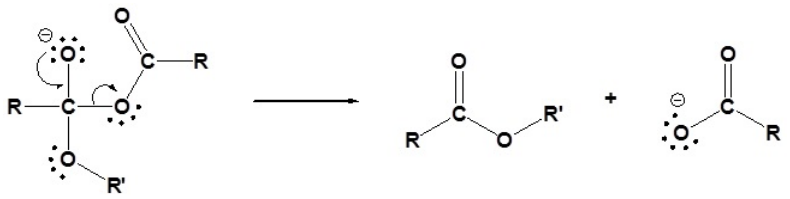
1) Nucleophilic Attack by the Alcohol



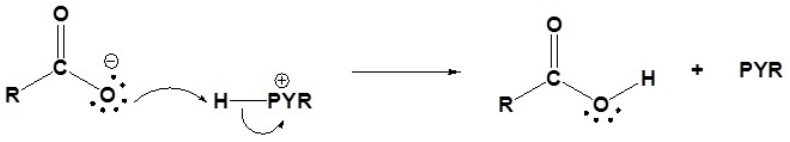
2) Deprotonation by pyridine



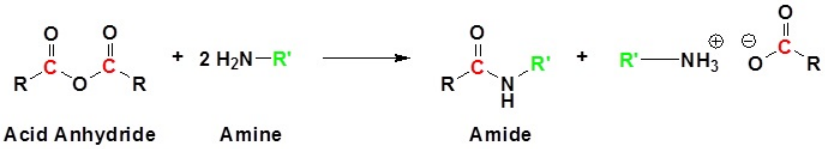
3) Leaving group removal



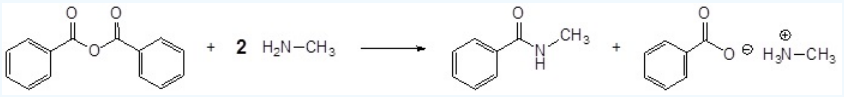
4) Protonation of the carboxylate



Acid Anhydrides react with amines to form amides

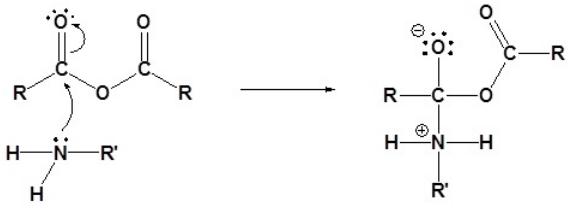


Example 21.5.2

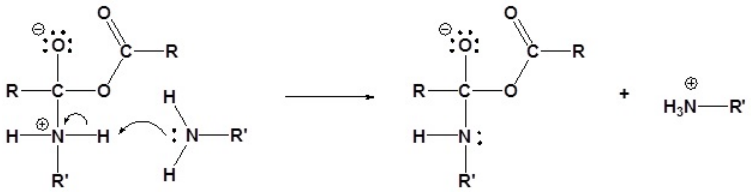


Mechanism

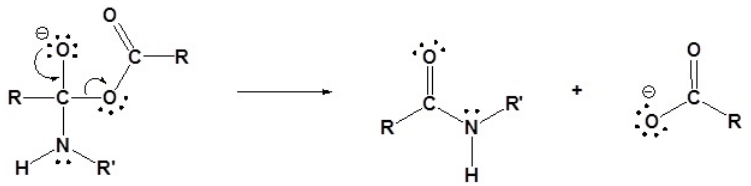
1) Nucleophilic Attack by the Amine



2) Deprotonation by the amine



3) Leaving group removal



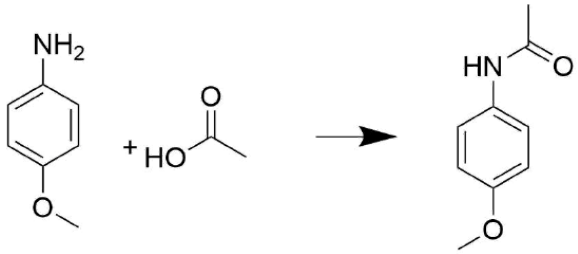
21.5 Chemistry of Acid Anhydrides

21.5 Exercises

Questions

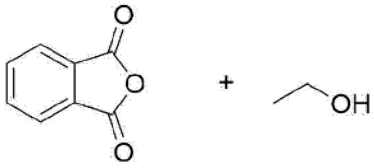
Q21.5.1

Draw out the mechanism for the following reaction.



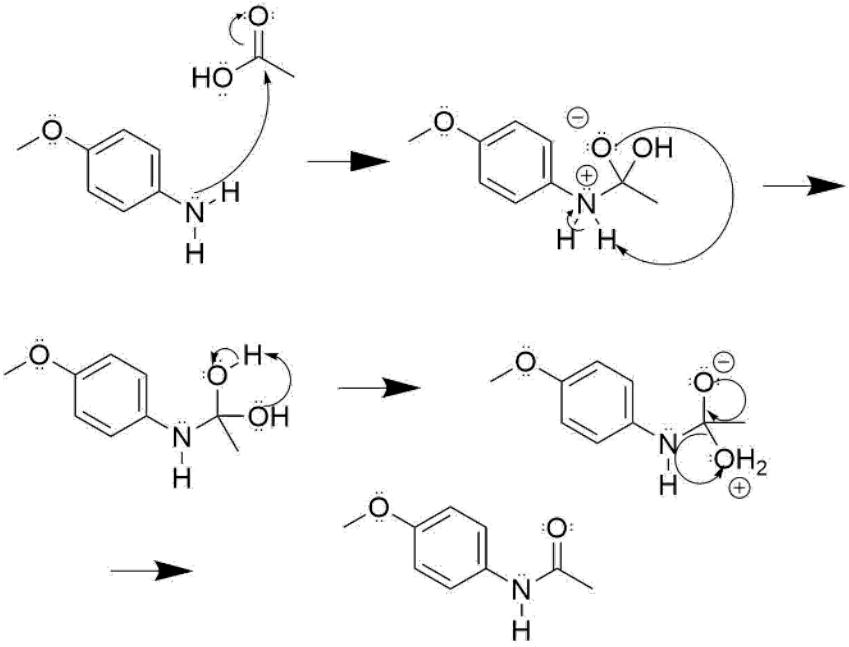
Q21.5.2

Draw the product of the reaction between these two molecules.

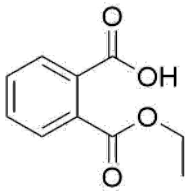


Solutions

S21.5.1



S21.5.1



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7.6: Chemistry of Esters

Objectives

After completing this section, you should be able to

1. discuss the wide occurrence of esters in nature, and their important commercial uses, giving one example of an ester linkage in nature, and one example of a commercially important ester.
2. write an equation to describe the hydrolysis of an ester under acidic or basic conditions.
3. identify the products formed from the hydrolysis of an given ester.
4. identify the reagents that can be used to bring about ester hydrolysis.
5. identify the structure of an unknown ester, given the products of its hydrolysis.
6. write the mechanism of alkaline ester hydrolysis.
7. write the mechanism of acidic ester hydrolysis.
8. write an equation to describe the reduction of an ester with lithium aluminum hydride.
9. identify the product formed from the reduction of a given ester (or lactone) with lithium aluminum hydride.
10. identify the ester, the reagents, or both, that should be used to prepare a given primary alcohol.
11. write a detailed mechanism for the reduction of an ester by lithium aluminum hydride.
12. identify diisobutylaluminum hydride as a reagent for reducing an ester to an aldehyde, and write an equation for such a reaction.
13. write an equation to describe the reaction of an ester with a Grignard reagent.
14. identify the product formed from the reaction of a given ester with a given Grignard reagent.
15. identify the ester, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
16. write a detailed mechanism for the reaction of an ester with a Grignard reagent.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- lactone
- saponification

Study Notes

Many esters have characteristic aromas and flavours. Some examples are listed below.

Basic structure:

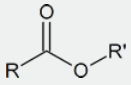
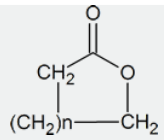


Table 21.1 Structures and characteristic odours of selected esters

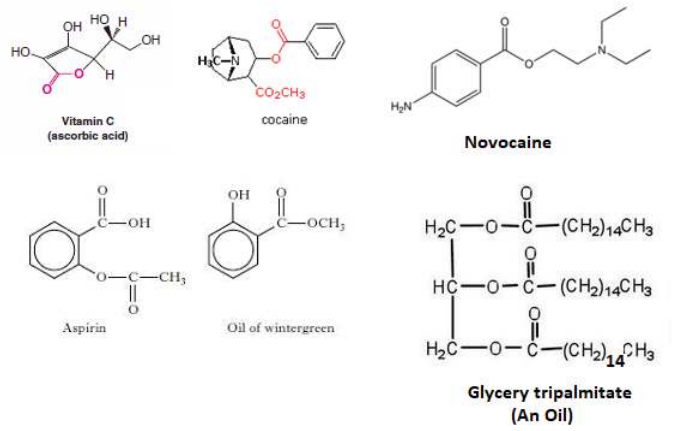
IUPAC name	R	R′	Aroma
octyl ethanoate	CH_3	$CH_3(CH_2)_6CH_2$	orange
propyl ethanoate	CH_3	$CH_3CH_2\ CH_2$	pear
2-methylpropyl propanoate	CH_3CH_2	$(CH_3)_2CHCH_2$	rum
methyl butanoate	$CH_3CH_2CH_2$	CH_3	apple
ethyl butanoate	$CH_3CH_2CH_2$	CH_3CH_2	pineapple

A “lactone” is a cyclic ester and has the general structure

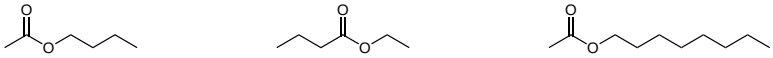


By recognizing that the steps in the acidic hydrolysis of an ester are exactly the same as those in a Fischer esterification (but in the reverse order!), you can again minimize the amount of memorization that you must undertake. The details of both mechanisms can be deduced from the knowledge that both reactions are acid-catalyzed nucleophilic acyl substitutions.

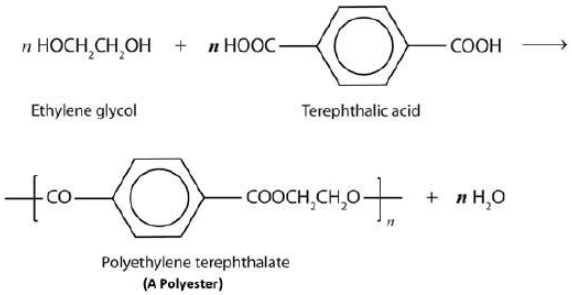
Esters are present in a many biologically important molecules, which have a wide range of effects including fats, waxes, Vitamin C, Cocaine, Novacaine, oil of wintergreen, and aspirin.



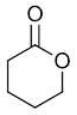
Esters compounds are often the source of the pleasant aromas of many fruits.



Esters are also present in a number of important commercial and synthetic application. For example, polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers. PET is used to make bottles for water and other beverages. It is also formed into films called Mylar which is used in balloons. Synthetic arteries can be made from PET, polytetrafluoroethylene (PTFE), and other polymers.



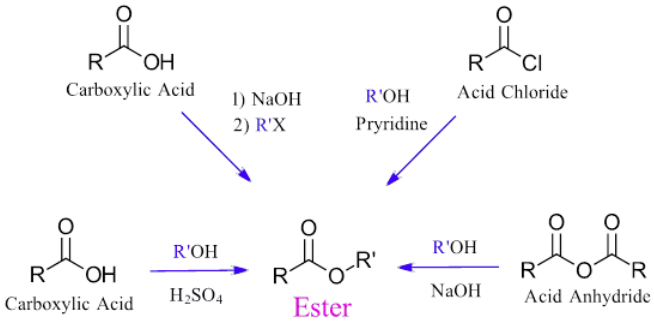
Lactones, cyclic esters, have similar reactivity as acyclic esters.



Lactone
(Cyclic Ester)

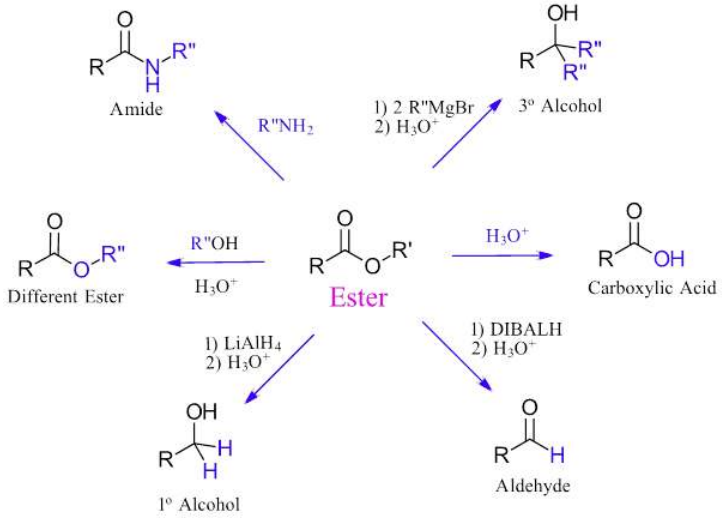
Preparation of Esters

The most versatile method for the preparations of esters is the nucleophilic acyl substitution of of an acid chloride with an alcohol. Acid ahydrides and carboxylic acids can also react with alcohols to form esters but both reactions are limited to formation of simple esters. Esters can also be formed by deprotonating a carboxylic acid to form a carboxylate and then reacting it with a primary alkyl halide using an S_N2 reaction.



Reactions of Esters

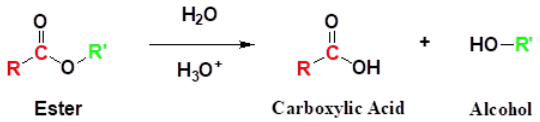
Esters are one of the more useful functional groups. Their low reactivity makes the easy to work with and they are stable enough to be used as a solvent in organic reactions (ex. ethyl acetate). Esters are still reactive enough to undergo hydrolysis to form carboxylic acids, alcoholysis, to form different esters, and aminolysis to form amides. Also, they can react with Grignard reagents to form 3° alcohols and hydride reagents to form 1° alcohols or aldehydes.



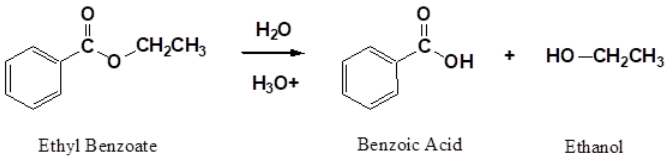
Conversion of Esters to Carboxylic Acids: Hydrolysis

Esters can be cleaved back into a carboxylic acid and an alcohol through reaction with water and a catalytic amount of strong acid. This reaction represents the reverse of the acid catalyzed esterification of a carboxylic acid and an alcohol discussed in Section 21.3. Both the ester formation and cleavage reactions are part of an equilibrium which can be manipulated using Le Chatelier's principle. For ester hydrolysis, the equilibrium is shifted toward carboxylic acid formation by using a large excess of water in the reaction.

General Reaction



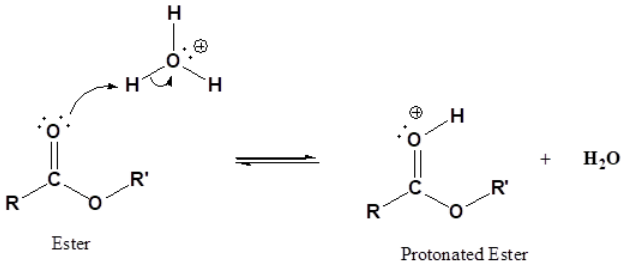
Example



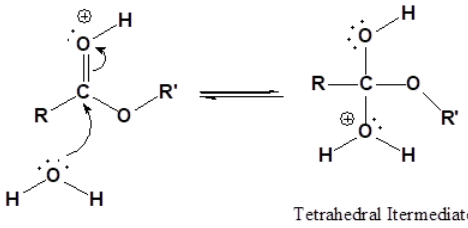
Mechanism

Acid catalysis is required during ester hydrolysis due to water being a weak nucleophile. Protonation of the ester carbonyl increases the partial positive charge on the carbonyl carbon increasing its electrophilicity. After protonation, water adds to the carbonyl carbon causing the formation of a tetrahedral alkoxide intermediate. Then a proton transfers to the –OR group, increasing its ability to act as a leaving group. Reforming the carbonyl double bond causes the elimination of an alcohol (HOR) as a leaving group, creating a protonated carboxylic acid. In the last step of the mechanism, water acts as a base, removing a hydrogen, to form a carboxylic acid and regenerating the acid catalyst.

1) Protonation of the carbonyl



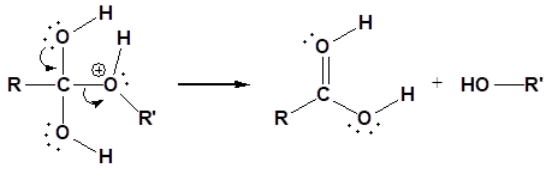
2) Nucleophilic attack by water



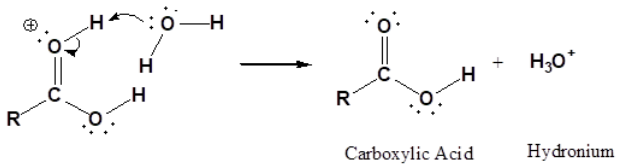
3) Proton transfer



4) Leaving group removal

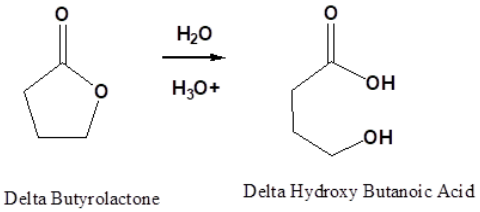


5) Deprotonation



Hydrolysis of Lactones

Lactones (Cyclic esters) undergo typical reactions of esters including hydrolysis. Hydrolysis of the lactone under acidic conditions creates a hydroxyacid.

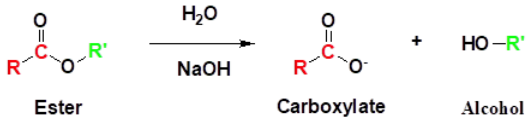


Conversion of Esters to Carboxylic Acids: Saponification

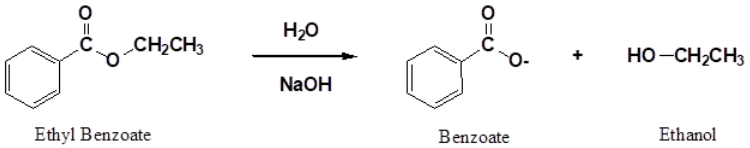
Esters can also be cleaved into a carboxylate and an alcohol through reaction with water and a base. The reaction is commonly called a saponification from the Latin sapo which means soap. This name comes from the fact that soap used to me made by the ester hydrolysis of fats.

Saponification reaction utilize a better nucleophile (hydroxide) and are typically faster than an acid catalyzed hydrolysis. The carboxylation ions produced by saponification are negatively charged and very unreactive toward further nucleophilic substitution which makes the reaction irreversible.

General Reaction



Example

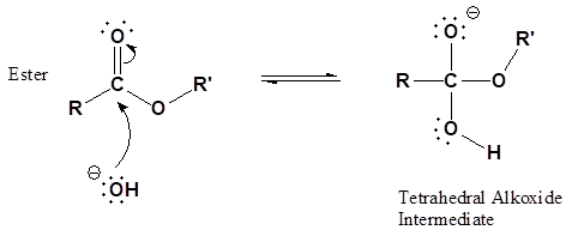


Mechanism

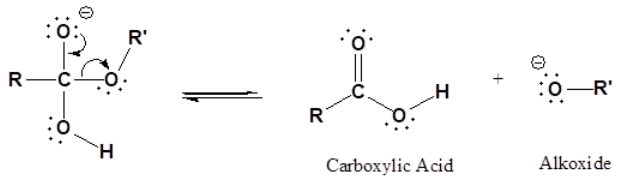
The base-promoted hydrolysis of an ester follows the typical nucleophilic acyl substitution mechanism. A full equivalent of hydroxide anion is used, so the reaction is called base-promoted and not base catalyzed. The mechanism of ester saponification begins with the nucleophilic addition of a hydroxide ion at the carbonyl carbon to give a tetrahedral alkoxide intermediate. The carbonyl bond is reformed along with the elimination of an alkoxide (-OR) leaving group yielding a carboxylic acid. The alkoxide base deprotonates the carboxylic acid to for a carboxylate salt and an alcohol as products.

The last deprotonation step essentially removes the carboxylic acid from the equilibrium which drives the saponification towards completion. Because the carboxylic acid is no longer part of the equilibrium the reaction is effectively irreversible.

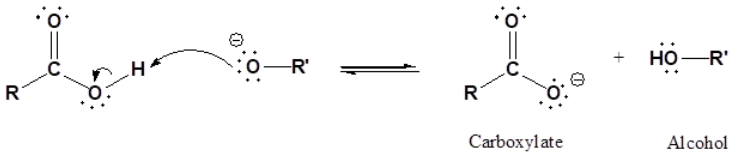
1) Nucleophilic attack by hydroxide



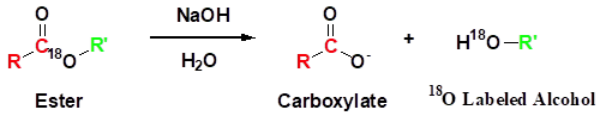
2) Leaving group removal



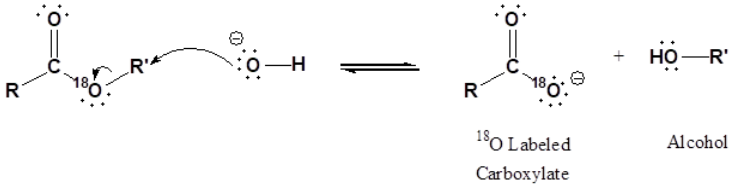
3) Deprotonation



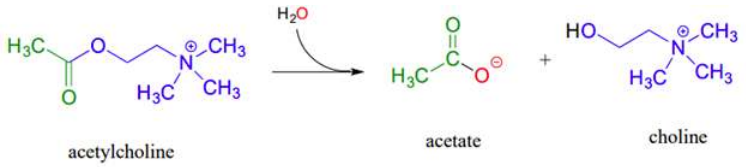
This mechanism is supported by experiments performed using isotopically labeled esters. When the ether-type oxygen of the ester was labeled with ^{18}O, the labeled oxygen showed up in the alcohol product after hydrolysis.



An alternative mechanism would be if the hydroxide participated in an S_N2 reaction to create the carboxylate product. If this were to happen the alcohol reaction product would not contain the labeled oxygen.



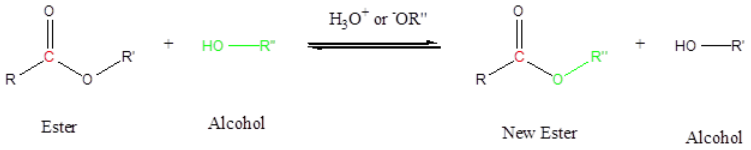
Ester saponification in biological systems, called hydrolytic acyl substitution reactions, are common. In particular, acetylcholinesterase, an enzyme present in the synapse, catalyzes hydrolysis of the ester group in acetylcholine which is a neurotransmitter that triggers muscle contraction. Like many other hydrolytic enzymes, the acetylcholinesterase reaction proceeds in two phases: first, a covalent enzyme-substrate intermediate is formed when the acyl group of acetylcholine is transferred to an active-site serine on the enzyme (a transesterification reaction). A water nucleophile then attacks this ester, driving off acetate and completing the hydrolysis



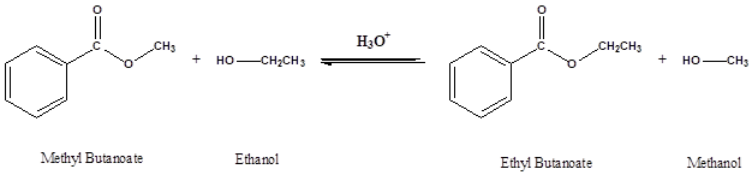
Conversion of Esters to Different Esters: Transesterification

Transesterification is a reaction where an ester is converted to a different ester through reaction with an alcohol. Because there is typically very little difference in stability between both esters, the equilibrium constant of this reaction is usually near one. Using a large excess of the reactant alcohol or removing the alcohol side-product can push the reaction equilibrium towards the products by Le Chatelier's principal. Transesterifications also shows that great care should be taken when an ester containing compound is used in a reaction involving an alcohol.

General Reaction



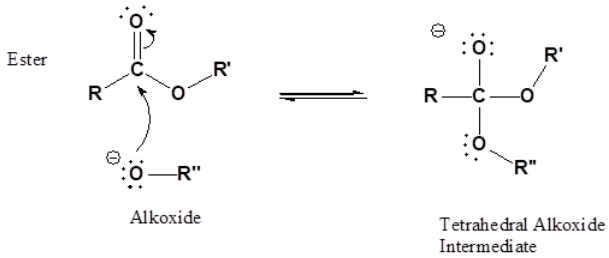
Example



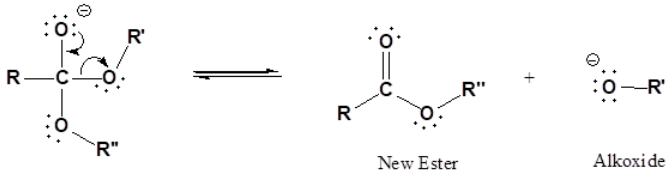
Mechanism in Basic Conditions

The reaction follows the basic mechanism of a nucleophilic acyl substitution. The alkoxide leaving group of the ester is replace by an incoming alkoxide nucleophile creating a different ester.

1) Nucleophilic attack by an alkoxide



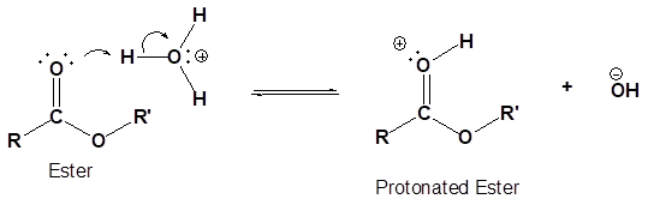
2) Leaving group removal



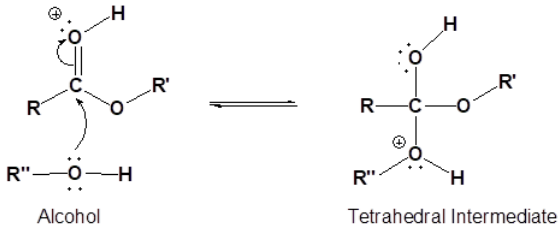
Mechanism in Acidic Conditions

Protonation allows the alcohol reactant to add to the ester carbonyl. Proton transfer to the ester's alkoxy group increases it ability to act as a leaving group. Reforming the C=O carbonyl bond removes the leaving group and subsequent deprotonation by water forms the ester product.

1) Protonation of the carbonyl



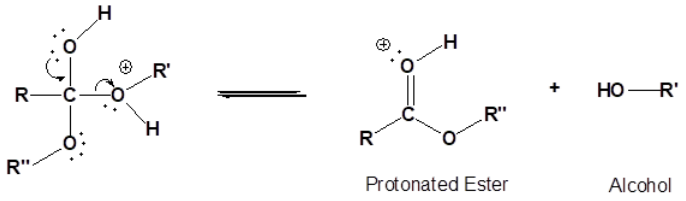
2) Nucleophilic attack on the carbonyl



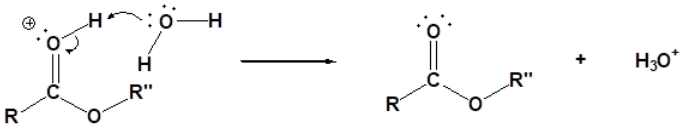
3) Proton transfer



4) Removal of the leaving group

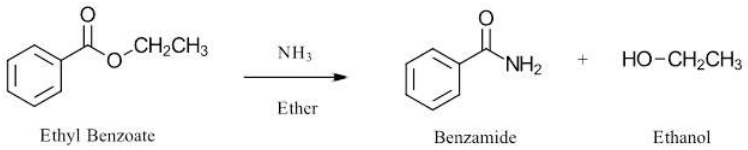


5) Deprotonation



Conversion of Ester to Amides: Aminolysis

It is possible to convert esters to amides through direct reaction with ammonia or amines. However, these reactions are not commonly used because the formation of an amide using an acid chloride is a much simpler reaction.

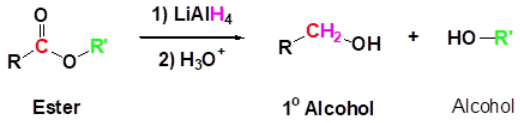


Conversion of Esters to 1° Alcohols: Hydride Reduction

Esters can undergo hydride reduction with $LiAlH_4$ to form two alcohols. The alcohol derived from the acyl group of the ester will be 1° and is typically considered the main product of the reaction. The other alcohol is derived from the ester's alkoxy group and is typically considered a side-product of the reaction. Note! Sodium borohydride ($NaBH_4$) is not a reactive enough hydride agent to

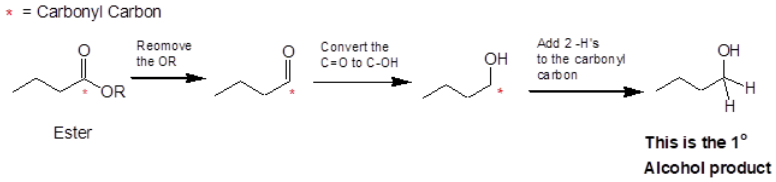
reduce esters or carboxylic acids. In fact, $NaBH_4$ can selectively reduce aldehydes and ketones in the presence of ester functional groups.

General Reaction

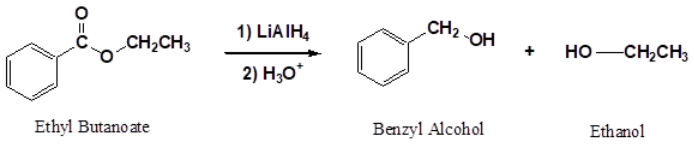


Predicting the Products of a Hydride Reduction

There are three major changes in bonding during this reaction: 1) The –OR leaving group is removed from the ester. 2) The C=O carbonyl bond is converted to a C-O-H, an alcohol. 3) Two C-H bonds are formed as two of the hydride nucleophiles are added to the original carbonyl carbon of the ester.



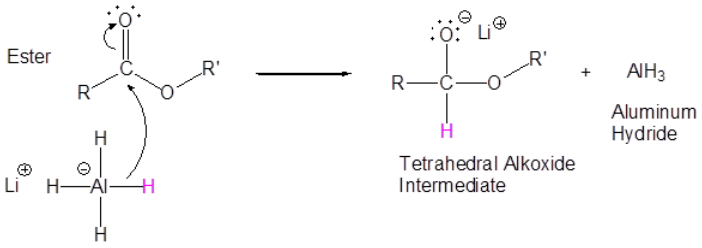
Example



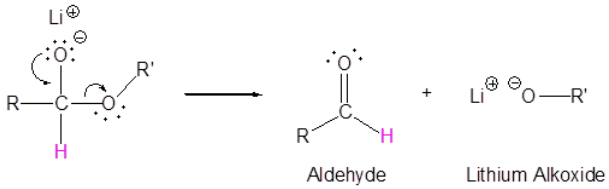
Mechanism

The mechanisms for the hydride reduction of esters is analogous to the hydride reduction of carboxylic acids. Nucleophilic acyl substitution replaces the –OR leaving group in ester with a hydride nucleophile to form an aldehyde intermediate. Because aldehydes are more reactive than esters, they rapidly undergo a second nucleophilic hydride addition to form a tetrahedral alkoxide intermediate. An acid work-up protonates the alkoxide to create a 1° alcohol.

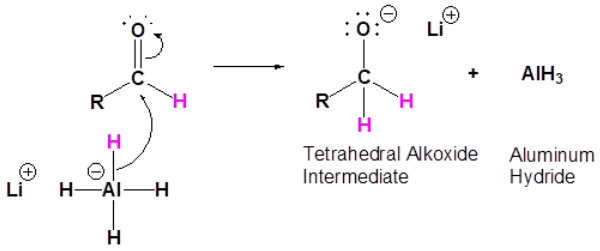
1) Nucleophilic attack by the hydride



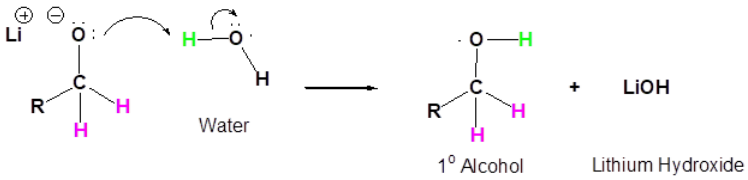
2) Leaving Group Removal



3) Nucleopilic attack by the hydride anion



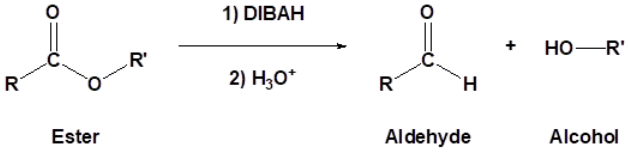
4) The alkoxide is protonated



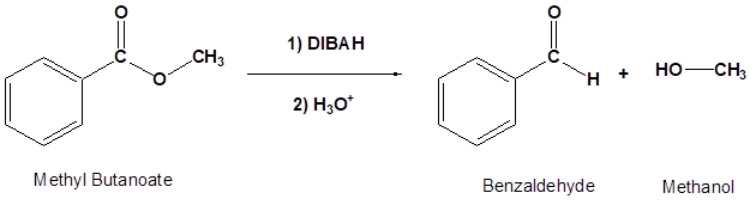
Conversion of Esters to Aldehydes: Hydride Reduction

Much like acid chlorides, esters can be converted to aldehydes using the weaker reducing reagent diisobutylaluminum hydride (DIBALH). As shown above, an aldehyde intermediate is produced after an ester undergoes nucleophilic acyl substitution with a hydride. When DIBALH is used as the hydride source, the aldehyde does not react further and is isolated as the product of the reaction. The reaction is usually carried out at -78 ^{o}C to help isolate the aldehyde product.

General Reaction



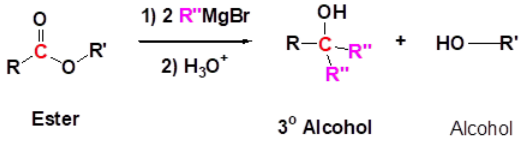
Example



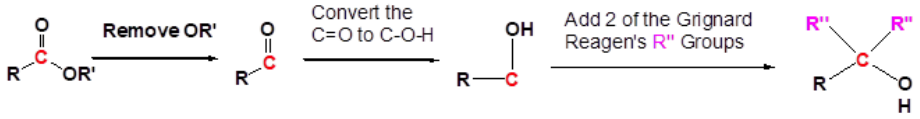
Conversion of Esters to 3° Alcohols: Grignard Reagents

Addition of Grignard reagents converts esters to two alcohols, one 3° alcohols (main product) and one 1° alcohol (considered a side product). The Grignard reagent adds to the ester twice, once during a nucleophilic acyl substitution to form a ketone intermediate then again during a nucleophilic addition to form the 3° alcohol product. Overall, during this reaction two C-C bonds are formed on the ester's original carbonyl carbon.

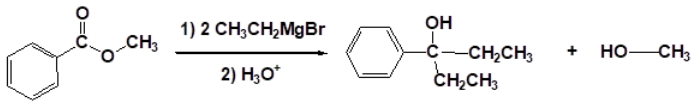
General Reaction



Predicting the Products of a Grignard Reaction



Example

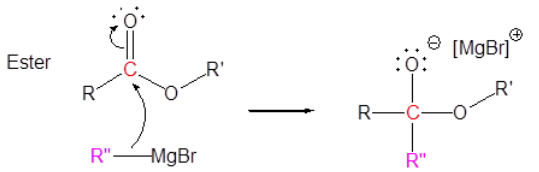


Methyl Benzoate | 3-Phenyl-3-Pentanol | Methanol

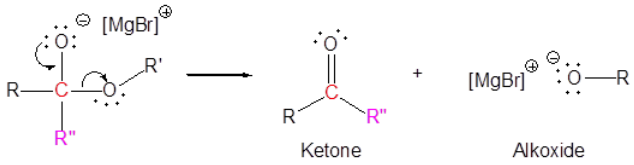
Mechanism

In the first two steps of the mechanism, the OR leaving group from the ester is replaced by the R group from the Grignard reagent through a nucleophilic acyl substitution. This forms a ketone intermediate which is not isolated because ketones, which are more reactive than esters, rapidly undergo nucleophilic addition with a second equivalent of the Grignard reagent to form an alkoxide intermediate. An acid work-up protonates the alkoxide to form the 3º alcohol product.

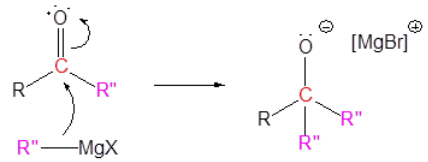
1) Nucleophilic Attack



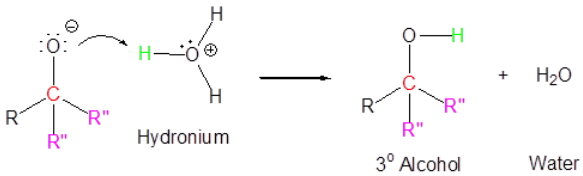
2) Leaving group removal



3) Nucleophilic attack

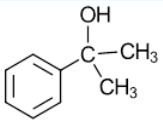


4) Protonation



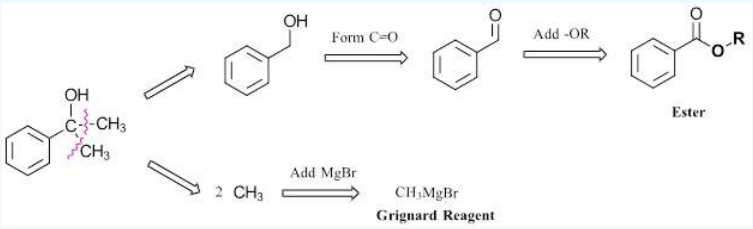
Example 7.6.1

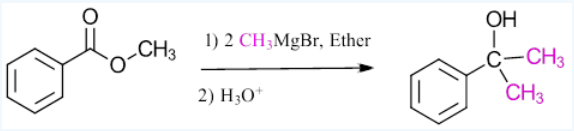
How could the following molecule be made using a Grignard reagent and an ester?



Solution

The key bond breaks for this example are two C-C sigma bonds between the carbonyl carbon and two alpha carbons. Reactions with esters involve a double addition of the Grignard reagent so the fragments removed must be the same. In this example, the C-C bonds involving the two methyl groups are broken. Breaking these bonds separate the target molecule into the required starting materials. The fragment which contains the alcohol carbon forms a C=O carbonyl bond and gains an –OR to become an ester. The R group of the ester is largely unimportant to the overall reaction and is typically a methyl or ethyl group. The alkyl fragments gain MgBr to form a Grignard reagent. Remember that the Grignard reagent only contains one alkyl fragment.

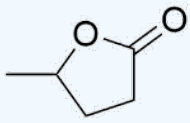




Exercises 7.6.1

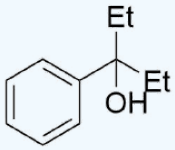
1) Why is the alkaline hydrolysis of an ester not a reversible process? Why doesn't the reaction with a hydroxide ion and a carboxylic acid produce an ester?

2) Draw the product of the reaction between the following molecule and $LiAlH_4$, and the product of the reaction between the following molecule and DIBAL.

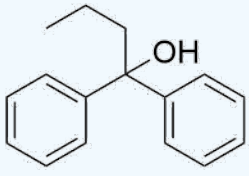


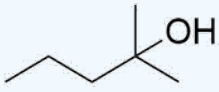
3) How might you Prepare the following molecules from esters and Grignard reagents?

(a)



(b)

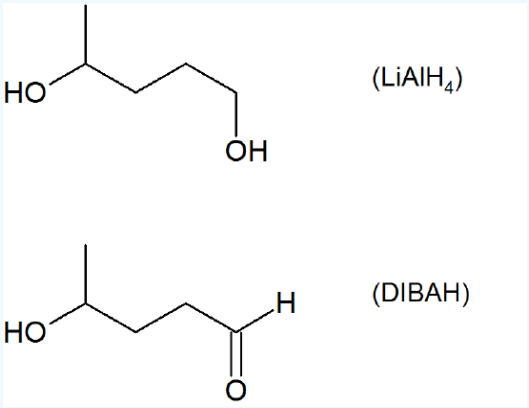


(c) 

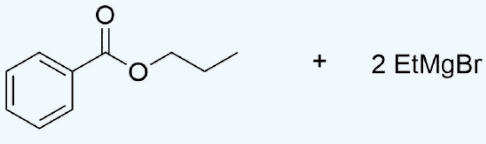
Answers

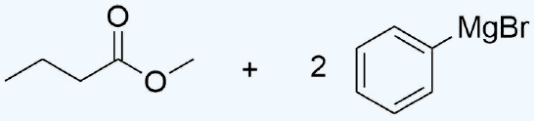
1) The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

2)



3)

(a) 

(b) 

(c)

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7.7: Chemistry of Amides

Objectives

After completing this section, you should be able to

1. write an equation to describe the preparation of an amide from an acid chloride.
2. identify the amide linkage as the basic unit from which all proteins are made, and hence recognize the importance of the amide linkage to biologists and biochemists.
3. write detailed mechanisms for the acidic and basic hydrolysis of amides.
4. write an equation to describe the reduction of an amide to an amine.
5. write a detailed mechanism for the reduction of an amide to an amine.
6. identify the product formed when a given amide is reduced with lithium aluminum hydride.
7. identify the amide, the reagents, or both, necessary to prepare a given amine by direct reduction.
8. identify lactams as being cyclic amides which undergo hydrolysis and reduction in a manner analogous to that of their acyclic counterparts.

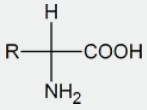
Key Terms

Make certain that you can define, and use in context, the key term below.

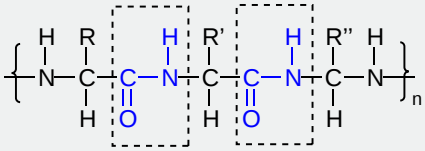
- lactam

Study Notes

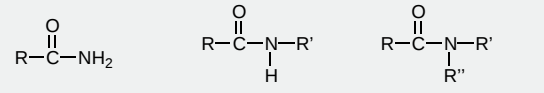
When we talk about amino acids, we are generally referring to α-amino acids; that is, compounds in which an amino (NH_2) group and a carboxyl group are attached to the same carbon atom:



Notice that such compounds contain a chiral carbon atom (unless R = H, which is glycine). Proteins can be considered to consist of amino acid residues joined by amide (or peptide) links. These peptide links consist of exactly the same structural units that we find in *N*-substituted primary amides.

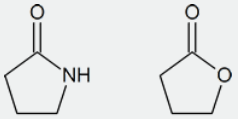


peptide (amide) links



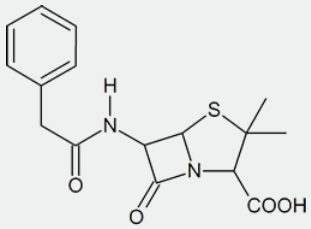
primary amide | *N*—substituted primary amide | *N*, *N*—disubstituted primary amide

A lactam is a cyclic amide, in the same way that a lactone is a cyclic ester:



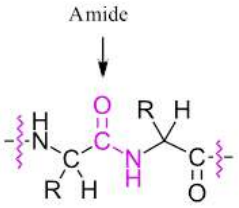
a lactam | a lactone

Among the most important molecules that contain lactam rings are the penicillins:



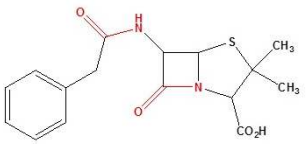
penicillin G (benzylpenicillin)

The amide functional group is extremely important for biological molecules because amides make up the backbone of proteins. Proteins are actually polymers of amino acids, linked by amide groups known as peptide bonds. Proteins (polymers of ~40 amino acids or more) and peptides (shorter polymers) are formed when the amino group of one amino acid monomer reacts with the carboxylate carbon of another amino acid to form an amide linkage, which in protein terminology is a **peptide bond**. The individual amino acids within a peptide or protein are called **amino acid residues**.

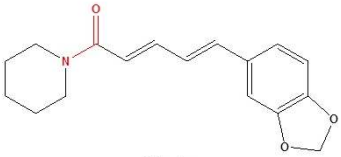


Protein Backbone

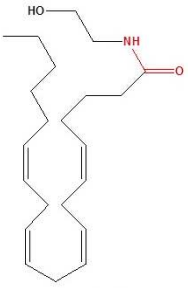
Compounds containing amides have a wide range of biological activity and include penicillin G an antibiotic, piperine which is responsible for the pungent flavor of black pepper, and anandamide which provides some of the pleasurable sensations gained from eating chocolate.



Penicillin G
(An Antibiotic)



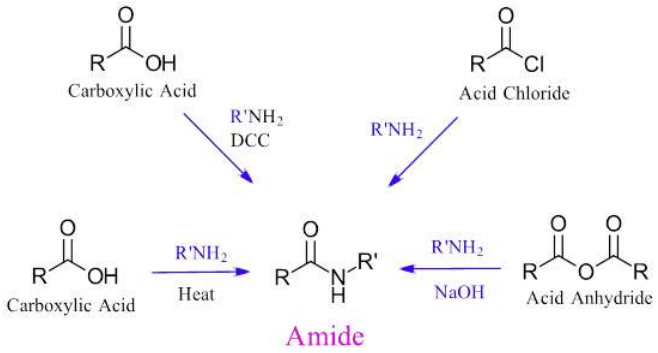
Piperine
(From Black Pepper)



Anandamide
(From Chocolate)

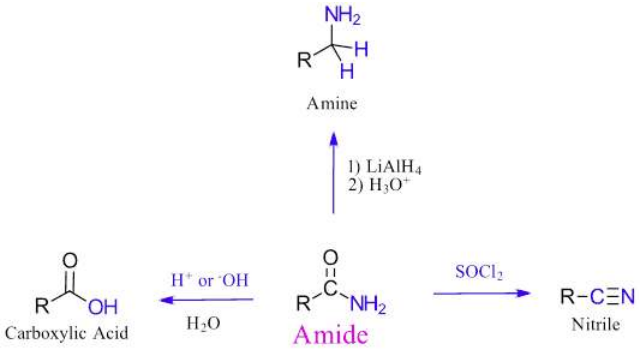
Preparation of Amides

Amides are most commonly prepared though the reaction of an acid chloride with ammonia, a 1° amine, or 2° amine. In an analogous reaction, an amide can be prepared through the reaction of a carboxylic acid and an amine using a coupling agent such as DCC. Simple amides can be prepared by reacting an acid anhydride with an amine. Lastly, amides can be formed through the direct reaction of a carboxylic acid and an amine. However, this reaction is rarely used because the conditions are relatively severe.



Reactions of Amides

Amides are relatively unreactive towards nucleophilic acyl substitutions due to the poor leaving group ability of its nitrogen containing Y group. Despite this, amides can react with water under acidic or basic conditions to create a carboxylic acid through nucleophilic acyl substitution. Reaction of primary amides with thionyl chloride ($SOCl_2$) creates nitriles. Hydride reduction using $LiAlH_4$ causes the carbonyl oxygen of the amide to eliminate as a leaving group creating the corresponding amine.



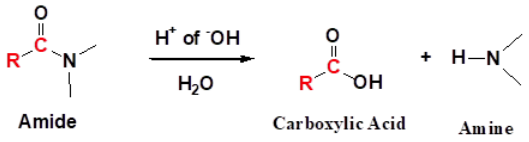
Lactams, cyclic amides, are affected by these reactions in the same fashion as acyclic amides.



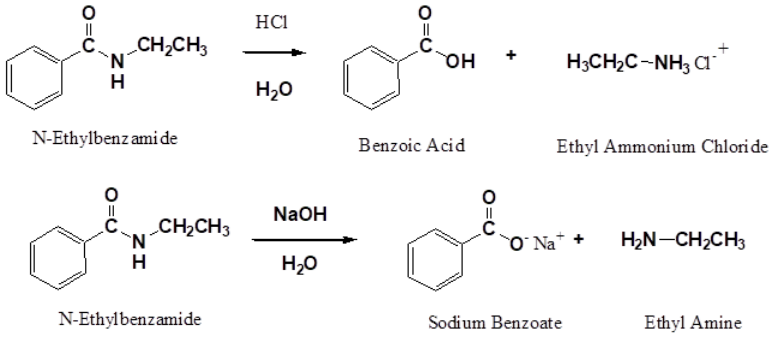
Conversion of Amides to Carboxylic Acids: Hydrolysis

Amides can be hydrolyzed into a carboxylic acid and ammonia or an amine by heating in an acidic or basic aqueous solution. In both cases, acid-base reactions occurring with the products make the overall reaction irreversible. Under acidic conditions the amine produced by the reaction is protonated to form a non-nucleophilic ammonium compound. Under basic conditions the carboxylic acid produced by the reaction is deprotonated to a non-electrophilic carboxylate.

General Reaction



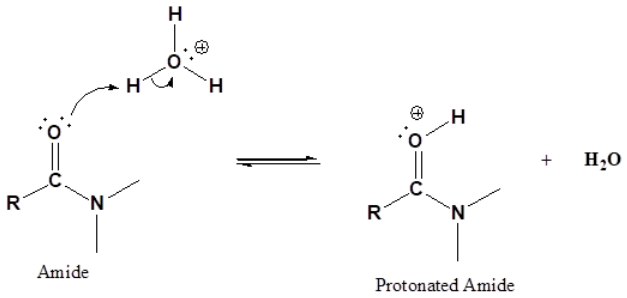
Examples



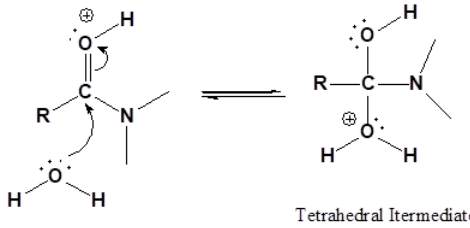
Mechanism Under Acidic Conditions

Protonation of the amide increases the electrophilicity of the carbonyl carbon allowing water to add causing formation of a tetrahedral oxonium intermediate. Next a proton is transferred to the amide nitrogen giving it a positive charge and increasing its ability to act as a leaving group. Reforming the carbonyl double bond causes the elimination of an amine as a leaving group, creating a protonated carboxylic acid. In the last step of the mechanism, the produced amine acts as a base, removing a hydrogen, to form a carboxylic acid and an ammonium compound. This final deprotonation step essentially removes the amine from the equilibrium which drives the reaction towards completion. Since the amine is no longer part of the equilibrium, the reaction is effectively irreversible.

1) Protonation of the carbonyl



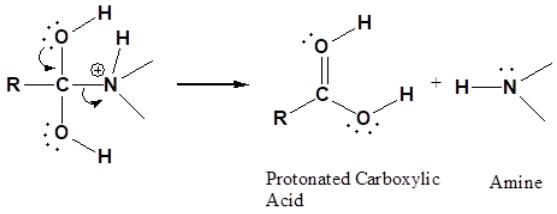
2) Nucleophilic attack by water



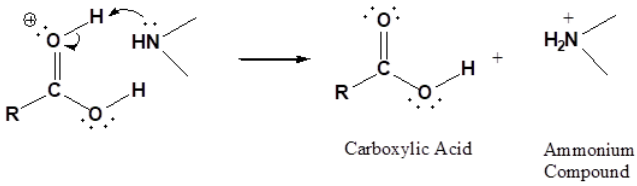
3) Proton transfer



4) Leaving group removal



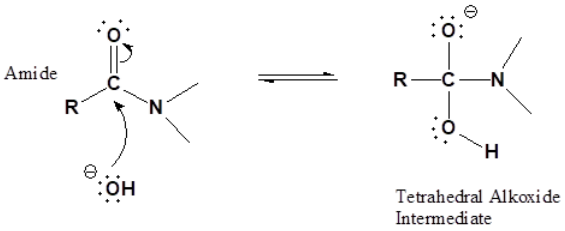
5) Deprotonation



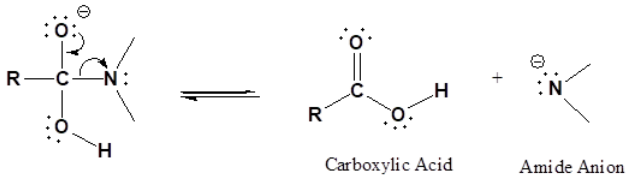
Mechanism Under Basic Conditions

The base-promoted hydrolysis of an amide follows the typical nucleophilic acyl substitution mechanism. A full equivalent of hydroxide anion is used, so the reaction is called base-promoted and not base catalyzed. The mechanism of basic amide hydrolysis begins with the nucleophilic addition of a hydroxide ion at the carbonyl carbon creating a tetrahedral alkoxide intermediate. The carbonyl bond is reformed along with the elimination of an amide ion (-NHR) leaving group (note this is a different use of the word amide meaning an amine anion), forming a carboxylic acid. In the last step, the amide ion deprotonates the carboxylic acid to form a carboxylate salt and an amine as products. This final deprotonation step essentially removes the carboxylic acid from the equilibrium which drives the reaction towards completion. Since the carboxylic acid is no longer part of the equilibrium, the reaction is effectively irreversible.

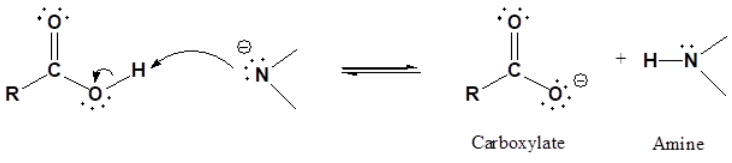
1) Nucleophilic attack by hydroxide



2) Leaving group removal



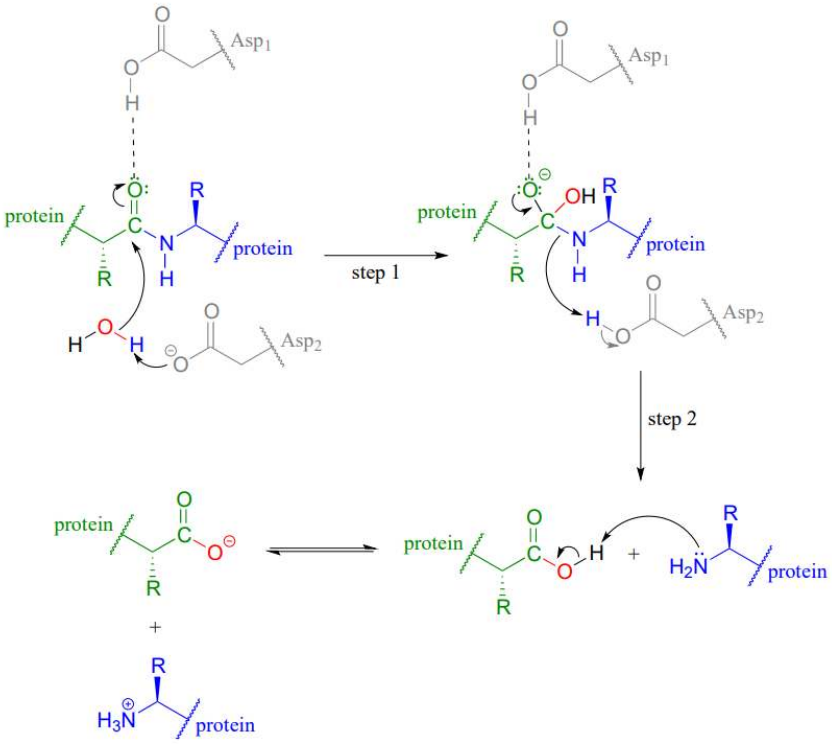
3) Deprotonation



Hydrolysis of Proteins

Hydrolysis of amide bonds is the first step in the metabolism of dietary proteins. Protein hydrolysis is catalyzed by protease enzymes (abbreviated Asp_1 and Asp_2 in the figure below). The mechanisms starts with the nucleophilic acyl substitution by water

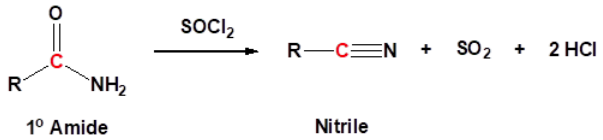
while breaking the amide C-N bond. This produces a protein fragment with an amine and another with a carboxylic acid. The amine fragment will deprotonate the carboxylic acid forming the carboxylate and ammonium fragments.

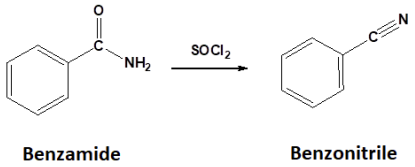


Conversion of 1º Amides to Nitriles: Dehydration

1º Amides can be converted into a nitrile through reaction with thionyl chloride ($SOCl_2$). Sulfurdioxide (SO_2) and hydrochloric acid are produced as byproducts.

General Reaction

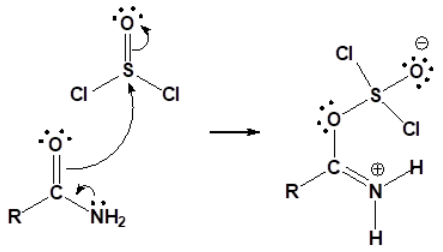




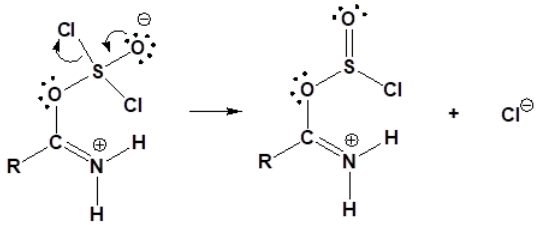
Mechanism for the Conversion of a 1º Amide to a Nitrile

During the first step of the mechanism, the amide acts as a nucleophile and attacks the electrophilic sulfur of thionyl chloride, pushing the pi electrons of the S=O bond onto oxygen. Removal of a chloride anion as a leaving group allows the sulfoxide S=O bond to reform creating a protonated imine chlorosulfite. Deprotonation forms an imine chlorosulfite intermediate. A second deprotonation eliminates the chlorosulfite leaving group as sulfur dioxide and a chloride anion and forms the C-N triple bond of the nitrile product.

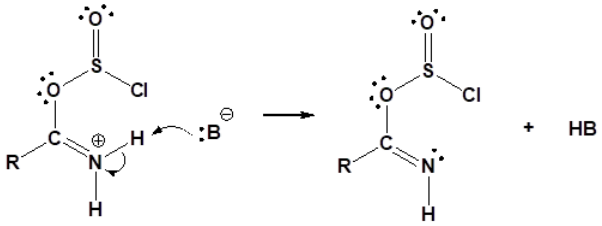
1) Nucleophilic attach on thionyl chloride



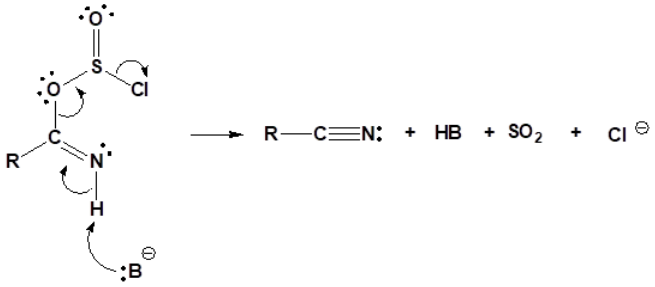
2) Leaving group removal



3) Deprotonation



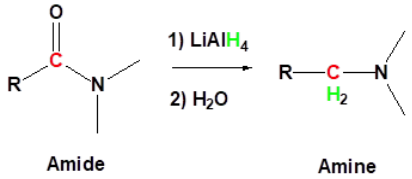
4) Leaving group removal



Conversion of Amides to 1°, 2° or 3° Amines: Hydride Reduction

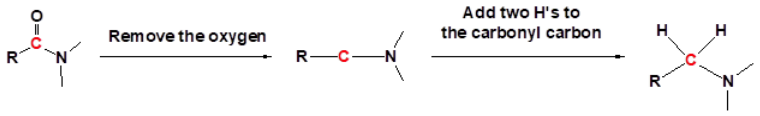
Amides are reduced to amines by treatment with $LiAlH_4$, and this has proven to be one of the most general methods for preparing all classes of amines (1º, 2º & 3º). Due to the nitrogen in the Y group of amides, the outcome of $LiAlH_4$ reductions is distinctly different than for esters since amide anions are poorer leaving groups than alkoxide anions. Furthermore, oxygen forms especially strong bonds to aluminum. During this reaction the carbonyl oxygen of the amide is removed as a leaving group and not the nitrogen containing Y group. Removal of the leaving group allows for a formation of a C=N iminium bond which can accept a second addition of a hydride nucleophile to form the amine.

General Reaction

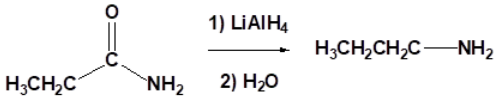


Predicting the Products of a Hydride Reduction

There are two major changes in bonding during this reaction: 1) The C=O carbonyl is removed from the starting material 2) Two hydride nucleophiles are added to what was the carbonyl carbon of the amide.

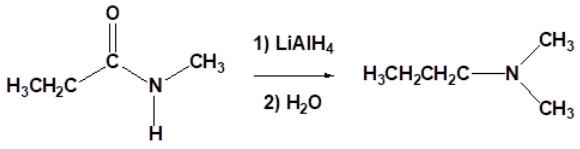


Example

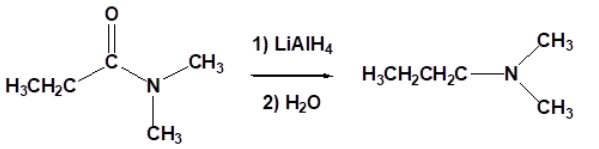


Propanamide — Propyl Amine

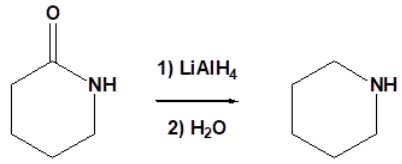
Alkyl groups attached to the nitrogen do not affect the reaction.



N-Methylpropanamide — N-Methylpropylamine



N,N-Dimethylpropanamide — N,N-Dimethylpropylamine

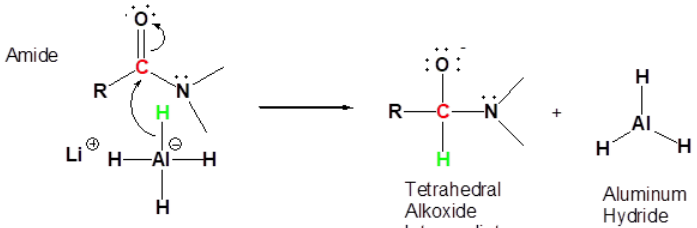


δ-Valerolactam — Piperidine

Mechanism for the Hydride Reduction of an Amide to Form an Amine

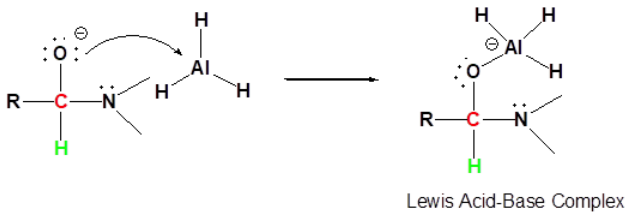
Addition of a hydride nucleophile to the carbonyl carbon of the amide produces a tetrahedral alkoxide intermediate. A Lewis acid-base interaction occurs between the alkoxide (Lewis Base) and AlH_3 (Lewis acid) forming a complex with an O-Al bond. The nitrogen lone pair forms a double bond with the previous carbonyl carbon ejecting a metal oxide species (e.g. $[H3Al–O]^{2–}$) as a leaving group, and while forming an iminium double bond. Addition of a second equivalent of hydride nucleophile to the iminium carbon produces an amine.

1) Nucleophilic attack by the hydride

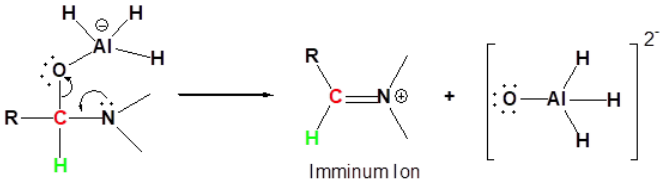


Lithium Aluminum Hydride — Tetrahedral Alkoxide Intermediate — Aluminum Hydride

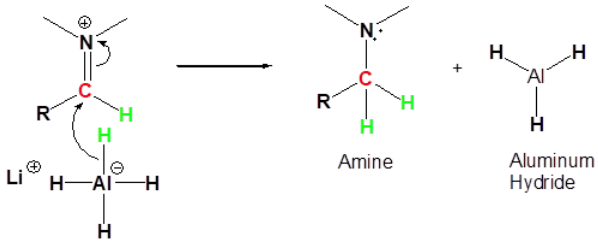
2) Complex formation



3) Leaving group removal

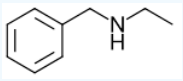


4) Nucleophilic attach by the hydride



Example 7.7.1

How could the following molecule be synthesized using an aminolysis of an acid chloride?



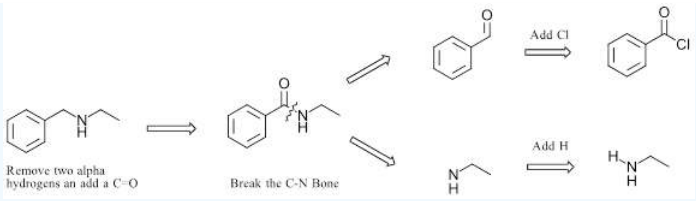
Answer

One of the preferred methods for making amines is through a nucleophilic acyl substitution using an acid chloride and amine to form an amide. The amide is then reduced to the amine during a hydride reduction with $LiAlH_4$.

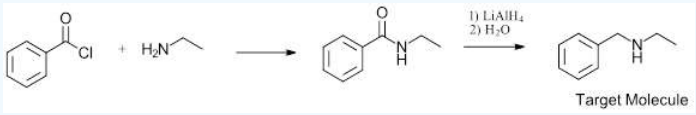
In the first step of retrosynthetic analysis, one of the carbons alpha to the amine nitrogen is converted to a carbonyl thus creating an amide intermediate. The key bond formed during this pathway is the C-N sigma bond between the carbonyl carbon and the nitrogen created during amide formation. Breaking this bond separated the target molecule into the two starting materials for the pathway. The carbonyl carbon gains a –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1° amine. In the forward reaction pathway, the acid chloride and the 1° amine are linked to from an amide in the first step of the reaction. Subsequent hydride reduction of the amide using $LiAlH_4$ produces the amine target molecule.

The target molecule has two alpha carbons which could possibly be converted to a carbonyl. This allows there to be two possible synthetic pathways.

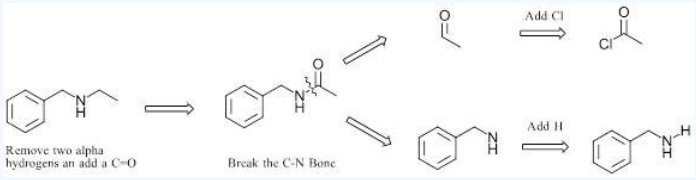
Pathway 1



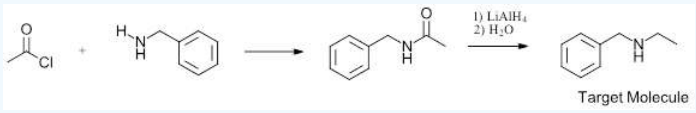
Solution 1



Pathway 2



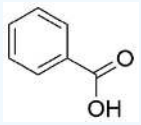
Solution 2



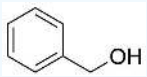
Exercise 7.7.1

1) How would you prepare the following compounds from N-Propypl benzamide?

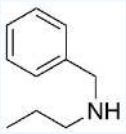
(a)



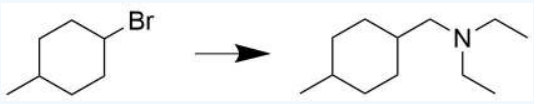
(b)



(c)



2) Propose a synthesis pathway for the following conversion:



Answer

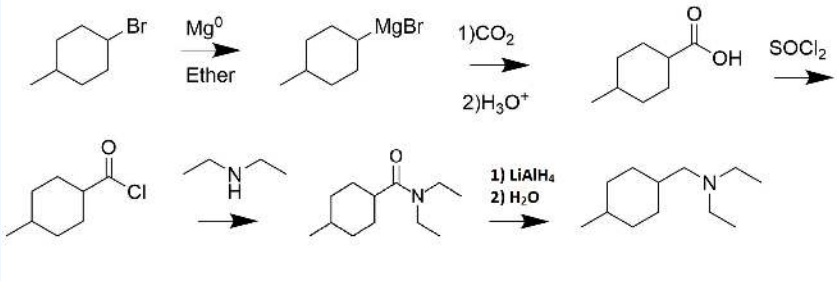
1) (a) NaOH, H_2O

https://chem.libretexts.org/@go/page/500438

(b) NaOH, H_2O, then $LiAlH_4$

(c) $LiAlH_4$

2)



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7.8: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives

Objectives

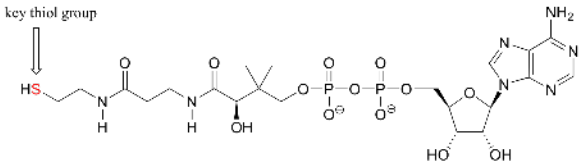
After completing this section, you should be able to

1. discuss, briefly, the role played in nature by acetylating agents, such as acetyl coenzyme A, and explain what is happening in reactions such as the acetylation in biological systems, without necessarily being able to write a detailed equation.
2. rank the reactivity of thioesters and acyl phosphates towards nucleophiles compared with other carboxylic acid derivatives.

Introduction to thioesters and Coenzyme A

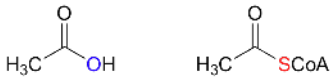
Acyl phosphates and acyl adenosine phosphates are not the only activated forms of carboxylate groups in biochemical reactions. Slightly lower on the reactivity scale are thioesters. In the metabolism of lipids (fats and oils), thioesters are the principal form of activated carboxylate groups. They are employed as acyl carriers, assisting with the transfer of acyl groups such as fatty acids from one acyl X substrate to another.

The 'acyl X group' in a thioester is a thiol. The most important thiol compound used to make thioesters is called coenzyme A, which has the following structure:



Coenzyme A
(HSCoA)

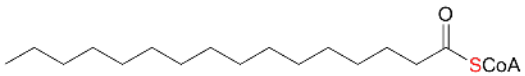
Coenzyme A is often abbreviated HSCoA, in order to emphasize that it is the thiol sulfur that provides the critical thioester linkage to acyl groups. When fuel (carbohydrate and fat) is broken down in your body, it is eventually converted to a simple two-carbon unit called acetyl CoA, which is essentially a thioester derivative of acetic acid:



acetic acid acetyl-SCoA

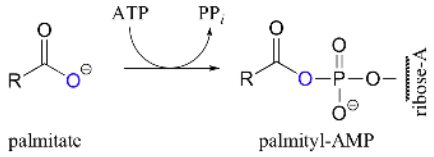
Activation of fatty acids by coenzyme A: a thioesterification reaction

In the biologically active form of fatty acids, the carboxylate groups have been converted to thioesters using coenzyme A. For example, the activated form of the C_{16} fatty acid palmitate is:

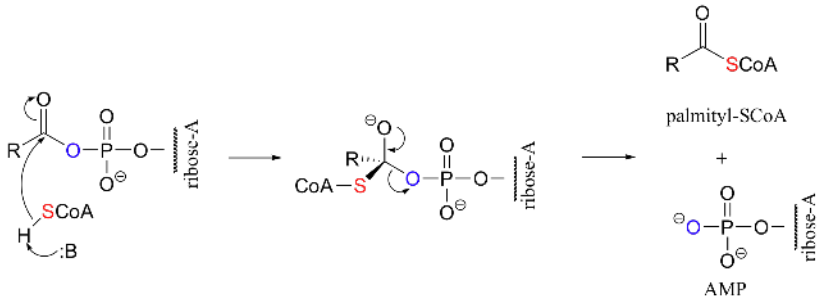


palmityl-SCoA

Let's take a look at how this activation takes place, in a reaction catalyzed by an enzyme called acyl CoA synthetase. You already know that carboxylates are not themselves good substrates for acyl substitution reactions, and must be activated. Thus, you might predict that the first step of this reaction requires ATP to make a high-energy acyl phosphate intermediate. In fact, the activated carboxylate in this case is an acyl-AMP, formed in the same way as the acyl-AMP intermediate in the asparagine synthetase reaction (section 12.2B).

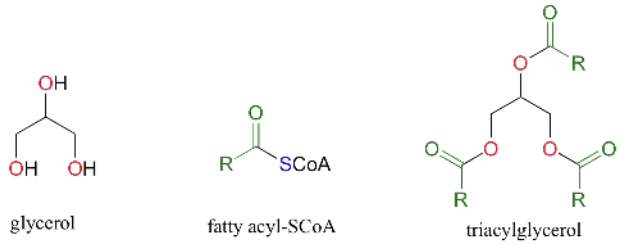


The activated acyl-AMP intermediate is then attacked by the thiol sulfur of coenzyme A, and the AMP group is expelled to form the fatty acyl CoA.

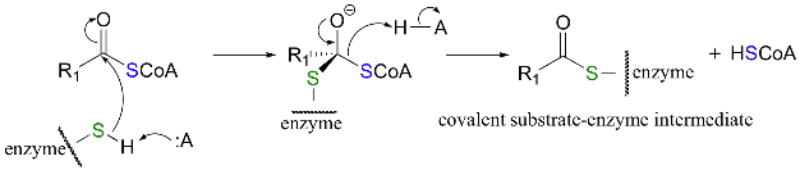


Transfer of fatty acyl groups to glycerol: a thioester to ester substitution

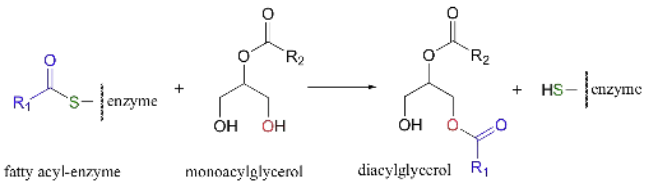
The -SCoA thioester form of the fatty acid is a good substrate for a number of metabolic transformations. This is the form of fatty acid, for example, that is oxidized and broken down for energy in the mitochondria of your cells. Fatty acyl CoA also serves as substrate for the construction of triacylglycerol, which is the fat molecule that your body uses to store energy in fat cells. Recall (section 12.1B) that triacylglycerol is composed of a glycerol 'backbone' connected to three fatty acid groups through ester linkages.



The reaction in which a fatty acid acyl group is linked to glycerol represents the conversion of a thioester (fatty acyl CoA) to an ester. First, however, a **transthioesterification** reaction occurs. A transthioesterification is merely the conversion of one thioester to another. In the case of monoacylglycerolacyltransferase, the fatty acyl group first trades its thioester link to coenzyme A for another thioester link to a cysteine residue in the active site of the enzyme. It is a common strategy for enzymes to first form a covalent link to one substrate before catalyzing the principle chemical reaction.



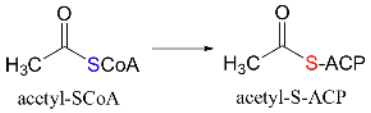
The fatty acyl group is now ready to be transferred to glycerol, trading its thioester linkage to the cysteine for a new ester linkage to one of the alcohol groups on glycerol. The attacking nucelophile in this reaction is of course the alcohol oxygen of monoacylglycerol.

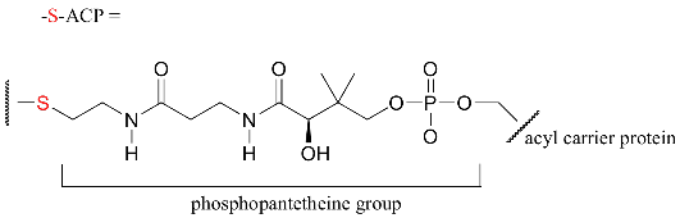


Because esters are more stable than thioesters, this is an energetically downhill reaction.

Transthioesterification reactions

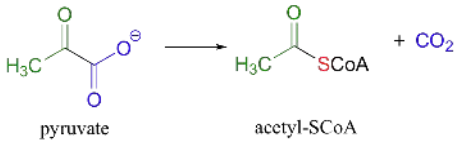
In the previous section we saw one example of a transthioesterification. Another important transthioesterification reaction involves acetyl CoA, the activated form of acetic acid and the basic two-carbon building block for fats and oils. Before it can be incorporated into a growing fatty acid molecule, acetyl CoA must first be linked to a so-called 'acyl carrier protein' (ACP). The acetyl group is linked to the acyl carrier protein *via* a thiol group on a carrier molecule that is covalently attached to the protein.



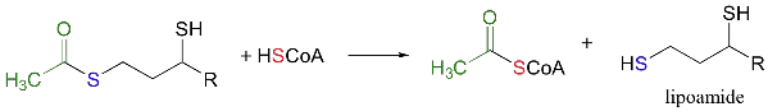


Notice that the structure of this carrier group (called phosphopantetheine) is identical to the region of coenzyme A (structure shown earlier in this section) near the thiol group. Once attached to the ACP, the two-carbon acetyl group condenses with another acyl group (which is also attached to its own ACP), and the fatty acid chain begins to grow. We will study these important carbon-carbon bond forming reactions in section 13.4.

Finally, a transthioesterification is the final step in one of the most important and well-studied reactions in animal metabolism: the conversion of pyruvate to acetyl CoA by a cluster of enzymes called the pyruvate dehydrogenase complex.



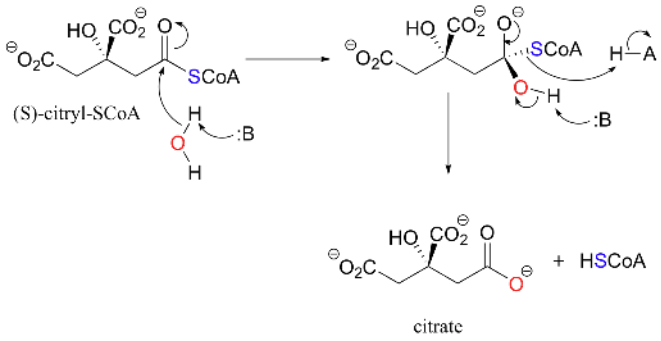
The overall reaction looks simple, but is actually quite complex and involves several intermediate species. The final step in the process is a transthioesterification, involving a dithiol molecule called lipoamide:



We will look more closely at the complete biochemical transformation catalyzed by the pyruvate dehydrogenase complex in section 16.12B.

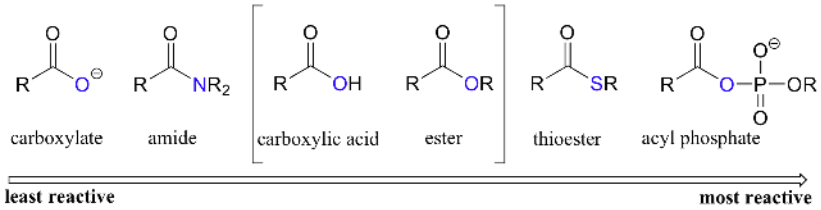
Hydrolysis of thioesters

The acyl group of a thioester can be transferred to a water molecule in a hydrolysis reaction, resulting in a carboxylate. An example of thioester hydrolysis is the conversion of (S)-citryl CoA to citrate in the citric acid cycle (also known as the Krebs cycle).



Reactivity of thioesters and acyl phosphates

Recall from Section 21.2 that thioesters and acyl phosphates are the most reactive among the biologically relevant acyl groups. However, neither is as reactive as an acid chloride or acid anhydride.



Relative reactivity of biologically relevant acyl groups

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7.9: Polyamides and Polyesters - Step-Growth Polymers

Objectives

After completing this section, you should be able to

1. write an equation to represent the formation of nylon 66 from adipic acid and hexamethylenediamine.
2. write an equation to represent the formation of nylon 6 from caprolactam.
3. predict the structure of the step-growth polymer formed from the reaction of two given monomers.
4. identify the monomers needed to prepare a step-growth polymer of a given structure.
5. write an equation to describe the formation of a polyester, such as poly(ethylene terephthalate), from a given diol and diester.
6. write an equation to describe the formation of a polycarbonate from a carbonate and a bisphenol.

Key Terms

Make certain that you can define, and use in context, the key terms below.

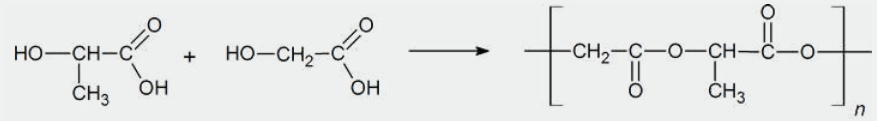
- chain-growth polymer
- polyamide
- polyester
- step-growth polymer

Study Notes

You may wish to review chain-growth polymerization in Section 8.10 and Section 14.6. In this section we discuss another important class of polymerization kknow as step-growth polymerization.

As you can see from the equation given in the discussion on forming condensation polymers, Dacron is formed from two monomers, one of which possesses two carboxylate groups and the other two hydroxyl groups.

It is also possible to form a polyester using two monomers that each possesse one carboxyl group and one hydroxyl group. An example is the polymer formed between lactic acid and glycolic acid. This polymer has been used to produce absorbable staples that provide surgeons with a convenient method of closing incisions made during operations on the bladder or intestines, or during hysterectomies. Two advantages of this polyester in such applications are, first, that it begins to hydrolyze in the body after six to eight weeks, and then, that the products of the hydrolysis are both compounds normally present in the body.

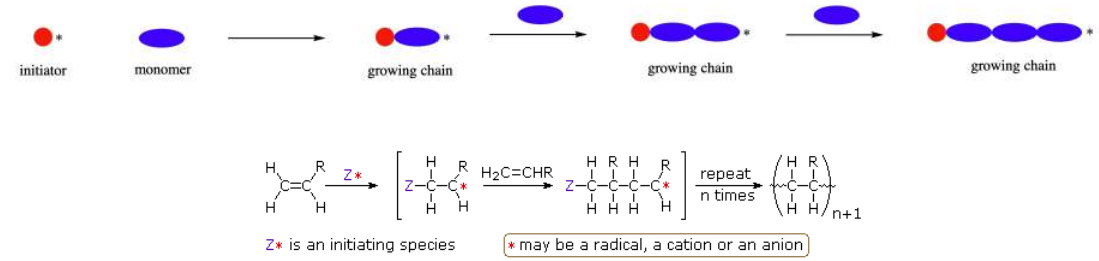


lactic acid
(2-hydroxypropanoic acid)

glycolic acid
(2-hydroxyethanoic acid)

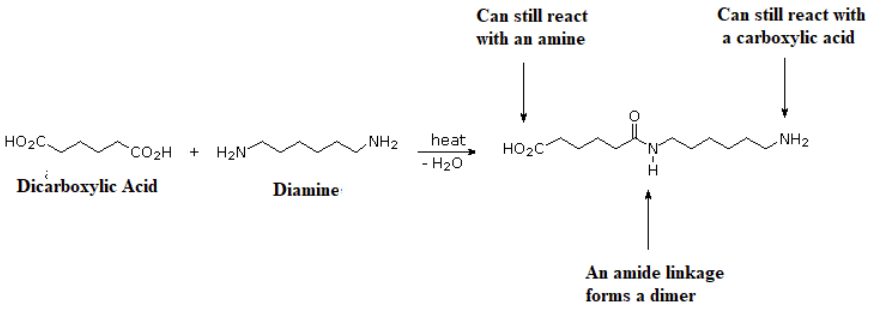
Step-Growth Polymerizations

Step-growth and chain-growth are two broad classes of polymerization methods. Sections 8.11 and 14.7 discussed how chain-growth polymers usually start with a single alkene containing monomer, which is unreactive until an initiator is added. The initiator converts one monomer molecule into a reactive intermediate (radical, cation, anion) which is capable of reacting with another monomer forming a C-C bond and creating a new reactive intermediate. This reactive intermediate reacts with another monomer and the process is repeated as a chain reaction to form a polymer.

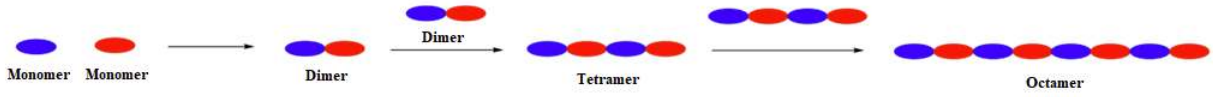


A Chain-Growth Polymerization

The process of step-growth polymerizations are fundamentally different than in chain-growth. In step-growth polymerizations, monomers are generally linked by a carbon-heteroatom bond (C-O & C-N) formed in non-sequential steps. Often, the reactions used to link these monomers include multiple nucleophilic acyl substitutions. Step-growth polymerizations usually use two different monomers, neither of which would undergo polymerization on its own. The two monomers are multifuntional and complementary to each other, such that each provides the other with a reactive partner. In this section, we will be focusing on monomers which are **difunctional**, meaning they contain two of the same reactive functional group. A step-growth polymerization starts with two complementary functional groups on different monomers reacting to form a dimer. Because both monomers were difunctional, each retains a reactive group and can react with additional complementary monomers.

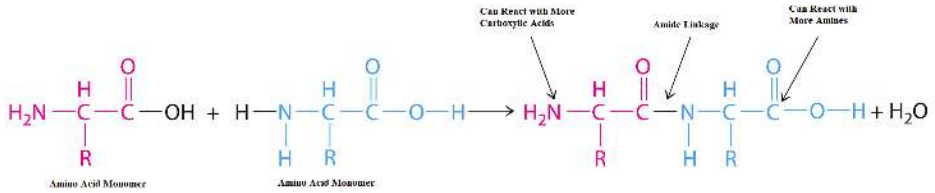


In fact the difuctionality of the monomers, allows step-growth polymers to grow in two directions at once. First, two complementary monomers react with each other to form a dimer. Assuming that monomers react at roughly similar rates, when one end of the dimer reacts again it will likely find another dimer and form a tetramer. Then when the tetramer goes to react again it will most likely find another tetramer and form an octamer. This process is repeated allowing the polymer to grow in two directions at the same time.



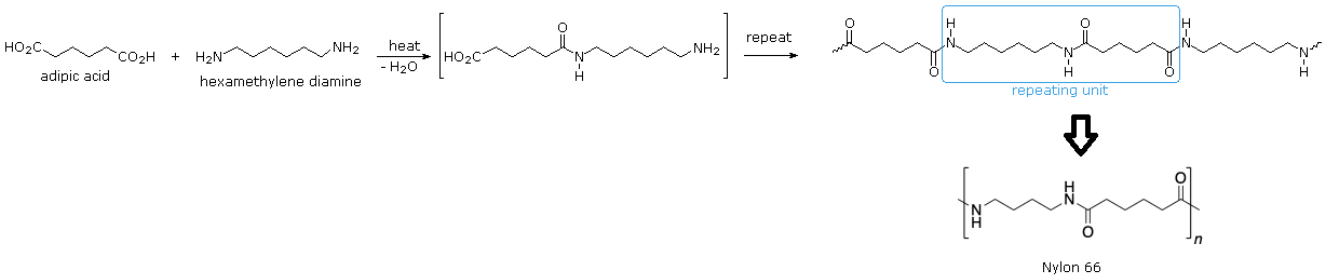
The Step-Growth Polymerization Process

Virtually all fibers are made from some form of polymer. In particular, silk and wool are composed of a naturally occurring protein polymer. The monomers of proteins are called **amino acid residues**. These residues are connected by amide linkages which are also called **peptide bonds**. Many of the early efforts of polymer chemistry were to artificially create fibers which mimicked the properties of silk and wool.

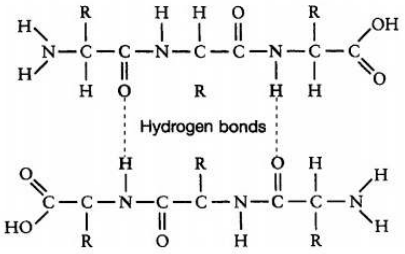


Polyamides

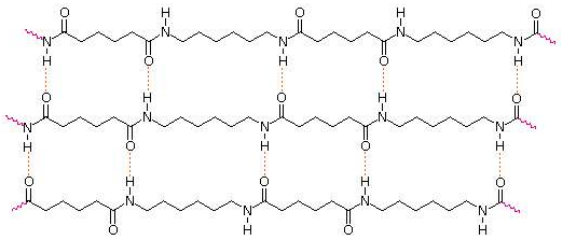
The first fully synthetic polymer fiber, nylon-6,6, was produced in 1938 by the company DuPont. The lead chemist of DuPont's work was Wallace H. Carothers, who reasoned that the properties of silk could be mimicked by constructing a polymer chain created with repeating amide bonds, just like the proteins in silk. Nylon-6,6 was created by first reacting 1,6-hexanedioic acid (adipic acid) and 1,6-hexanediamine to give a salt which was then heated creating multiple amide bonds through nucleophilic acyl substitution. The product of this particular reaction is a polyamide called nylon-6,6. The numbers of the name indicate how many carbons are contained in each monomer. The first “6” stands for the number of carbons in the diamine monomer while the second number indicated the number of carbons in the dicarboxylic acid. Simply by varying the number of carbons in each monomer, a wide variety of nylon polymers can be made.



Nylons are among the most widely used synthetic fibers—for example, they are used in ropes, sails, carpets, clothing, tires, brushes, and parachutes. Known for their high strength and abrasion resistance, nylons can be molded into blocks for use in electrical equipment, gears, bearings, and valves. The strength of nylon fibers comes, in part, from their ability to form strong hydrogen bonding intermolecular forces with each other in much the same fashion as proteins.



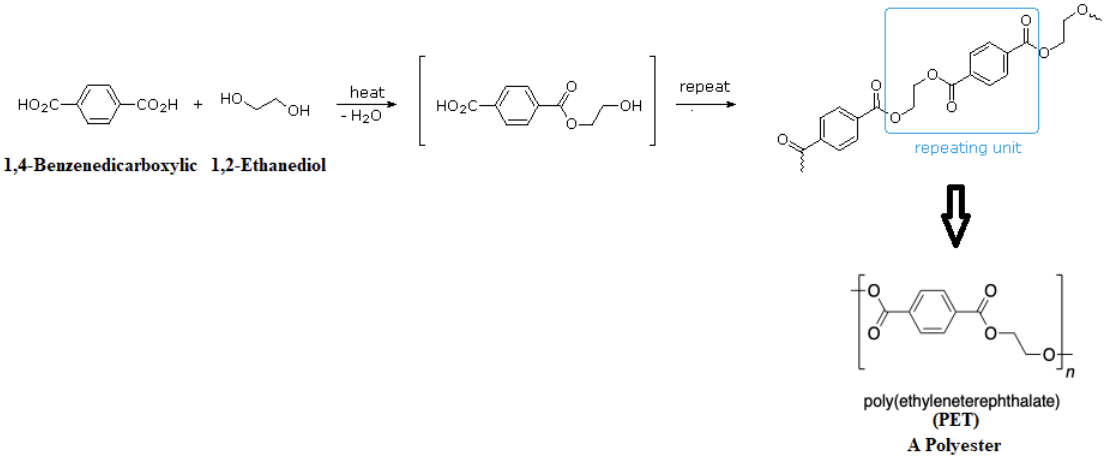
The Hydrogen Bonding between Proteins



The Hydrogen Bonding between Nylon Polyamides

Polyesters

Esterfication, via nucleophilic acyl substitutions, can also be used to form the primary linkages in step-growth polymers. A polyester is typically produced when a dicarboxylic acid and a diol are reacted together. After the initial reaction, the ester product contains a free (unreacted) carboxyl group at one end and a free alcohol group at the other. Further esterification using a step-growth polymerization, produces a polyester. The most important polyester, polyethylene terephthalate (PET), is made from the reaction of 1,4-benzenedicarboxylic (terephthalic acid) and 1,2-ethanediol (ethylene glycol) monomers.



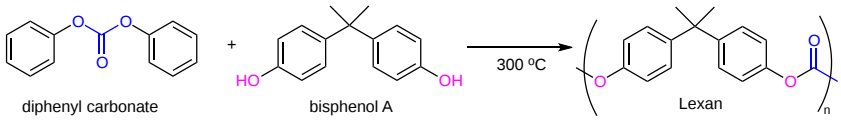
Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes.

Polycarbonates

Beyond carboxylic acid derivatives, virtually any reaction which involves reactive species on two different molecules can be used to perform a step-growth polymerization. A variation involves using a monomer containing a carbonate functional group. A carbonate acts like a double ester and can undergo a type of double transesterification reaction with two alcohols to form a new carbonate containing compound.

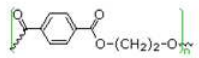
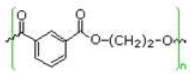
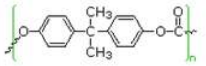
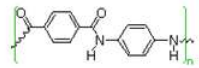
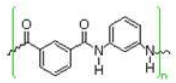


In effect, a carbonate is difunctional and can be reacted with a diol to form polymers containing repeated carbonate groups in their structure called polycarbonates. An example of a polycarbonate is the polymer, Lexan, which is created when diphenyl carbonate and bisphenol A (a diol) are reacted together.



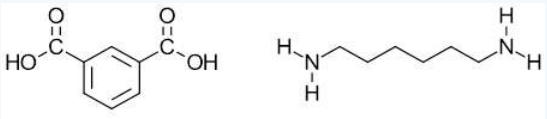
Polycarbonates used in engineering are strong, tough materials, and some grades are optically transparent. They are easily worked, molded, and thermoformed. Because of these properties, polycarbonates find many applications. One major application of polycarbonates is the production of compact discs, DVDs, and Blu-ray discs.

Bisphenol (BPA), primarily used to make polycarbonate, is one of the highest-volume chemicals produced in the world, with over six billion pounds made each year. Because polycarbonate is used to make plastic bottles, the lining for food cans, and the lining for beverage cans there has been much concern about trace amounts of BPA leaching from the containers and being ingested. A study conducted in 2003 and 2004 by the Center for Disease Control and Prevention found trace amounts BPA in the tissues of 93% of people in the United States. Consequently, this has led to many beverage companies switching to non-polycarbonate polymers.

Formula	Type	Components	T_g ºC	T_m ºC
~[CO(CH$_2$)$_4$CO-OCH$_2$CH$_2$O]$_n$~	**polyester**	HO$_2$C-(CH$_2$)$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	< 0	50
	**polyester** Dacron, Mylar	para HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	70	265
	**polyester**	meta HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	50	240
	**polycarbonate** Lexan	(HO-C$_6$H$_4$-)$_2$C(CH$_3$)$_2$ (Bisphenol A) X$_2$C=O (X = OCH$_3$ or Cl)	150	267
~[CO(CH$_2$)$_4$CO-NH(CH$_2$)$_6$NH]$_n$~	**polyamide** Nylon 66	HO$_2$C-(CH$_2$)$_4$-CO$_2$H H$_2$N-(CH$_2$)$_6$-NH$_2$	45	265
~[CO(CH$_2$)$_5$NH]$_n$~	**polyamide** Nylon 6 Perlon		53	223
	**polyamide** Kevlar	para HO$_2$C-C$_6$H$_4$-CO$_2$H para H$_2$N-C$_6$H$_4$-NH$_2$	---	500
	**polyamide** Nomex	meta HO$_2$C-C$_6$H$_4$-CO$_2$H meta H$_2$N-C$_6$H$_4$-NH$_2$	273	390

Example 7.9.1

Provide the structure of the polyamide made from the monomers as indicated. Please use bracketed notation.

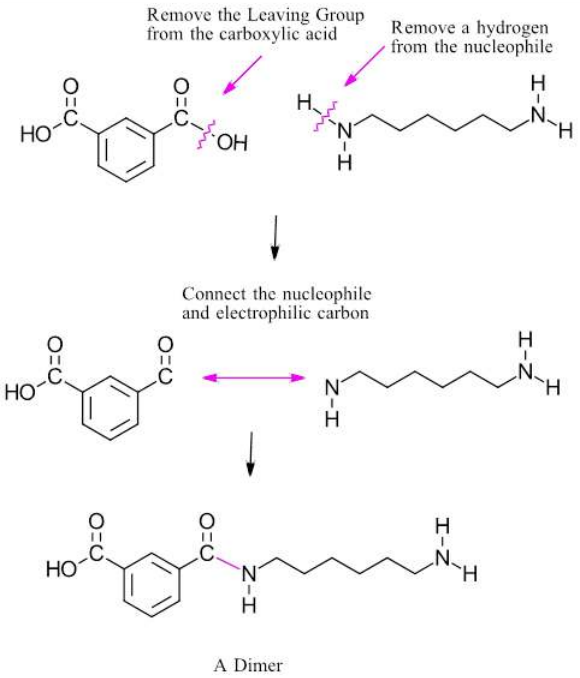


Solution

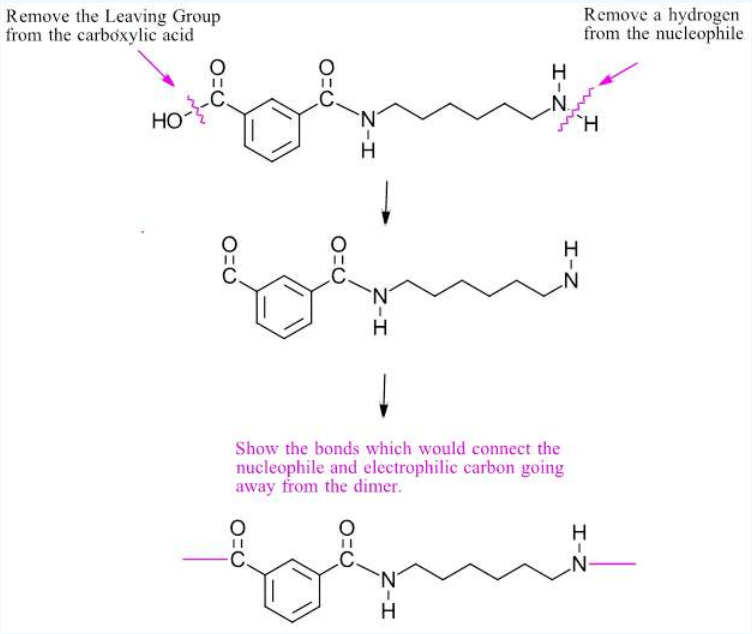
When drawing the polymer product of a step-growth polymerization, it is important to first identify the reaction which forms the repetitive linkage between monomers. In this case, the reaction is anucleophilic acyl substitution btween a carboxylic acid and an amine to form an amide. In total, the bracket structure of a polymer shows two versions of the linkage formation. The first is clearly shows connecting the monomers to form the dimer making up the repeating unit in the polymer. The second version involves bonds going out of the bracket and represents how the linkage repeats throughout the polymer.

1) The connect two monomers to make a dimer using the indicated reaction.

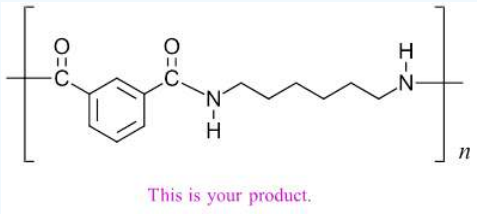
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2) Beak the same bonds as before ecepptt the bonds for the final connection will be shown going away from the dimer.



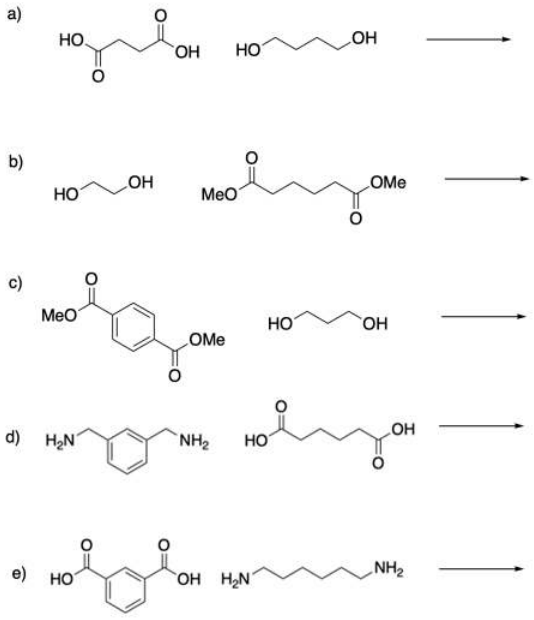
3) Place brackets around the dimer and put an italicized lower case "n" in the lower right.



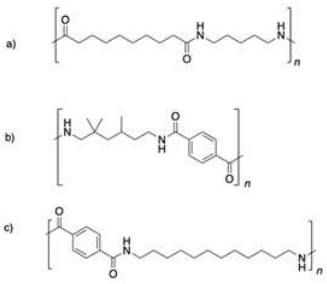
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Exercises

1) Provide structures of the polyesters made from the monomers as indicated.



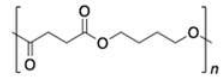
2) Identify the monomers that would be used to produce these polymers.

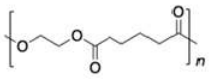


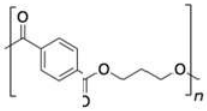
Solutions

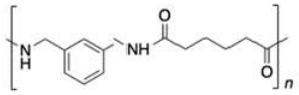
1)

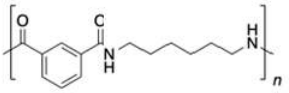
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a) 

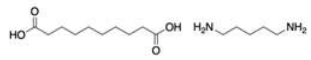
b) 

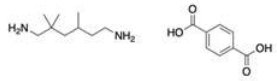
c) 

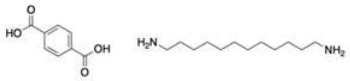
d) 

e) 

2)

a) 

b) 

c) 

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7.10: Spectroscopy of Carboxylic Acid Derivatives

Objectives

After completing this section, you should be able to

1. identify the region of the infrared spectrum in which absorptions resulting from the carbonyl group of carboxylic acid derivatives occur.
2. identify the characteristic features of the infrared spectra of acid anhydrides and nitriles that allow us to use infrared spectroscopy to distinguish between these compounds and the others discussed in this unit.
3. use a table of characteristic infrared absorptions to interpret the infrared spectra of carbonyl-containing compounds.
4. use infrared spectroscopy and ^{1}H NMR spectroscopy in the deduction of the structure of an unknown compound.

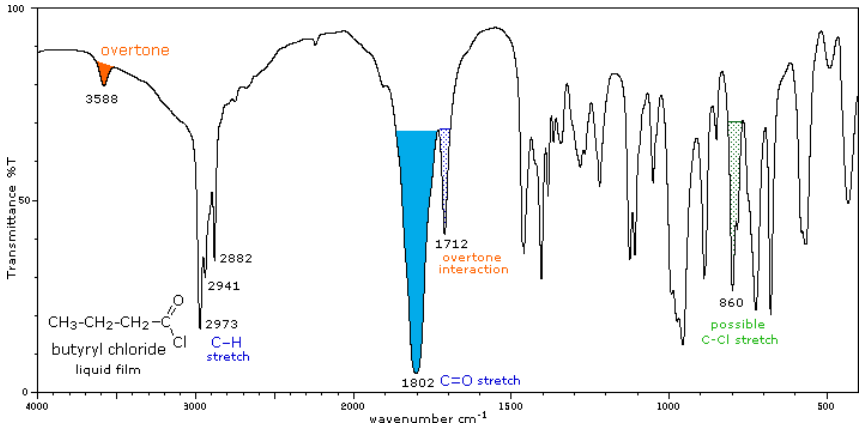
Study Notes

Note: You should recognize that protons on carbon atoms next to carbonyl groups are slightly deshielded, and absorb near 2 δ in the ^{1}H NMR spectrum.

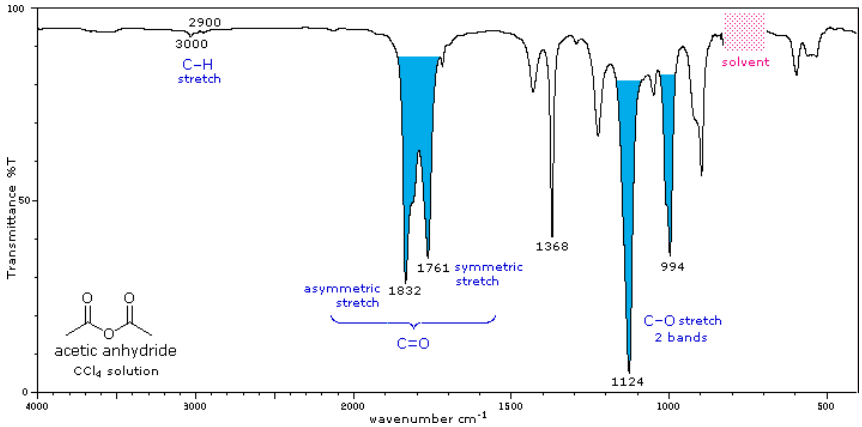
The influence of heteroatom substituents on the reactivity of carbonyl functions toward nucleophiles was discussed earlier with respect to carboxylic acid derivatives. A useful relationship exists between the reactivity of these derivatives and their carbonyl stretching frequencies. Thus, the very reactive acyl halides and anhydrides absorb at frequencies significantly higher than ketones, whereas the relatively unreactive amides absorb at lower frequencies. These characteristics are listed below.

Infrared spectra of many carboxylic acid derivatives will be displayed in the figure below the table by clicking the appropriate buttons presented there.

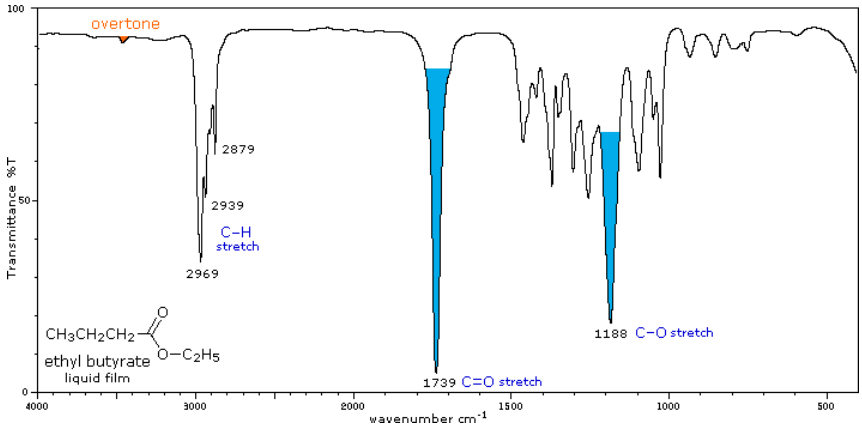
Carbonyl Derivative	Carbonyl Absorption	Comments
Acyl Halides (RCOX) X = F X = Cl X = Br	**C=O stretch** 1860 ± 20 cm^{-1} 1800 ± 15 1800 ± 15	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones. In acyl chlorides a lower intensity shoulder or peak near 1740 cm^{-1} is due to an overtone interaction.
Acid Anhydride, $(RCO)_2O$ acyclic 6-membered ring 5-membered ring	**C=O stretch** (2 bands) 1750 & 1820 cm^{-1} 1750 &1820 1785 & 1865	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones. The two stretching bands are separated by 60 ± 30 cm^{-1}, and for acyclic anhydrides the higher frequency (asymmetric stretching) band is stronger than the lower frequency (symmetric) absorption. Cyclic anhydrides also display two carbonyl stretching absorptions, but the lower frequency band is the strongest. One or two -CO-O-CO- stretching bands are observed in the 1000 to 1300 cm^{-1} region.
Esters & Lactones (RCOOR') esters 6-membered lactone 5-membered lactone 4-membered lactone	**C=O stretch** 1740 cm ± 10 cm^{-1} 1740 cm ± 10 1765 cm± 5 1840 cm ± 5	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones Strong CO-O stretching absorptions (one ot two) are found from 1150 to 1250 cm^{-1}
Amides & Lactams ($RCONR_2$) 1° & 2°-amides 3°-amides 6-membered lactams 5-membered lactams 4-membered lactams	**C=O bands** 1510 to 1700 cm^{-1} (2 bands) 1650± 15 (one band) 1670 ± 10 (one band) 1700 ± 15 1745 ± 15	The effect of conjugation is much less than for aldehydes & ketones. The higher frequency absorption (1665± 30) is called the **Amide I band**. The lower frequency **Amide II band** (1620± 30 in 1° amides & 1530± 30 in 2° amides) is largely due to N-H bending trans to the carbonyl oxygen. In concentrated samples this absorption is often obscured by the stronger amide I absorption. Hydrogen bonded association shifts some of these absorptions, as well as the prominent N-H stretching absorptions. **N-H stretch**: 3170 to 3500 cm^{-1}. Two bands for 1°-amides, one for 2°-amides.



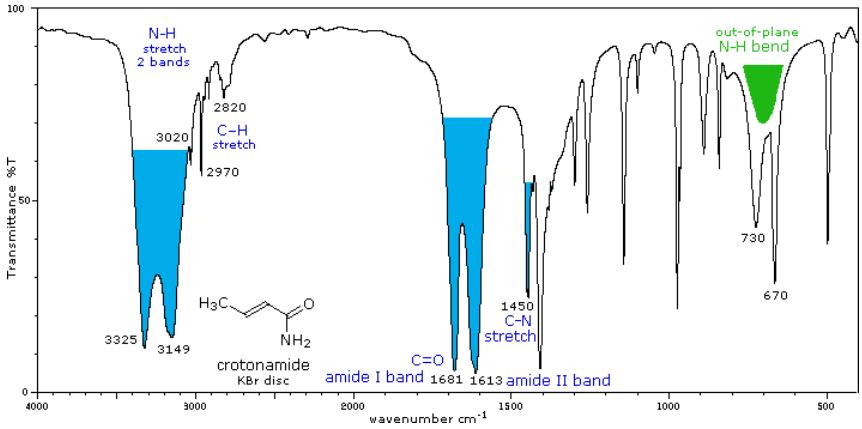
IR - Carbonyl peak of an acid halide



IR - Carbonyl and carbon-oxygen single bond peaks of an acid anhydride



IR - Carbonyl and carbon-oxygen single bond peaks of an ester



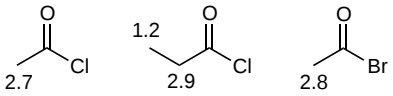
IR - Carbonyl, carbon-nitrogen and nitrogen-hydrogen bond peaks of an amide

^{1}H Nuclear Magnetic Spectroscopy

Alpha protons of carboxylic acid derivatives, due to the presence of a carbonyl, resonate in the 2.0-3.0 ppm region of a ^{1}H NMR spectra. The downfield shift occurs from deshielding due to higher electronegativity of the sp^2 hybridized carbonyl carbon relative to the sp^3 hybridized alpha carbons. This effect is reduced for protons which are further from the carbonyl group as seen in the figure below.

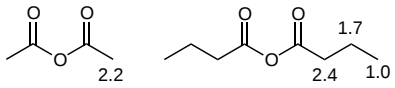
Acid halides

The X groups of acid halides do not contain additional protons and thus do not provide any distinctive ^{1}H NMR peaks. The protons on carbon adjacent to the carbonyl appear at similar chemical shift to other carbonyl containing compounds (2-3 ppm).



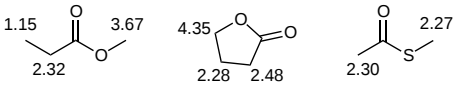
Acid anhydrides

Many anhydrides used in organic chemistry are symmetrical, therefore the alkyl chains on either side of the carbonyls produce equivalent protons.



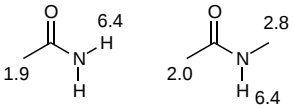
Esters and Thioesters

The Y groups of esters, and thioesters have alkyl groups attached to their heteroatom which provide additional ^{1}H NMR peaks. Protons on carbons attached to the alkoxide oxygen in esters show up in the 3.5-4.5 ppm region while those attached to the sulfur in thioesters show up in the 2.0-3.0 ppm region. The downfield shift in these protons is attributable to the deshielding caused by the electronegativity of oxygen and sulfur.

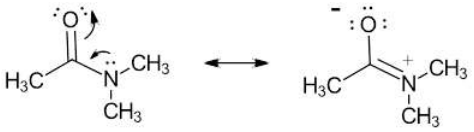


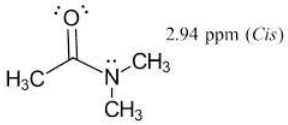
Amides

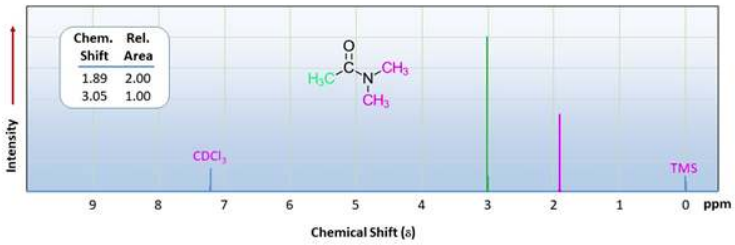
Amides have the possibility of alkyl groups or hydrogens attached to their Y group both of which provide distinctive ^{1}H NMR peaks. Resonances from protons directly attached to the carbon bonded to nitrogen in an amide tend to resonate in the 2.0-3.0 ppm region of an NMR spectra. The NH protons of primary and secondary amides resonate in the 7.5-8.5 ppm regions. Like other hydrogen bonding protons, these NH proton peaks appear broad and can be washed out by the hydrogen-deuterium exchange created by D_2O addition.



An interesting facet of amide structure is shown when looking at the ^{1}H NMR spectra of N,N-dimethylacetamide. The two N-methyl groups are in fact non-equivalent and appear as two singlets with difference chemical shifts. Resonance in the amide bond provides a significant amount of double bond character reducing the rate of rotation about the OC-N bond. The rotation is slow enough that on the time scale of an NMR experiment the two methyl appears to be frozen as if it is part of a double bond. This causes the N-methyl groups to have different chemical shifts because one appears to be cis to the carbonyl oxygen and the other trans during an NMR experiment.

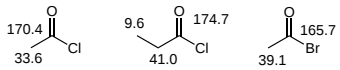




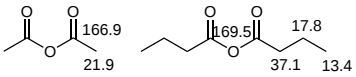


^{13}C Nuclear Magnetic Spectroscopy

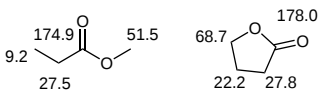
The carbonyl carbons of carboxylic acid derivatives are strongly deshielded (160-180 ppm) due to the close presence (due to the double bond) of a highly electronegative oxygen. However, they are not as deshielded as the carbonyl carbon of an aldehyde or ketone (180-220 ppm) due to the electron donating effects of the Y group. Carbons attached to the alkoxide oxygen of esters appear in the range of 50-90 ppm. Carbons attached to the nitrogen of an amide appear in the 20-65 ppm range and those attached to the sulfur of thioesters appear at 20-45 ppm.



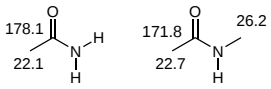
Acid halide ^{13}C NMR chemical shifts (ppm)



Anhydride ^{13}C NMR chemical shifts (ppm)



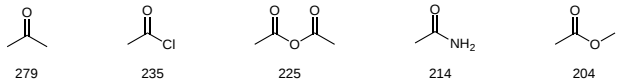
Ester ^{13}C NMR chemical shifts (ppm)



Amide ^{13}C NMR chemical shifts (ppm)

UV/Vis Spectroscopy

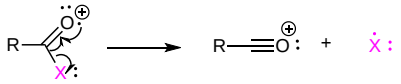
Carboxylic acid derivatives show the n→π* absorption typical for carbonyl containing compounds. The Y group of acid derivatives give a hypsochromic shift (wavelength lowering) to the absorption due to the inductive effect of the electronegative oxygen, nitrogen, and halogens present. Electrons are inductively removed from the carbonyl carbon which causes the lone pair electrons on the carbonyl oxygen to be held more firmly. This causes them to require higher energy photons to transition which corresponds to a lower wavelength λ_{max} when compared to other carbonyls such as a ketone.



UV-Visible absorption of carbonyl compounds (showing λ_{max} in nm)

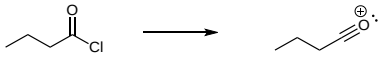
Mass Spectrometry

In the mass spectra of most carboxylic acid derivatives, the base peak is due to the cleavage of C-Y bond to form an acylium ion ($R\text{-}CO^+$). Other than the molecular ion peak, the acylium ion is one of the only major peaks present in the mass spectra of acid halides and thioesters. Amide and ester often show additional fragmentations.



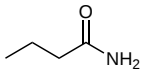
Acid halides

The molecular ion peak of acid chlorides is often not seen. When they do occur, acid chlorides and acid bromides would have an important M + 2 peak due to the two isotopic forms of the halogens. The base peak fragmentation involves the alpha cleavage of C-X bond to from an acylium ion. In butanoyl chloride this peak shows up at m/z = 72.

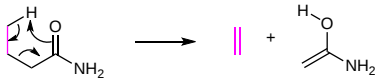


Amide

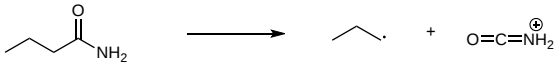
Amides, like other compounds containing nitrogen, follow the Nitrogen Rule. This means that a compound with an odd number of nitrogen atoms will also have an odd-numbered molecular weight. This is shown in butanamide (C_4H_9NO) which has the odd-numbered molecular weight of 87.12 g/mol.



Primary amides show a base peak due to the McLafferty rearrangement which appears at m/z = 59. Secondary and tertiary amides give analogous peaks at higher m/z values.

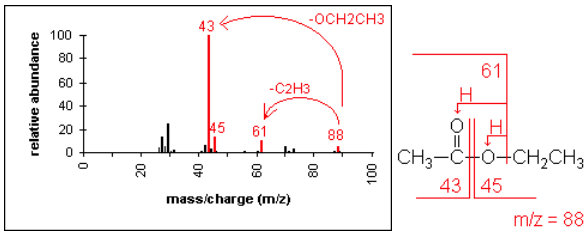


Amides can also cleave the alkyl group attached to the carbonyl forming an amide stabilized acelium ion. For butanamide, like other primary amines, this peak shows up at m/z = 44.



Ester

Esters have multiple fragmentation pathways which are often dependent on the overall size of the ester. The most important fragmentation appears due to alpha-cleavage bond of the C-O to produce the corresponding acylium ion RCO^+. In the mass spectra of ethyl acetate the acylium ion peak appears at 43 m/z and the alkoxy ion peak (RO^+) shows up a 45 m/z. Other important fragments include the loss or the alkyl group (R^+) from the acyl side and the alkoxy side of the ester. Loss of the alkyl group on the alkyoxy side of ethyl acetate ($^+CH_2CH_3$) produces a peak at m/z 61.



SDBSWeb : https://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, date of access

NIST Chemistry WebBook: https://webbook.nist.gov/chemistry/ (National Insitute of Standards and Technology)

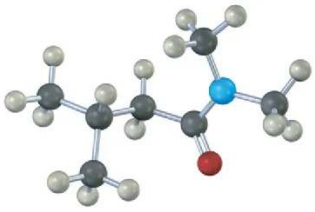
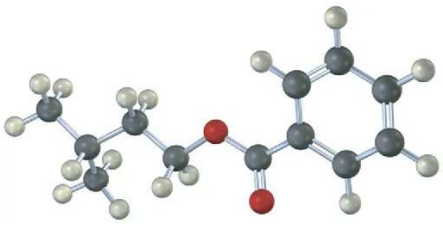
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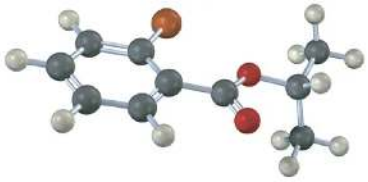
7.11: Additional Problems

Visualizing Chemistry

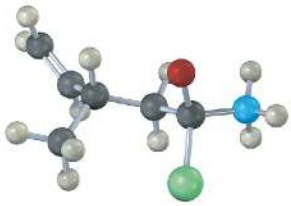
PROBLEM 21-27 Name the following compounds:

(a)  (b) 

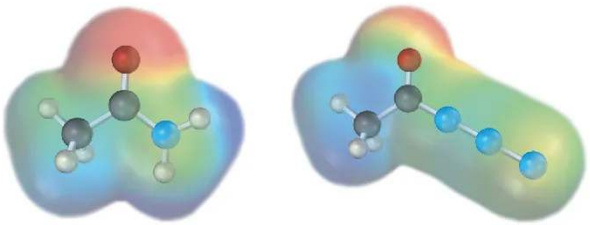
PROBLEM 21-28 How would you prepare the following compounds starting with an appropriate carboxylic acid and any other reagents needed? (reddish brown = Br.)

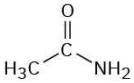
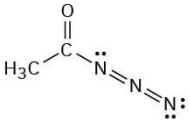
(a)  (b) 

PROBLEM 21-29 The following structure represents a tetrahedral alkoxide-ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product (green = Cl).



PROBLEM 21-30 Electrostatic potential maps of a typical amide (acetamide) and an acyl azide (acetyl azide) are shown. Which of the two do you think is more reactive in nucleophilic acyl substitution reactions? Explain.

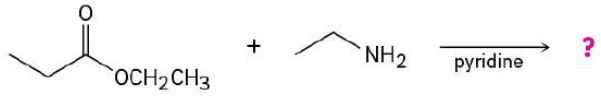


Acetamide   **Acetyl azide**

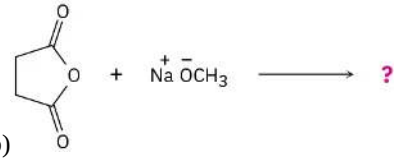
Mechanism Problems

PROBLEM 21-31 Predict the product(s) and write the mechanism for the following reactions:

(a)

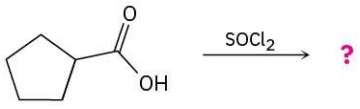


(b)

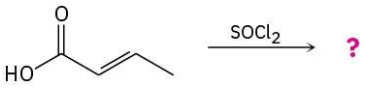


PROBLEM 21-32 Predict the product(s) and write the mechanism for the following reactions:

(a)

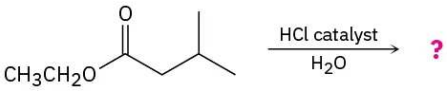


(b)

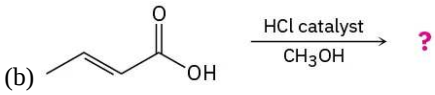


PROBLEM 21-33 Predict the product(s) and write the mechanism for the following reactions: (a) <p"> Predict the product(s) and write the mechanism for each of the following reactions:

(a)

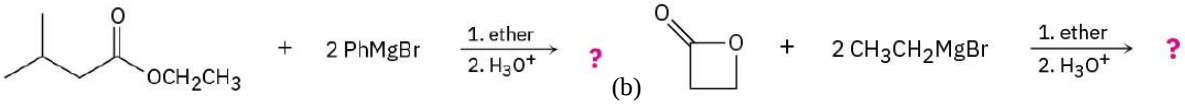


(b)



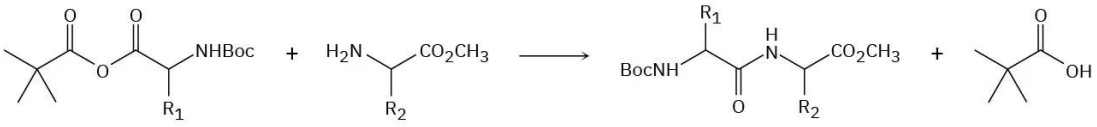
PROBLEM 21-34 Predict the product(s) and write the mechanism for the following reactions: (a) <p"> Predict the product(s) and write the mechanism for the following reactions:

(a)



(b)

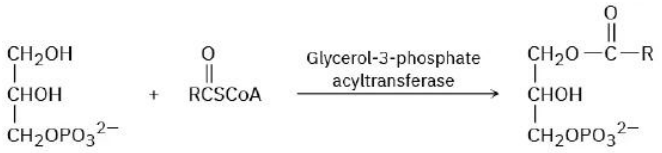
PROBLEM 21-35 Pivalic mixed anhydrides are often used to form amide bonds between amino acids. Unlike with a symmetrical anhydride, this reaction is highly regioselective, with the nucleophile adding only to the amino-acid carbonyl. Provide the complete mechanism for the following reaction and explain the regioselectivity.



Pivaloyl/amino-acid mixed anhydride

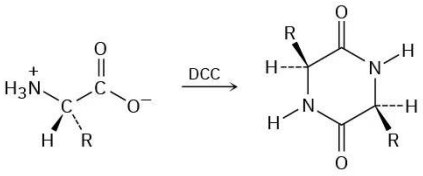
PROBLEM 21-36 When 4-dimethylaminopyridine (DMAP) is added in catalytic amounts to acetic anhydride and an alcohol, it significantly increases the rate of ester formation. The process begins with a reaction between acetic anhydride and DMAP to form a highly reactive acetylpyridinium intermediate that is more reactive than acetic anhydride itself. Propose a mechanism for this process that includes the formation and reaction of the acetylpyridinium intermediate.

PROBLEM 21-37 Fats are biosynthesized from glycerol 3-phosphate and fatty-acyl CoA's by a reaction sequence that begins with the following step. Show the mechanism of the reaction.



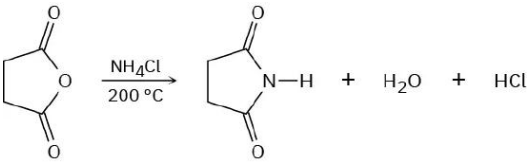
Glycerol 3-phosphate | **Fatty-acyl CoA** | **1-Acylglycerol 3-phosphate**

PROBLEM 21-38 Treatment of an α-amino acid with DCC yields a 2,5-diketopiperazine. Propose a mechanism.

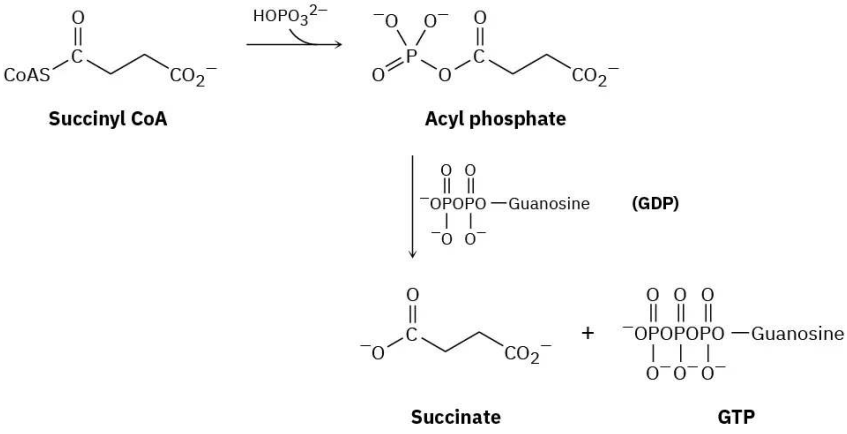


An α-amino acid **A 2,5-diketopiperazine**

PROBLEM 21-39 Succinic anhydride yields the cyclic imide succinimide when heated with ammonium chloride at 200 °C. Propose a mechanism for this reaction. Why do you suppose such a high reaction temperature is required?

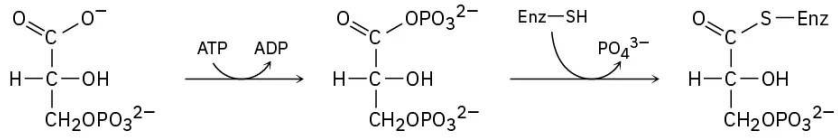


PROBLEM 21-40 The hydrolysis of a biological thioester to the corresponding carboxylate is often more complex than the overall result might suggest. The conversion of succinyl CoA to succinate in the citric acid cycle, for instance, occurs by initial formation of an acyl phosphate, followed by reaction with guanosine diphosphate (GDP, a relative of adenosine diphosphate [ADP]) to give succinate and guanosine triphosphate (GTP, a relative of ATP). Suggest mechanisms for both steps.

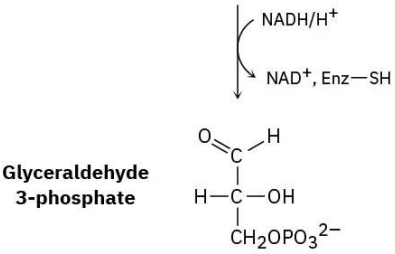


Succinyl CoA **Acyl phosphate** **Succinate** **GTP**

PROBLEM 21-41 One step in the *gluconeogenesis* pathway for the biosynthesis of glucose is the partial reduction of 3-phosphoglycerate to give glyceraldehyde 3-phosphate. The process occurs by phosphorylation with ATP to give 1,3-bisphosphoglycerate, reaction with a thiol group on the enzyme to give an enzyme-bound thioester, and reduction with NADH. Suggest mechanisms for all three reactions.

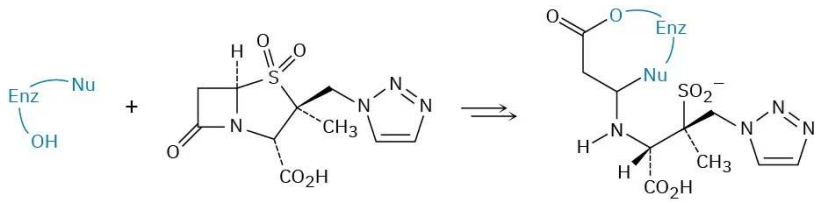


3-Phosphoglycerate **1,3-Bisphosphoglycerate** **(Enzyme-bound thioester)**



Glyceraldehyde 3-phosphate

PROBLEM 21-42 Bacteria typically develop a resistance to penicillins and other β-lactam antibiotics (see *Chemistry Matters* at the end of this chapter) due to bacterial synthesis of β-lactamase enzymes. Tazobactam, however, is able to inhibit the activity of the β-lactamase by trapping it, thereby preventing a resistance from developing.



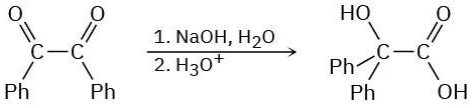
β-Lactamase **Tazobactam** **Trapped β-lactamase**

(a) The first step in trapping is reaction of a hydroxyl group on the β-lactamase to open the β-lactam ring of tazobactam. Show the mechanism.

(b) The second step is opening the sulfur-containing ring in tazobactam to give an acyclic imine intermediate. Show the mechanism.

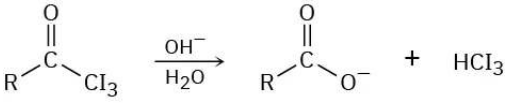
(c) Cyclization of the imine intermediate gives the trapped β-lactamase product. Show the mechanism.

PROBLEM 21-43 The following reaction, called the *benzilic acid rearrangement*, takes place by typical carbonyl-group reactions. Propose a mechanism (Ph = phenyl).



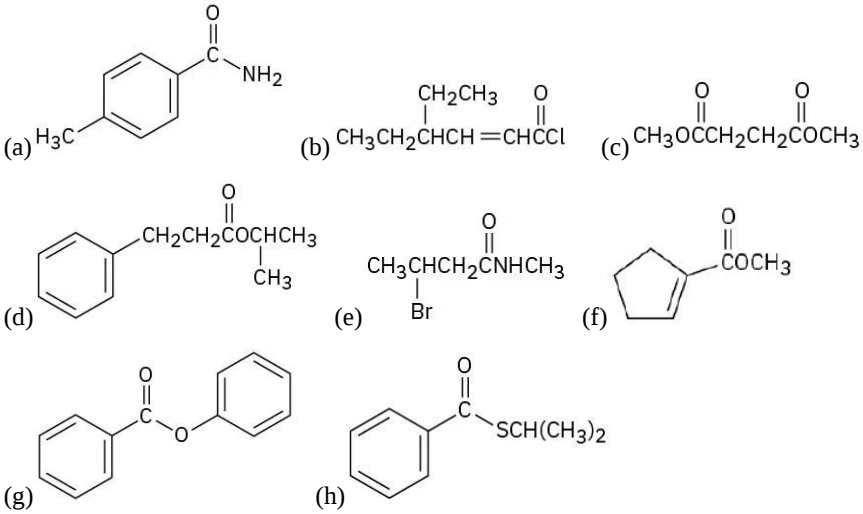
Benzil **Benzylic acid**

PROBLEM 21-44 In the *iodoform reaction*, a triiodomethyl ketone reacts with aqueous NaOH to yield a carboxylate ion and iodoform (triiodomethane). Propose a mechanism for this reaction.



Naming Carboxylic Acid Derivatives

PROBLEM 21-45 Give IUPAC names for the following compounds:



PROBLEM 21-46 Draw structures corresponding to the following names:

(a) *p*-Bromophenylacetamide **(b)** *m*-Benzoylbenzamide **(c)** 2,2-Dimethylhexanamide

(d) Cyclohexyl cyclohexanecarboxylate **(e)** Ethyl 2-cyclobutenecarboxylate **(f)** Succinic anhydride

PROBLEM 21-47 Draw and name compounds that meet the following descriptions:

(a) Three acid chlorides having the formula C_6H_9ClO

(b) Three amides having the formula $C_7H_{11}NO$.

Nucleophilic Acyl Substitution Reactions

PROBLEM 21-48 Predict the product, if any, of reaction between propanoyl chloride and the following reagents:

(a) $Li(Ph)_2Cu$ in ether **(b)** $LiAlH_4$, then H_3O^+ **(c)** CH_3MgBr, then H_3O^+ **(d)** H_3O^+ **(e)** Cyclohexanol **(f)** Aniline **(g)** $CH_3CO_2^-\ Na^+$

PROBLEM 21-49 Answer Problem 21-48 for reaction of the listed reagents with methyl propanoate.

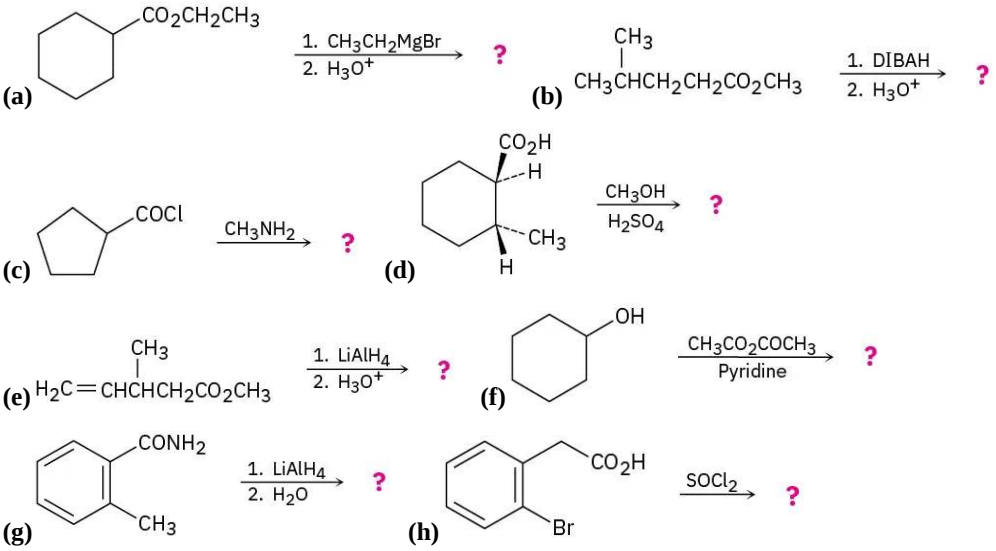
PROBLEM 21-50 Answer Problem 21-48 for reaction of the listed reagents with propanamide.

PROBLEM 21-51 What product would you expect to obtain from Grignard reaction of an excess of phenylmagnesium bromide with dimethyl carbonate, $CH_3OCO_2CH_3$?

PROBLEM 21-52 How might you prepare the following compounds from butanoic acid?

(a) 1-Butanol **(b)** Butanal **(c)** 1-Bromobutane **(d)** Pentanenitrile **(e)** 1-Butene **(f)** *N*-Methylpentanamide **(g)** 2-Hexanone **(h)** Butylbenzene **(i)** Butanenitrile

PROBLEM 21-53 Predict the product(s) of the following reactions:



PROBLEM 21-54 The following reactivity order has been found for the saponification of alkyl acetates by aqueous NaOH. Explain.

$$CH_3CO_2CH_3 > CH_3CO_2CH_2CH_3 > CH_3CO_2CH(CH_3)_2 > CH_3CO_2C(CH_3)_3$$

PROBLEM 21-55 Explain the observation that attempted Fischer esterification of 2,4,6-trimethylbenzoic acid with methanol and HCl is unsuccessful. No ester is obtained, and the acid is recovered unchanged. What alternative method of esterification might be successful?

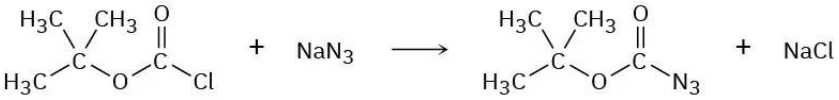
PROBLEM 21-56 Outline methods for the preparation of acetophenone (phenyl methyl ketone) starting from the following:

(a) Benzene **(b)**Bromobenzene **(c)** Methyl benzoate **(d)** Benzonitrile **(e)** Styrene

PROBLEM 21-57 Treatment of 5-aminopentanoic acid with DCC (dicyclohexylcarbodiimide) yields a lactam. Show the structure of the product and the mechanism of the reaction.

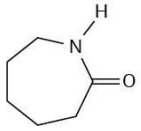
PROBLEM 21-58 When *ethyl* benzoate is heated in methanol containing a small amount of HCl, *methyl* benzoate is formed. Propose a mechanism for the reaction.

PROBLEM 21-59 *tert*-Butoxycarbonyl azide, a reagent used in protein synthesis, is prepared by treating *tert*-butoxycarbonyl chloride with sodium azide. Propose a mechanism for this reaction.



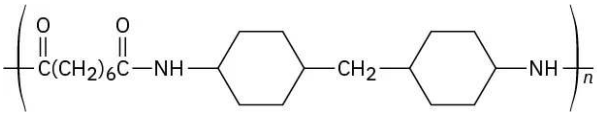
Step-Growth Polymers

PROBLEM 21-60 The step-growth polymer nylon 6 is prepared from caprolactam. The reaction involves initial reaction of caprolactam with water to give an intermediate open-chain amino acid, followed by heating to form the polymer. Propose mechanisms for both steps, and show the structure of nylon 6.



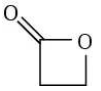
Caprolactam

PROBLEM 21-61 *Qiana*, a polyamide fiber with a silky texture, has the following structure. What are the monomer units used in the synthesis of Qiana?



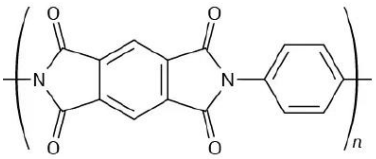
Qiana

PROBLEM 21-62 What is the structure of the polymer produced by treatment of β-propiolactone with a small amount of hydroxide ion?



β-Propiolactone

PROBLEM 21-63 Polyimides with the structure shown are used as coatings on glass and plastics to improve scratch resistance. How would you synthesize a polyimide? (See Problem 21-39.)



A polyimide

PROBLEM 21-64 How would you distinguish spectroscopically between the following isomer pairs? Tell what differences you would expect to see.

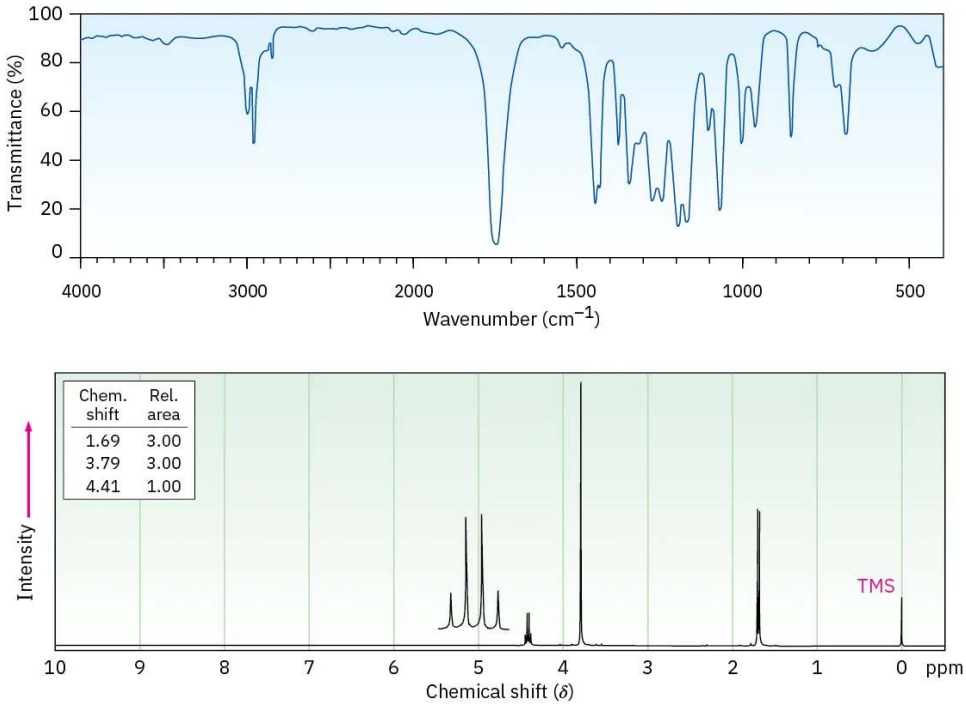
(a) *N*-Methylpropanamide and *N*,*N*-dimethylacetamide

(b) 5-Hydroxypentanenitrile and cyclobutanecarboxamide

(c) 4-Chlorobutanoic acid and 3-methoxypropanoyl chloride

(d) Ethyl propanoate and propyl acetate

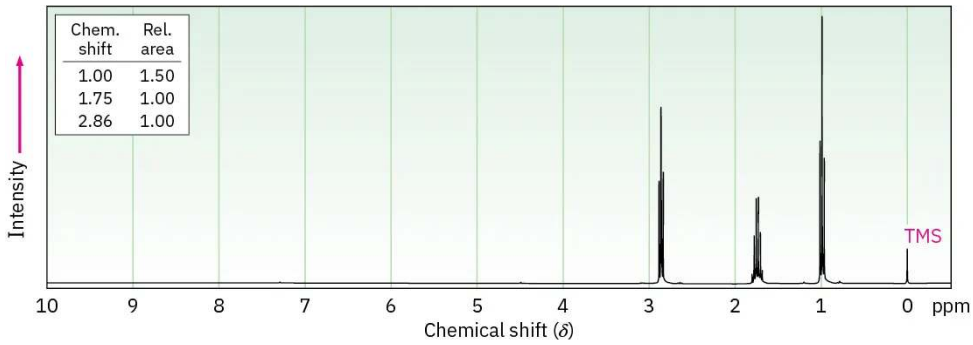
PROBLEM 21-65 Propose a structure for a compound, $C_4H_7ClO_2$, that has the following IR and ^1H NMR spectra:



PROBLEM 21-66 Assign structures to compounds with the following <sup">1H NMR spectra:

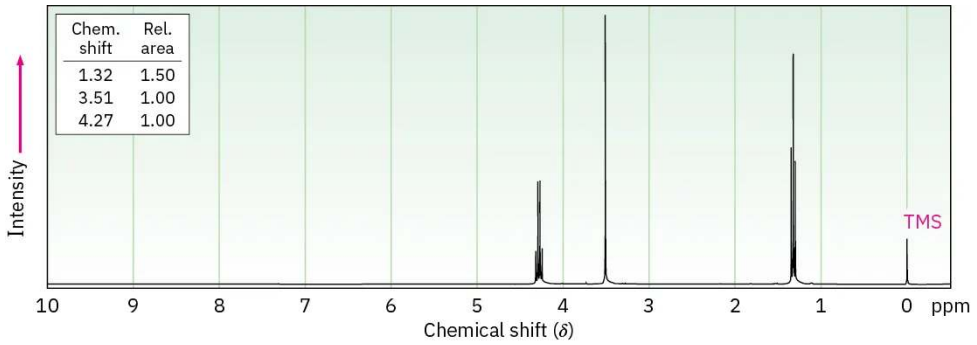
(a) C_4H_7ClO

IR: 1810 cm^{-1}



(b) $C_5H_7NO_2$

IR: 2250, 1735 cm^{-1}

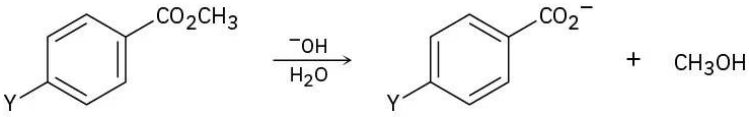


General Problems

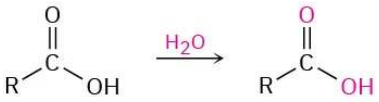
PROBLEM 21-67 The following reactivity order has been found for the basic hydrolysis of *p*-substituted methyl benzoates:

$$Y{=}NO_2 > Br > H > CH_3 > OCH_3$$

How can you explain this reactivity order? Where would you expect Y=C≡ N, Y=CHO, and Y=NH_2 to be in the reactivity list?

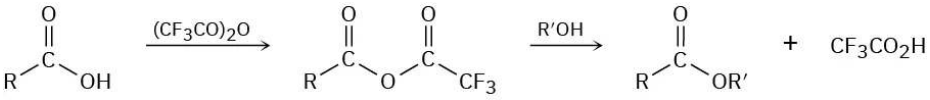


PROBLEM 21-68 When a carboxylic acid is dissolved in isotopically labeled water, the label rapidly becomes incorporated into both oxygen atoms of the carboxylic acid. Explain.



PROBLEM 21-69 We said in Section 21.6 that mechanistic studies on ester hydrolysis have been carried out using ethyl propanoate labeled with ^{18}O in the ether-like oxygen. Assume that ^{18}O-labeled acetic acid is your only source of isotopic oxygen, and then propose a synthesis of the labeled ethyl propanoate.

PROBLEM 21-70 Treatment of a carboxylic acid with trifluoroacetic anhydride leads to an unsymmetrical anhydride that rapidly reacts with alcohol to give an ester.

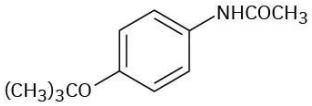


(a)Propose a mechanism for formation of the unsymmetrical anhydride.

(b) Why is the unsymmetrical anhydride unusually reactive?

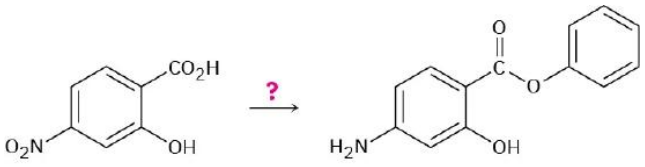
(c) Why does the unsymmetrical anhydride react as indicated rather than giving a trifluoroacetate ester plus carboxylic acid?

PROBLEM 21-71 Butacetin is an analgesic (pain-killing) agent that is synthesized commercially from *p*-fluoronitrobenzene. Propose a synthesis.



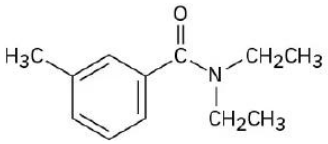
Butacetin

PROBLEM 21-72 Phenyl 4-aminosalicylate is a drug used in the treatment of tuberculosis. Propose a synthesis of this compound starting from 4-nitrosalicylic acid.



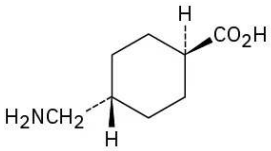
4-Nitrosalicylic acid **Phenyl 4-aminosalicylate**

PROBLEM 21-73 *N*,*N*-Diethyl-*m*-toluamide (DEET) is the active ingredient in many insect-repellent preparations. How might you synthesize this substance from *m*-bromotoluene?



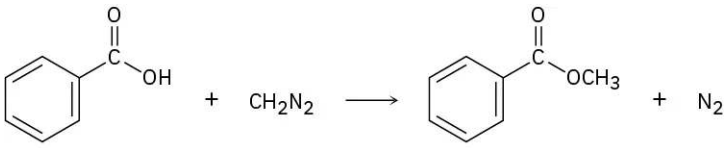
***N*,*N*-Diethyl-*m*-toluamide**

PROBLEM 21-74 Tranexamic acid, a drug useful against blood clotting, is prepared commercially from *p*-methylbenzonitrile. Formulate the steps likely to be used in the synthesis. (Don't worry about cis–trans isomers; heating to 300 °C interconverts the isomers.)



Tranexamic acid

PROBLEM 21-75 One frequently used method for preparing methyl esters is by reaction of carboxylic acids with diazomethane, CH_2N_2.



Benzoic acid **Diazomethane** **Methyl benzoate (100%)**

The reaction occurs in two steps: (**1**) protonation of diazomethane by the carboxylic acid to yield methyldiazonium ion, $CH_3N_2^+$, plus a carboxylate ion; and (**2**) reaction of the carboxylate ion with $CH_3N_2^+$.

(a) Draw two resonance structures of diazomethane, and account for step 1.

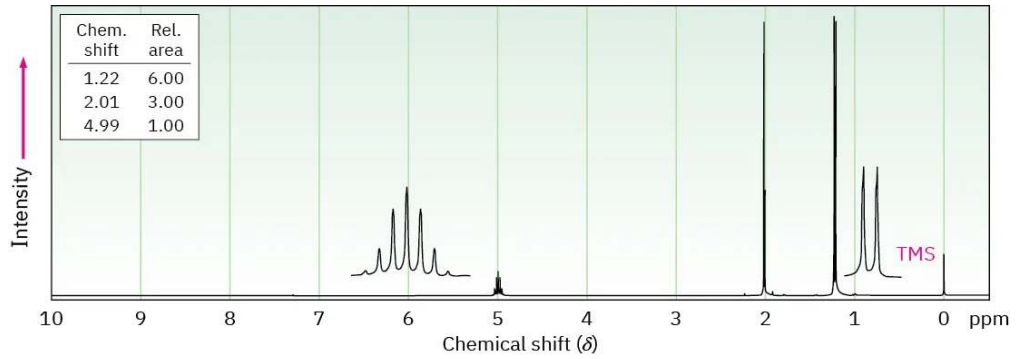
(b) What kind of reaction occurs in step 2?

PROBLEM 21-76 Draw the structure of the polymer you would expect to obtain from reaction of dimethyl terephthalate with a triol such as glycerol. What structural feature would this new polymer have that was not present in Dacron (Table 21.2)? How do you think this new feature might affect the properties of the polymer?

PROBLEM 21-77 Assign structures to compounds with the following ^1H NMR spectra:

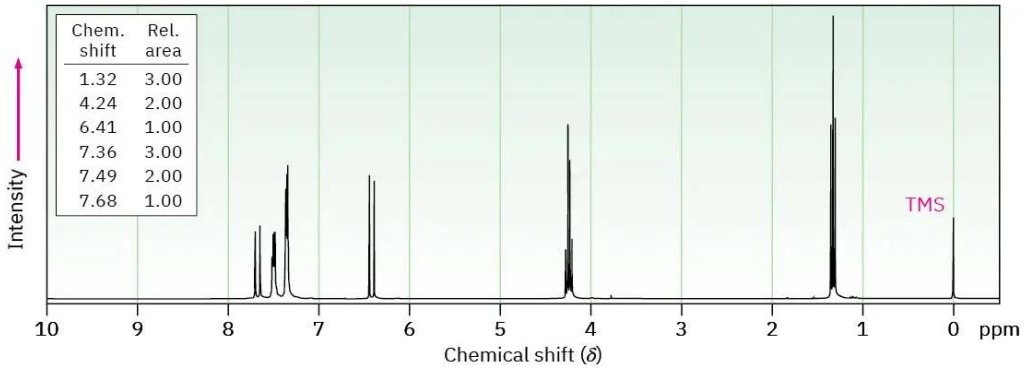
(a)$C_5H_{10}O_2$

IR: 1735 cm^{-1}



(b) $C_{11}H_{12}O_2$

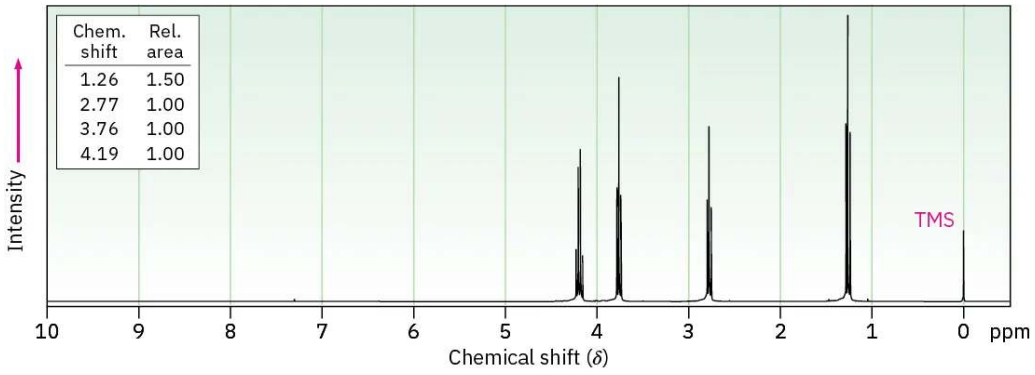
IR: 1710 cm^{-1}



PROBLEM 21-78 Propose structures for compounds with the following ^1H NMR spectra:

(a) $C_5H_9ClO_2$

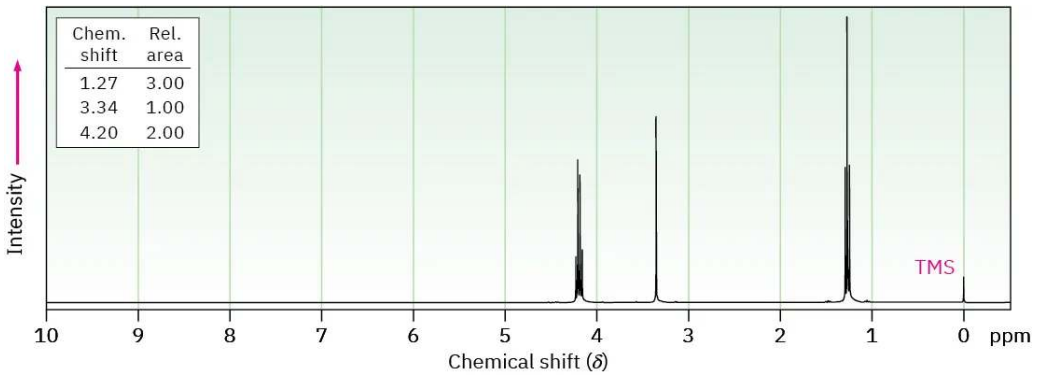
IR: 1735 cm^{-1}



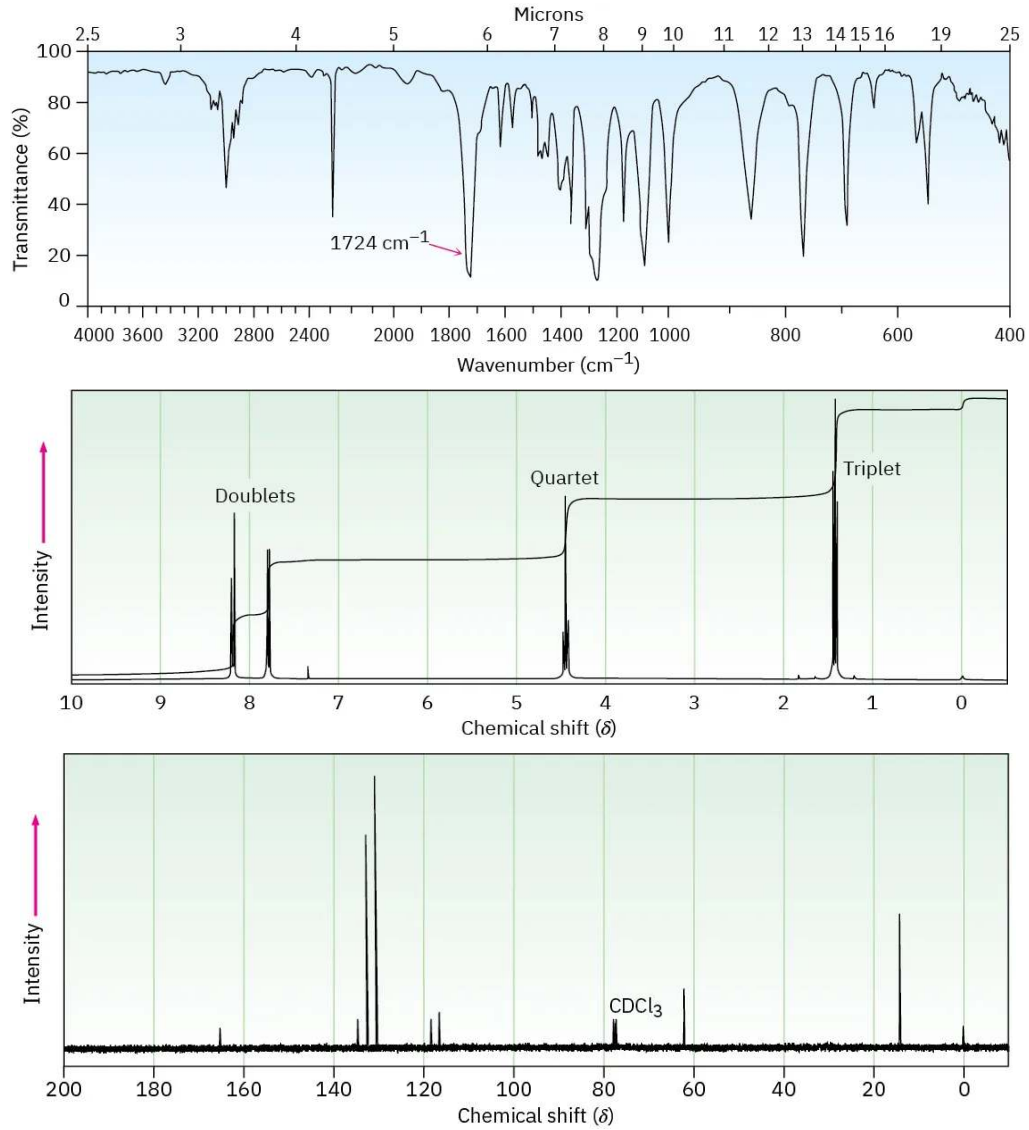
(b) $C_7H_{12}O_4$

IR: 1735 cm^{-1}

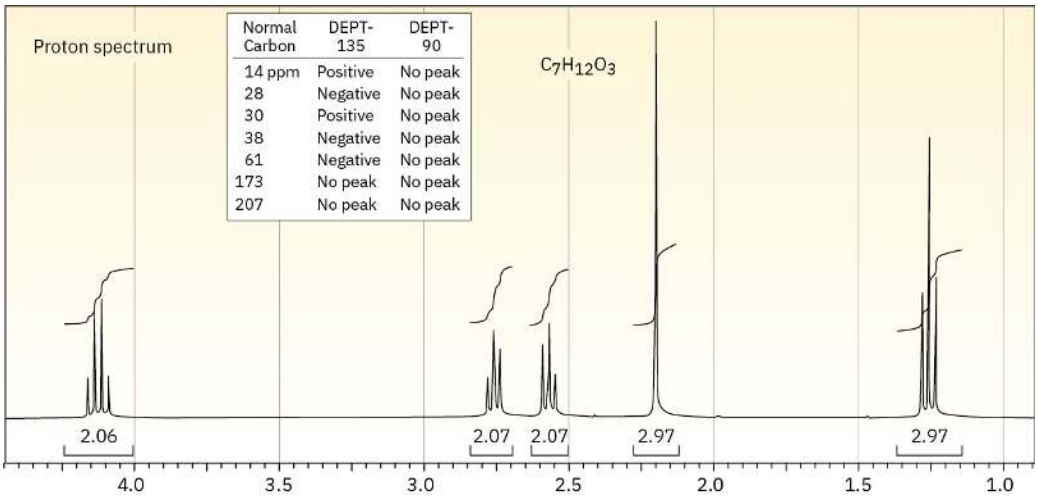
https://chem.libretexts.org/@go/page/507242



PROBLEM 21-79 Propose a structure for the compound with the formula $C_{19}H_9NO_2$ and the following IR and NMR spectra

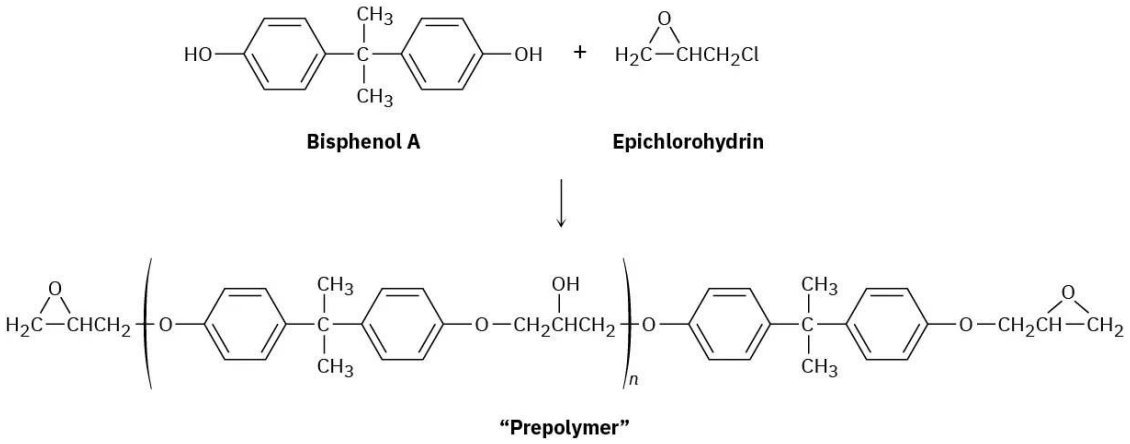


PROBLEM 21-80 Draw the structure of the compound that produced the following spectra. The infrared spectrum has strong bands at 1720 and 1738 cm^{-1}.



PROBLEM 21-81 When an amide is formed from an acid chloride or an anhydride, two equivalents of base are required. However, when an ester is used as the starting material, only one equivalent of base is needed. Explain this reactivity in terms of basicity of the leaving groups.

PROBLEM 21-82 Epoxy adhesives are prepared in two steps. S_N2 reaction of the disodium salt of bisphenol A with epichlorohydrin forms a "prepolymer," which is then "cured" by treatment with a triamine such as $H_2NCH_2CH_2NHCH_2CH_2NH_2$.



"Prepolymer"

Draw structures to show how the addition of triamine results in the strengthening of the polymer.

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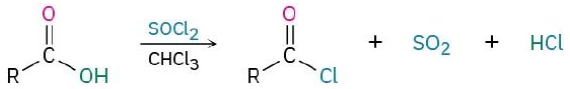
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7.S: Carboxylic Acid Derivatives (Summary)

Summary of Reactions by type of Reactions

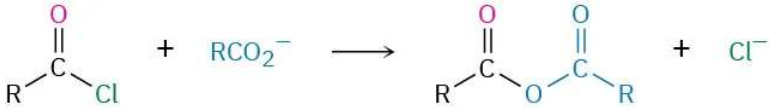
Synthesis of Acid Chlorides

Conversion of carboxylic acids into acid chlorides.



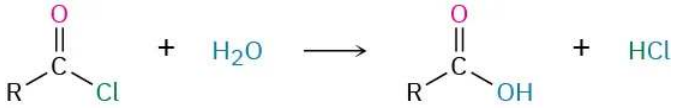
Synthesis of Anhydrides

Conversion of Acid Chlorides into anhydrides.

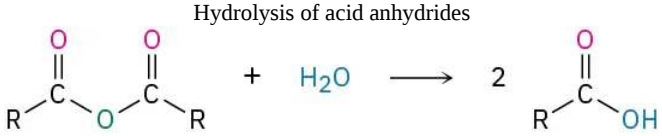


Synthesis of Carboxylic Acids (Hydrolysis)

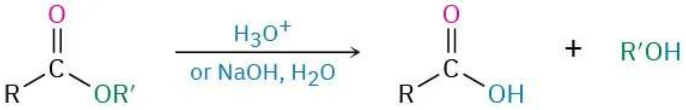
Hydrolysis of acid chlorides



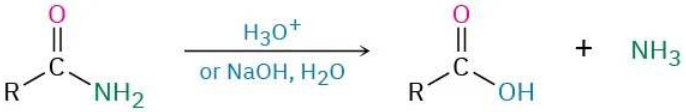
Hydrolysis of acid anhydrides



Hydrolysis of esters

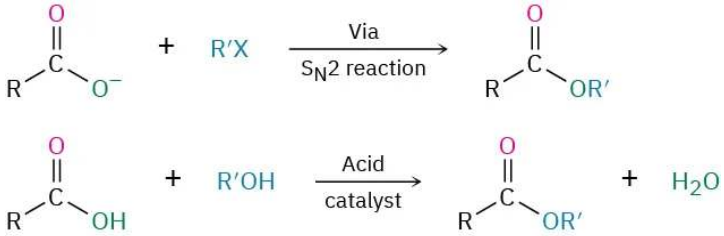


Hydrolysis of amides

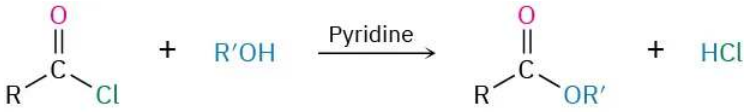


Synthesis of Esters (Alcoholysis)

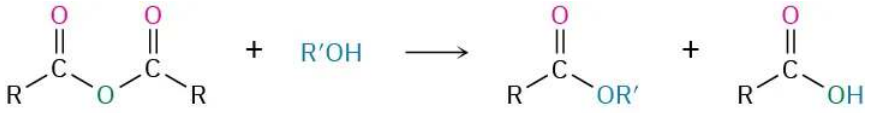
Conversion of Carboxylic Acids into Esters



Conversion of Acid Chlorides into Esters.

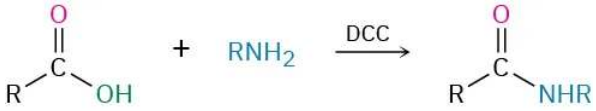


Conversion of Anhydrides into Esters and Carboxylic Acid.

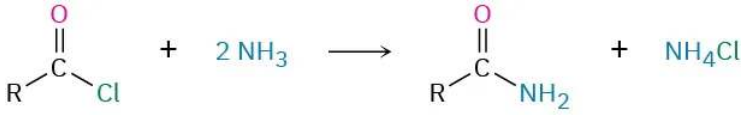


Synthesis of Amides (Aminolysis)

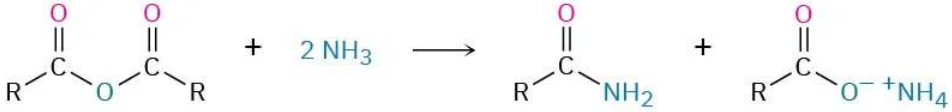
Conversion of carboxylic acids.



Conversion of Acid Chlorides



Conversion of Anhydrides

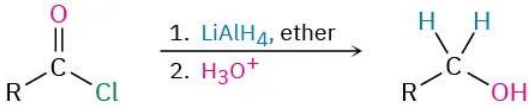


Reduction Reactions

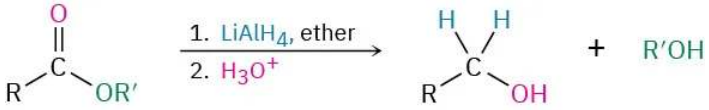
Reduction of carboxylic acids to yield primary alcohols



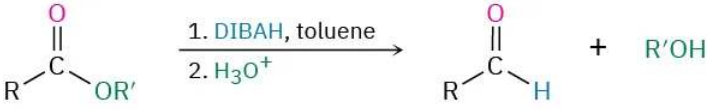
Reduction of Acid Chlorides to yield primary alcohols



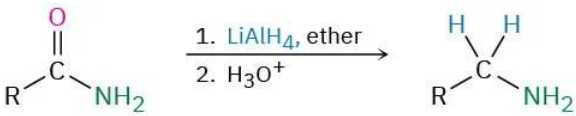
Reduction of Esters to yield primary alcohols



Partial reduction of Esters to yield aldehydes



Conversion of Amides into Amines.

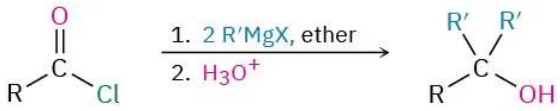


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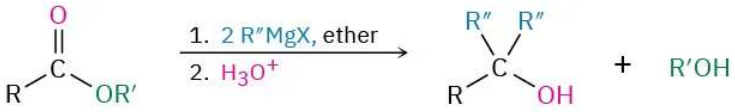
Organometallic Reactions

Grignard Reactions

Conversion of Carboxylic Acids to yield tertiary alcohols

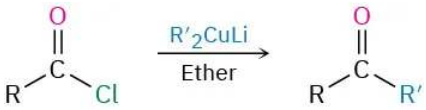


Conversion of Esters to yield tertiary alcohols



Gilman Reaction

Diorganocopper reaction to yield ketones



Concepts & Vocabulary

7.1 Chapter Objectives and Introduction to Carboxylic Acid Derivatives

- Carboxylic acid derivatives formed when the hydroxyl group of the carboxylic acid is replaced by a different group.
- Carboxylic acid derivatives are also known as acyl derivatives.
- Many types of carboxylic acid derivatives, the chapter focused on acid halides (acyl halides), anhydrides, esters, amides, thioesters, and acylphosphates.
- Cyclic esters are referred to as lactones and cyclic amides are referred to as lactams.
- Nucleophilic acyl substitution reactions convert the carboxylic acid to one of the derivatives.

7.2 Naming Carboxylic Acid Derivatives

- Acid halides are named following the IUPAC rules with the carboxylic acid ending with -oyl or -yl and the halide ending in an -ide.
- Anhydrides are named following the IUPAC rules with the carboxylic acid ending -acid being replaced by -anhydride.
- Esters are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -ate and the alkoxy alkyl chain as a substituent.
- Thioesters are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -thioate and the sulfide alkyl chain as a substituent.
- Primary amides are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -amide.
- Secondary or tertiary amides are named as primary amides are, but in additon an upper case N is used to designate the alkyl groups attached to the nitrogen atom, which are names as substituents.
- Cyclic amides (lactams) use a Greek letter to identify the location of the nitrogen in relation the carbonyl group.
- Acyl phosphates are named following the IUPAC rules with the carboxylic acid ending with -oyl or -yl and -phosphate.

7.3 Nucleophilic Acyl Substitution Reactions

- Carboxylic acid derivatives contain an electronegative heteroatom (typically oxygen, nitrogen, sulfur, or phosphorus) bonded directly to the carbonyl carbon represented by the symbol Y.
- The acyl group is the remainder of the molecule, which includes the carbonyl and the attached alkyl group.
- The Y group acts as a leaving group during the nucleophilic acyl substitution reaction.
- Stability of the negative charge on the Y group can be guaged by the pK_a of its corresponding acid (HY).
- Carboxylic acid derivatives undergo a reaction called nucleophilic acyl substitution.
- The electrophile is the carbon of the carbonyl, which undergoes an attack by a nucelophile followed by the elimination of the Y group in the carboxylic acid derivative.
- The Y group is substituted for the nucleophile.
- The reactivity of the carboxylic acid derivatives depends on the stability of the carbonyl and the effectiveness of the leaving group.
- Stabilization of the carbonyl reduces the electrophilic character of the carbonyl group.
- The ability of the leaving group to stabilize negative charge creates a more effective leaving group.
- More reactive carboxylic acid derivatives can be used to make less reactive carboxylic acid derivatives.

7.4 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

- The hydroxyl of a carboxylic acid is a poor leaving group, but activating the carbonyl and converting the hydroxyl to a better leaving group allow for reactions to occur.
- Carboxylic acids can be converted to acid chlorides using thionyl chloride ($SOCl_2$).
- Carboxylic acids can be converted into anhydrides by condensing two carboxylic acids together and the loss of water.
- Carboxylic acids can be converted into esters in two ways.
  - Using the carboxylate in an S_N2 mechanism.
  - The Fischer Esterification
    - Acid catalyzed
    - Pushing equilibrium in the forward direction using Le Chatelier's principle
- Carboxylic acids can be converted into amides in two ways.
  - Direct conversion by heating ammonium carboxylate salts
  - Using a coupling agent like dicyclohexylcarbodiimide (DCC)
- Carboxylic acids can be reduced to primary alcohols using lithium aluminum hydride or borane tetrahydrofurane (THF).
- In biological chemistry, carboxylate anions are converted to an acyl phosphate, which requires phosphrylation using TAP as the phosphate donor or thioesters using coenzyme A.

7.5 Chemistry of Acid Halides

- Carboxylic acids react with thionyl chloride to form acid chlorides.
- Carboxylic acids react with phosphorus tribromide to form acid bromides.
- Acid chlorides are the most reactive carboxylic acid derivative, which allows them to easily convert to other acyl compounds.
- Acid chlorides undergo hydrolysis to form carboxylic acids.
- Acid chlorides react with carboxylic acid to form anhydrides through a nucleophilic acyl substitution.
- Acid chlorides react with alcohol nucleophiles to produce esters with pyridine being used to neutralize the HCl produced.
- Acid chlorides can be reduced to aldehydes using hindered reducing agents that have only one equivalent of hydride.
- Acid chlorides react with amines to form amides, usually an excess of amine is used to neutralize the HCl produced.
- Acid chlorides react with Grignard reagents to form tertiary alcohols.
- Acid chlorides react with Gillman reagents to produce ketones.

7.6 Chemistry of Acid Anhydrides

- Anhydrides are generally made by nucleophilic acyl substitution reactions using an acid chloride and a carboxylic acid or carboxylate anion.
- Anhydrides are not as reactive as acid chlorides, but still undergo many of the same reactions.
- Asymmetrical anhydrides not used to make amides or esters since multiple products can be formed.

- Anhydrides undergo hydrolysis to form carboxylic acids.
- Anhydrides react with alcohol nucleophiles to produce esters.
- Anhydrides can react with amines to form the corresponding amides.

7.7 Chemistry of Esters

- Esters are present in many biologically important molecules.
- Esters are often the sources of pleasant aromas of many fruits and perfumes.
- Esters are also present in commercial and synthetic applications.
- Esters are prepared
  - most often using nucleophilic acyl substitution using an acid chloride and an alcohol
  - using nucleophilic acyl substitution using an anhydride and an alcohol
  - using nucleophilic acyl substitution using a carboxylic acid and an alcohol
  - deprotonating a carboxlylic acid for an SN_2 reaction
- Esters can be converted to a carboxylic acid through a reaction witt water and a catalytic amount of strong acid.
- Saponification is the reaction between an ester and water under basic conditions to produce a carboxylate anion.
- Esters can be inter-converted using a transesterfication reaction.
- Esters can be converted into amides using an ester and a large excess of amine.
- Esters can be reduced to primary alcohols using lithium aluminum hydride.
- Like acid chlorides, esters can be reduced to aldehydes using weak, bulky reducing agents.
- Esters can react with Grignard reagents to form tertiary alcohols.

7.8 Chemistry of Amides

- Amides make up the backbone of proteins when the amino group of one amino acid reacts with the carboxylate carbon of another amino acid and from an amide linkage (peptide bond).
- Amides are most commonly prepared through the reaction of an acid chloride and amine.
- Amides are relatively unreactive towards nucleophilic acyl substitutions due to the poor leaving group ability of its nitrogen containing Y group.
- Amides can be hydrolzyed to a carboxylic acid and ammonia or amine by heating the reaction under acidic or basic aqueous solutions.
- Hydrolysis of amines is the first step in metabolism of dietary proteins.
- Primary amines can be converted into a nitrile through a reaction with thionyl chloride.
- Amides are reduced to amines by treatment with lithium aluminum hydride.

7.9 Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives

- Acyl phosphates, acyl adenosine phosphophates, and thioesters are all activated forms of carboxylate groups in biochemical reactions.
- Carboxylate groups of fatty acids are converted to thioesters using coenzyme A
- Thioesters are a good substrate for a number of metabolic transformations.
- Thioesters can be hydrolyzed, resulting back to a carboxylate anion.
- Thioesters and acyl phosphates are the most reactive biologically relevant acyl groups, but not as reactive as an acid chloride or anhydride.

7.10 Polyamides and Polyesters - Step-Growth Polymers

- Step-growth is one of two broad classes of polymerization methods.
- Step-growth polymerizations are linked by a carbon-heteroatom bond formed in non-sequential steps.
- A step-growth polymerization starts with two complementary functional groups on different monomers reacting to form a dimer.
- Using a difunctional monomer, allows step-growth polymers to grow in two directions at once.
- Fibers are made from some form of polymer.
- Nylon

- First successful fully synthetic polymer was nylon-6,6 in 1938 by the company DuPont, which is a polyamide.
- Nylons are widely used synthetic fibers, which are found in commercial products such as rope, sails, clothing, and more.

- Esterfication
  - Can also be used to form primary linkages in step-growth polymers.
  - Polyester is typically produced when a dicarboxylic acid and a diol react together.
  - The most important polyester is polyethylene terephthalate (PET), which is used to make bottles for soda.
  - Polyesters are fibers often used in many fabrics.
- Polycarbonates
  - Monomer is a carbonate, which acts like a double ester and can undergo a type of double transesterification reaction with two alcohols.
  - A carbonate is difunctional and can react with a diol to form polymers called polycarbonates.
  - Used in engineering because they are strong materials, but easily molded.
  - Polycarbonates are found in DVDs, compact discs, and Blu-ray discs.

7.11 Spectroscopy of Carboxylic Acid Derivatives

- IR of acid chlorides shows a strong carbonyl stretch around 1800 cm^{-1}.
- IR of anhydrides show two strong carbonyl stretch around 1750 and 1820 cm^{-1}.
- IR of esters shows a strong carbonyl stretch around 1740 cm^{-1} and a strong CO-O stretch around 1150 to 1250 cm^{-1}.
- IR of amides shows a strong carbonyl stretch around 1700 cm^{-1}, primary and secondary amides have two bands and tertiary amides have one band and a strong N-H stretch around 3170 to 3500 cm^{-1} in primary and secondary amides.
- ^{1}H NMR of acid halides do not have any distinctive peaks.
- ^{1}H NMR of anhydrides do not have any distinctive peaks, but symmetrical anhydrides will produce equivalent protons on either side.
- ^{1}H NMR of esters and thioesters have an alkyl group attached to the heteroatom. For esters, the alkoxide protons will show up in the 3.5-4.5 ppm region, while those attached to the sulfur in thioesters will show up in the 2.0-3.0 ppm region.
- ^{1}H NMR of amides have the possibility of alkyl groups or hydrogens attached. Resonances for protons attached to the carbon bonded to the nitrogen of the amide resonate between 2.0-3.0 ppm region. The NH protons of primary and secondary amides resonate in the 7.5-8.5 ppm regions, which will be broad.
- ^{13}C NMR of carboxylic acid derivatives show the carbonyl carbon at 160-180 ppm.
- ^{13}C NMR of esters also have the carbon attached to the alkoxide of the ester, which appears at 50-90 ppm.
- ^{13}C NMR of amides also have the carbon attached to the nitrogen of the amide, which appears at 20-65 ppm.
- ^{13}C NMR of thioesters also have the carbon attached to the sulfur, which appears at 20-45 ppm.
- Mass spectra of carboxylic acid derivatives show a base peak due to the acylium ion.

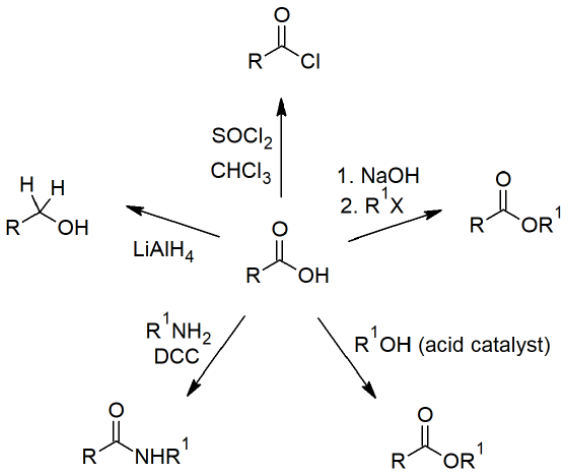
Skills to Master

- 1 Name carboxylic acid derivatives using IUPAC rules.
- 2 Draw the structure of carboxylic acid derivatives from the IUPAC name.
- 3 Compare the stability of different carboxylic acid derivatives to determine reactivity.
- 4 Determine the products for nucleophilic acyl substitution reactions.
- 5 Provide step-by-step mechanism for the Fischer esterification.
- 6 Show how to synthesize an ester from a carboxylic acid and alcohol.
- 7 Show mechanisms for the different carboxylic acid derivatives starting from an acid chloride.
- 8 Show how to synthesize the different carboxylic acid derivatives starting from an acid chloride.
- 9 Provide step-by-step mechanisms for the different carboxylic acid derivatives starting from an anhydride.
- 10 Show how to synthesize the different carboxylic acid derivatives starting from an anhydride.
- 11 Understand why the hydrolysis of an ester is not reversible under basic conditions and why the reverse does not produce an ester.
- 12 Be able to synthesize tertiary alcohols from esters.
- 13 Provide a step-by-step mechanism for the hydrolysis of an amide under acidic and basic conditions.

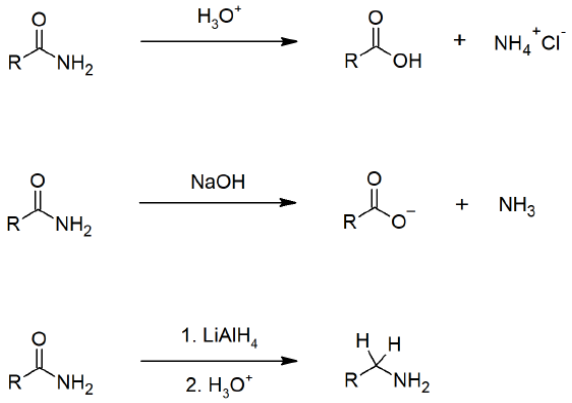
- 14 Provide the structure of different polymers using the bracketed notation and the monomers from the polymer.
- 15 Use IR, NMR, and MS to identify different carboxylic acid derivatives.

Summary of Reactions by Functional Groups

Carboxylic Acid Reactions

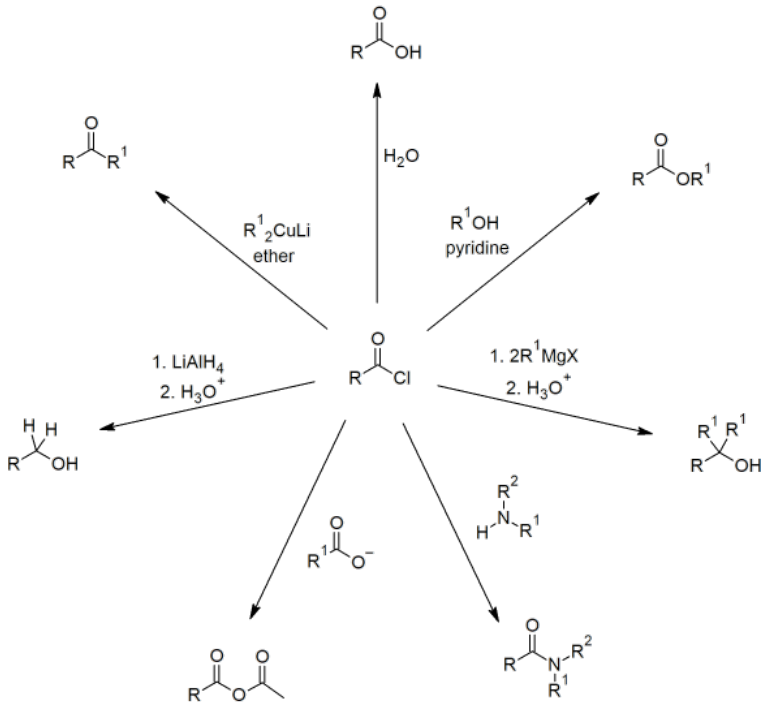


Amide Reactions

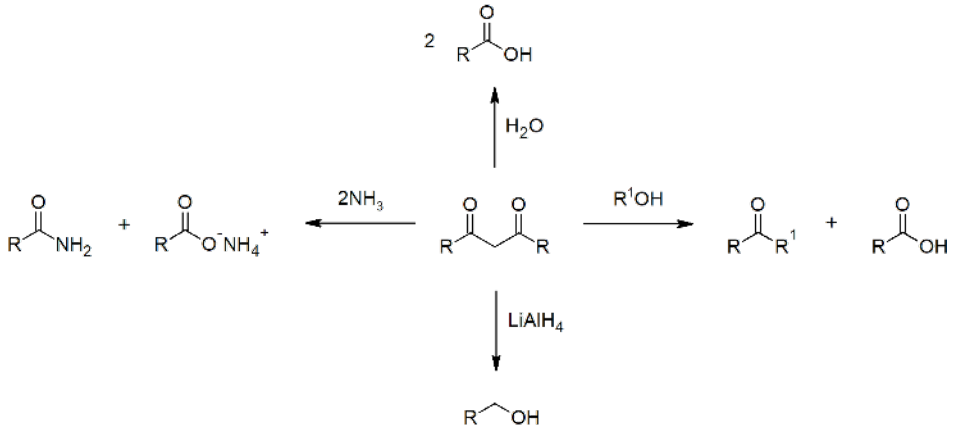


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Acid Chloride Reactions

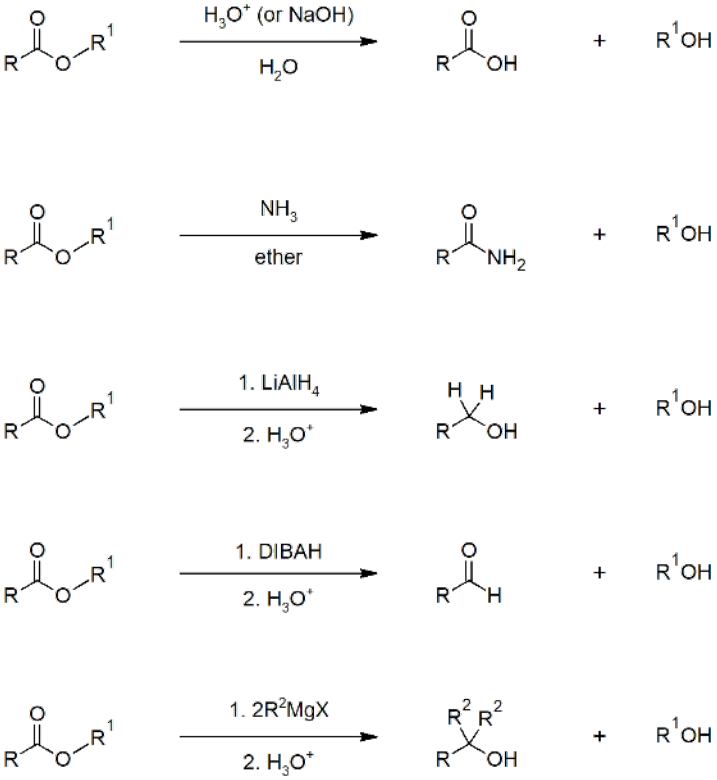


Acid Anhydride Reactions



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Ester Reactions



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CHAPTER OVERVIEW

8: Carbonyl Alpha-Substitution Reactions

Learning Objectives

When you have completed Chapter 8, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
3. solve road-map problems that require a knowledge of carbonyl alpha-substitution reactions.
4. define, and use in context, the key terms introduced.

Alpha-substitution reactions are the third major type of reaction that you will study in your investigation of the chemistry of carbonyl compounds. As you will see, these reactions proceed through the formation of the enol form of the carbonyl compound.

After a brief review of keto-enol tautomerism, we begin our discussion of alpha-substitution reactions by looking at the methods in which the enol form of the carbonyl compound is directly involved. After discussing the factors that influence the formation and stability of enolate anions, we will examine some halogenation reactions in which an enolate ion is formed as an intermediate.

The chapter concludes with a study of the alkylation of enolate anions. These reactions are of tremendous use in organic syntheses, as they provide a method of forming new carbon-carbon bonds, and hence facilitate the laboratory preparation of increasingly complex compounds.

8.0: Chapter Objectives and Introduction to Carbonyl Alpha-Substitution Reactions
8.1: Keto-Enol Tautomerism
8.2: Reactivity of Enols- The Mechanism of Alpha-Substitution Reactions
8.3: Alpha Halogenation of Aldehydes and Ketones
8.4: Alpha Bromination of Carboxylic Acids
8.5: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation
8.6: Reactivity of Enolate Ions
8.7: Alkylation of Enolate Ions
8.8: Additional Problems
8.S: Carbonyl Alpha-Substitution Reactions (Summary)

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8.0: Chapter Objectives and Introduction to Carbonyl Alpha-Substitution Reactions

Objectives

After completing this section, you should be able to write a general mechanism for an alpha-substitution reaction of a carbonyl compound.

Key Terms

Make certain that you can define, and use in context, the key terms below.

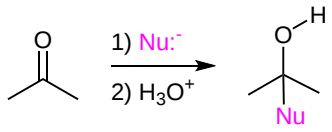
- alpha (α) position
- alpha-substitution reaction

Study Notes

An “alpha-substitution reaction” of a carbonyl compound is a reaction in which one of the hydrogen atoms on the carbon adjacent to the carbonyl group is substituted by some other atom or group. Attack by the electrophile (E^+) can occur on the enol or enolate intermediate.

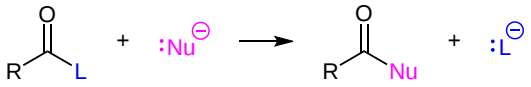
There are four common types of reactions involving compounds containing a carbonyl bond. The first two, nucleophilic addition and nucleophilic acyl substitution, have been discussed in previous chapters.

Nucleophilic Addition occurs due to the electrophilic nature of the carbonyl carbon. After addition of a nucleophile, the carbonyl becomes a tetrahedral alkoxide intermediate which is usually protonated to become an -OH group.



Nucleophilic Addition to a Carbonyl

Nucleophilic Acyl Substitution is similar in that a tetrahedral alkoxide intermediate is formed after nucleophilic addition to the carbonyl. However, subsequent removal of the leaving group allows for the C=O (carbonyl) bond to reform. Overall, there is a substitution of the leaving group with the incoming nucleophile.

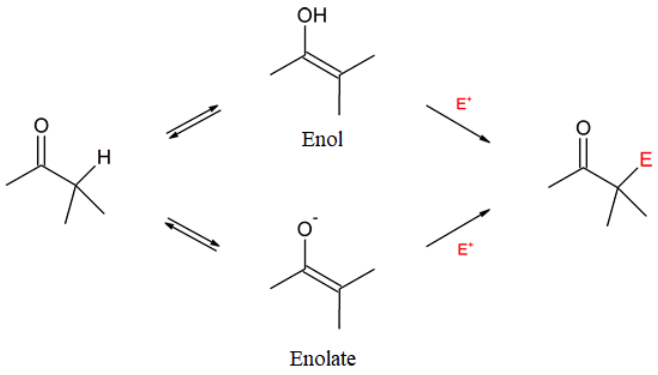


L = Leaving Group

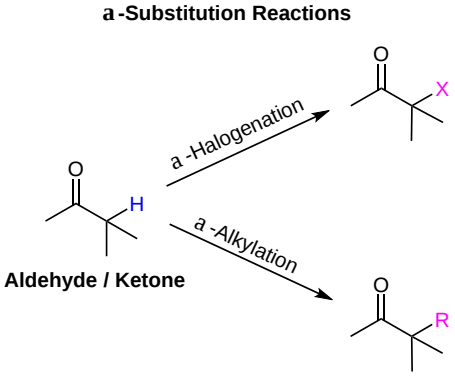
Nucleophilic Acyl Substitution Involving a Carbonyl

Reactions at The Alpha Carbon

The remaining common carbonyl reaction types are α-substitutions and carbonyl condensations. Both utilize the special properties of carbons directly adjacent to carbonyls which are called **α-carbons**. These reactions, which can be regarded as the backbone of much synthetic organic chemistry, usually result in the replacement of a hydrogen attached to an α-carbon with some type of electrophile. These reactions involve two new nucleophilic species called the enol and the enolate.



This chapter will focus on α-substitutions reactions. Although there are many carbonyl containing functional groups, the initial investigation in this chapter will focus on α-substitutions reactions using aldehydes and ketones. Important examples considered in this chapter include α-halogenation and α-alkylation.



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8.1: Keto-Enol Tautomerism

Objectives

After completing this section, you should be able to

1. write an equation to illustrate keto-enol tautomerism.
2. write a detailed mechanism for acid-catalyzed keto-enol tautomerism.
3. write a detailed mechanism for base-catalyzed keto-enol tautomerism.
4. draw the structure of the enol form of a given carbonyl compound.

Key Terms

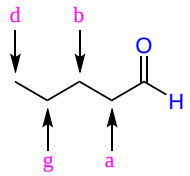
Make certain that you can define, and use in context, the key terms below.

- enol
- keto
- tautomerism
- tautomers
- enolate ion

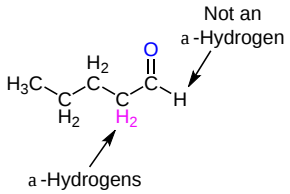
Study Notes

Keto-enol tautomerism was first introduced in Section 9.4, in the discussion of the hydration of alkynes. The subject was raised again in the chapter entitled A Preview of Carbonyl Compounds, during the brief overview of the alpha-substitution reactions of carbonyl compounds. You may wish to review these sections before proceeding.

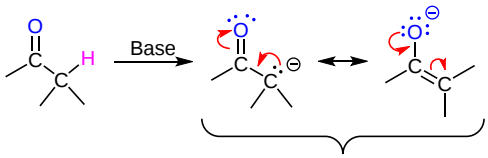
Often, the position of a carbon atom near a carbonyl group is designated using Greek letters. The atom adjacent to the carbonyl is alpha, the next removed is beta and so on. The carbon in the carbonyl group is used as reference point and is not assigned a Greek letter. Likewise, hydrogens bare the same Greek letter as the carbon atoms to which they are attached. α-Hydrogens are bonded to α-carbons and β-hydrogens are bonded to β-carbons etc.



The presence of α-hydrogens in a molecule provides the possibility of certain chemical reactions, which will be discussed in this chapter and in **Chapter 9**. Because of this, the ability to identify α-hydrogens is an important skill. As shown below, pentanal has two α-hydrogens. Note that aldehyde hydrogens are not given a Greek letter, they are simply referred to as an aldehyde hydrogen.

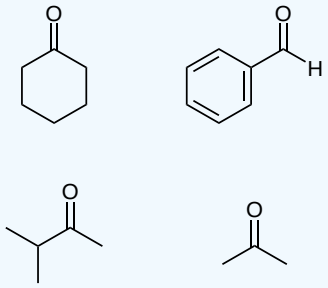


α-hydrogens, which are attached to a carbon directly adjacent to a carbonyl group, display unusual acidity. This is almost exclusively due to the resonance stabilization of the carbanion conjugate base, called an enolate, as illustrated in the diagram below. The effect of the stabilizing C=O is seen when comparing the pK_a for the α-hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to that of a typical alkyl C-H bond (~40-50).

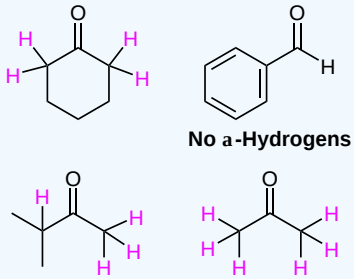


Example 8.1.1

Indicate any α-hydrogens contained in the following molecules:

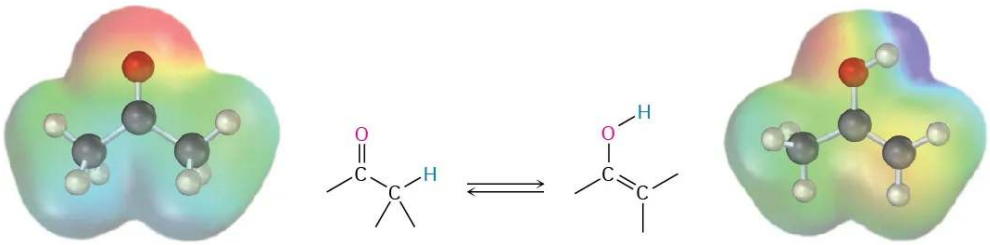


Solution



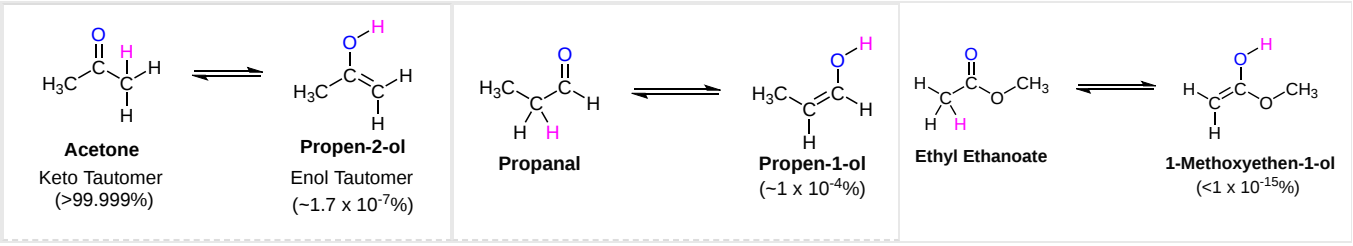
Keto-enol Tautomerization

Because of the acidity of α-hydrogens, many carbonyl containing compounds undergo a proton-transfer equilibrium called tautomerism. Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group. Because tautomers involve the rearrangement of atoms, they are distinctly different than resonance forms, which only differ in the position of bonds and lone pair electrons. This discussion focuses on carbonyl groups with α-hydrogens, which undergo keto-enol tautomerism. Keto implies that the tautomer contains a carbonyl bond while enol implies the presence of a double bond and a hydroxyl group.

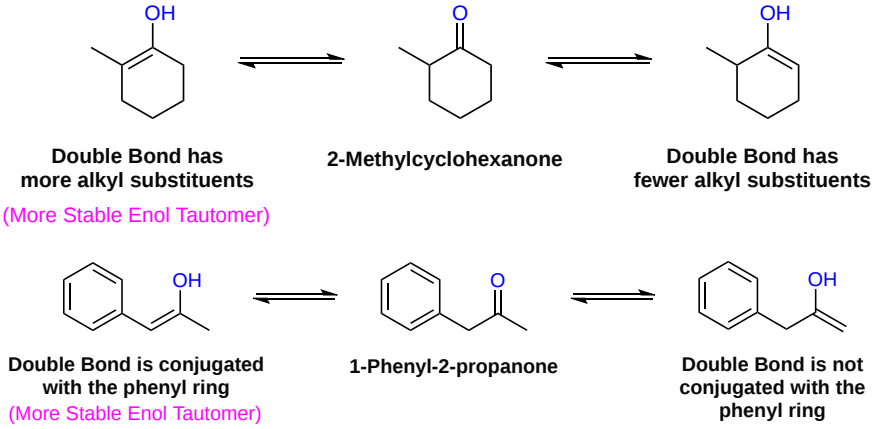


The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer. For simple carbonyl compounds under normal conditions, the equilibrium usually strongly favors the keto tautomer (acetone, for example, is >99.999% keto tautomer). The keto tautomer is preferred because it is usually more stable than the enol tautomer by about 45–60 kJ/mol, which is mainly due to the C=O double bond (-749 kJ/mol) being stronger than the C=C double bond (-611

kJ/mol). Because ketones have two alky groups donating electron density into the carbonyl carbon, they tend to be more stable and therefore less apt to form the enol tautomer than aldehydes. For example, propanal is 1000 times more likely to be in its enol tautomer than acetone. With carboxylic acid derivatives, the leaving group tends to stabilize the carbonyl through electron donation which makes the formation of the enol tautomer much less likely. In general, ketones are over 100,000,000 times more likely to be in an enol tautomer form than esters.

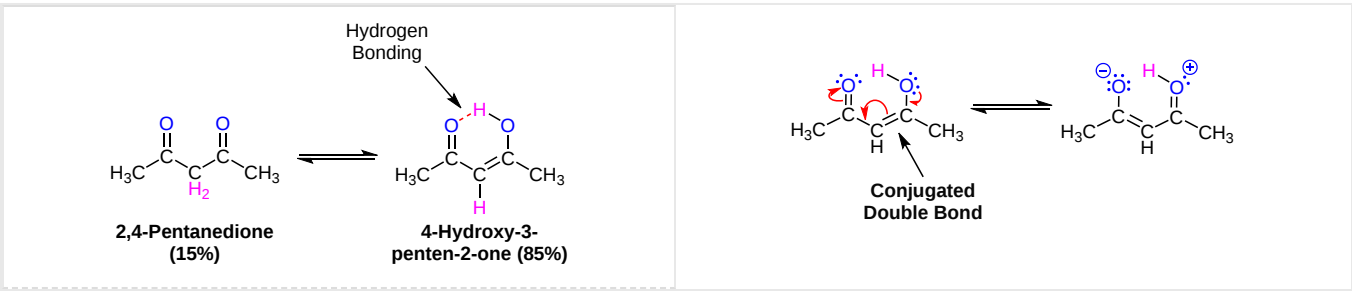


Aldehydes and symmetrical ketones typically only have one possible enol tautomer while asymmetrical ketones can have two or more. The preferred enol tautomer formed can be often be predicted by considering effects which can stabilize alkenes, such as conjugation and alkyl group substitution. The asymmetrical ketone, 2-methylcyclohexanone has two possible enol tautomers. Of the two tautomers, 2-methyl-1-cyclohexen-1-ol, is the more stable and therefore preferred due to the presence of an additional alkyl substituent. Likewise, 1-phenyl-1-propen-2-ol is the more stable enol tautomer of 1-phenyl-2-propanone due to conjugation with the phenyl ring.

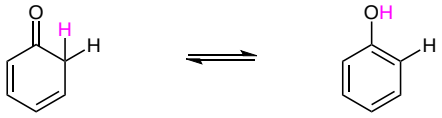


1,3-Dicarbonyls

In certain cases, additional stabilizing effects allow the enol tautomer to be preferred in the tautomerization equilibrium. In particular, the 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium. The diketone, 2,4-pentanedione, is in its enol form 85% of the time under normal conditions. The positioning of the carbonyl groups allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen. The alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization. Both of these stabilizing effects are not possible in the keto tautomer.



Another effect which can stabile an enol tautomer is aromaticity. When considering the molecule 2,4-cyclohexadienone, the enol tautomer is the aromatic molecule phenol. The stabilization gained by forming an aromatic ring is sufficient to make phenol the exclusive tautomer present in the equilibrium.

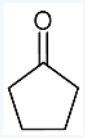
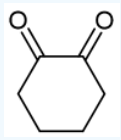
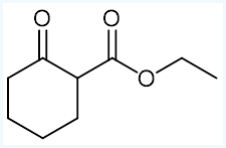


2,4-Cyclohexandienone
(Keto form, Non-aromatic)

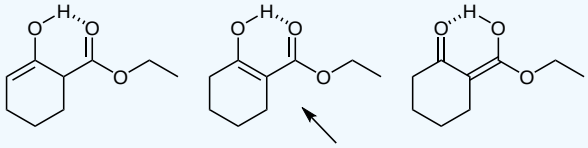
Phenol
(Enol form,aromatic)

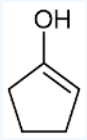
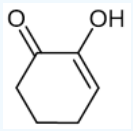
Example 8.1.2

Please list all the possible enol tautomers for the following compounds. If more than one is possible then indicate which is the most stable and why.

a)  b)  c) 

Solution



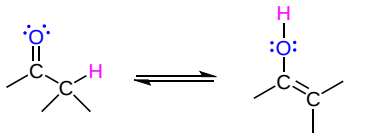
a)  b)  c)

This enol tautomer is the most stable due to hydrogen bonding, conjugation, and the ketone being in the enol form rather than the ester.

Mechanism for Catalyzed Keto-Enol Tautomerization

The enol tautomer has valuable nucleophilic characteristics. In neutral media, tautomerization is slow but it can be speed up by catalysis with acids or bases. Both pathways involve two separate proton transfer steps. Because enols are a key reactive intermediate, these mechanistic steps will be used repeatedly in later reactions. The following mechanistic steps represent the continuous interconversion between the keto and enol tautomers.

Overall Process

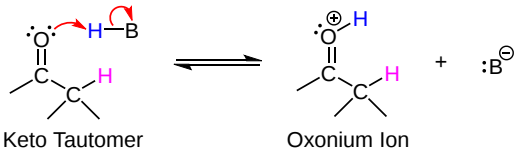
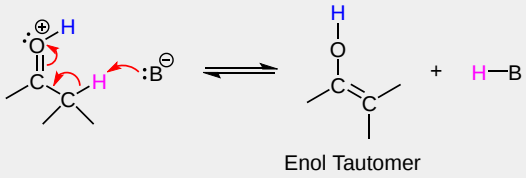


Keto Tautomer **Enol Tautomer**

Acidic Conditions

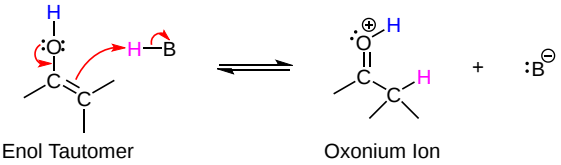
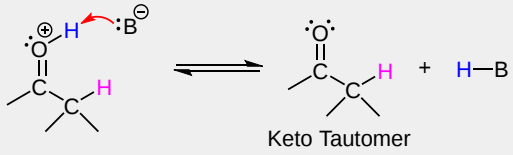
Keto Tautomer → Enol Tautomer

In the first step, the carbonyl oxygen is protonated by an acid to form an intermediate oxonium ion. A base removes an α-hydrogen during the second step forming a double bond by an E2 type reaction. This causes the pi electrons of the protonated carbonyl to move to the oxygen to form the hydroxyl group of the enol product and regenerating the acid catalyst.

1) Protonation of the carbonyl to form an oxonium ion	
2) Deprotonation of an α-hydrogen to form an enol	

Enol Tautomer → Keto Tautomer

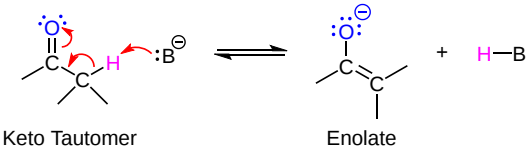
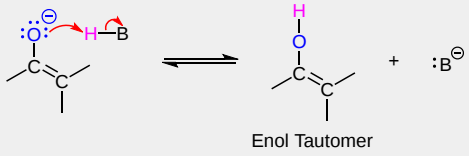
First, one of the lone pairs of electrons on the enol oxygen moves to form a pi bond with the adjacent carbon to create a oxonium ion. This also causes the pi bond electrons from the enol double bond to attack the electrophilic H^+ provided by acid catalyst forming a C-H bond in the α-position. This produced oxonium ion intermediate is subsequently deprotonated to form the neutral ketone and regenerate the acid catalyst.

1) Protonation at the α-carbon	
2) Deprotonation	

Under Basic Conditions

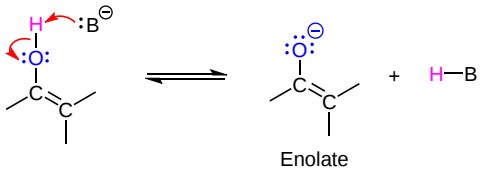
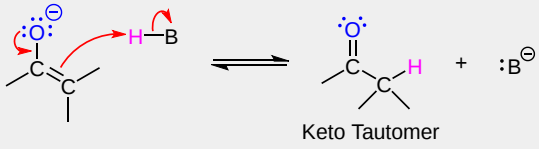
Keto Tautomer → Enol Tautomer

In the first step, a base removes an α-hydrogen from a carbonyl containing compound to form an alkene by an E2 like process. The causes the pi electrons of the carbonyl bond to move onto the carbonyl oxygen to form an enolate anion. The oxygen of the enolate anion is protonated in the second step to create a neutral enol and regenerate the base catalyst.

1) Deprotonation of a α-hydrogen to form an enolate ion	
2) Protonation the enolate ion to form an enol	

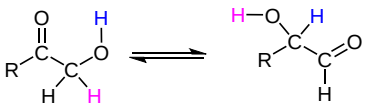
Enol Tautomer → Keto Tautomer

The mechanistic return to the keto tautomer begins with deprotonation of the hydroxyl hydrogen to produce an enolate ion. Then lone pair electrons from the enolate anion attack an electrophilic H^+ through conjugation with the double bond. This simultaneously forms the carbonyl double bond, adds an alpha hydrogen, and regenerates the base catalyst.

1) Deprotonation of the enol hydrogen	
2) Protonation of the α-carbon	

Biological Enol Forming Reactions

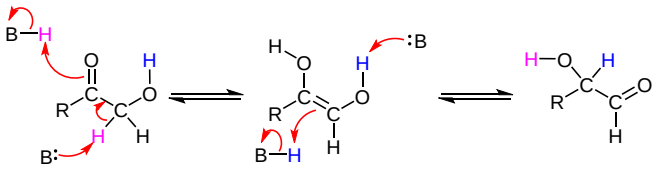
One very important family of isomerase enzymes catalyzes the shifting of a carbonyl group in sugar molecules using a process called an carbonyl isomerization. Carbonyl isomerization often involves converting between a ketose and an aldose. (recall that the terms ketose and aldose refer to sugar molecules containing ketone and aldehyde groups, respectively).



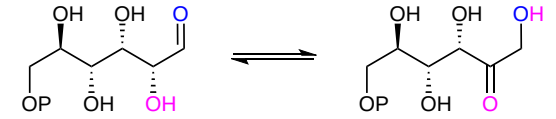
Carbonyl Isomerization

Mechanism

Carbonyl isomerization can only occur if there is an OH group adjacent to the carbonyl. Isomerization forms an ene-diol intermediate which has both OH hydrogens available to be removed to form a carbonyl. If the hydrogen from the original OH group is removed a new carbonyl bond is formed.



Carbonyl isomerization is involved in the metabolism of carbohydrates (starches and sugars) to their eventual conversion to CO_2 and H_2O. First, starches are broken down into glucose in the digestive tract. In the cells, the first step of the glycolysis pathway involves an enzyme converting glucose to glucose-6-phosphate. This is followed by the enzyme-catalyzed tautomerization of glucose-6-phosphate (an aldose) to fructose-6-phosphate (a ketose) through an enediol intermediate. Notice how the carbonyl has moved from the 1-carbon (terminal) to the 2-carbon.



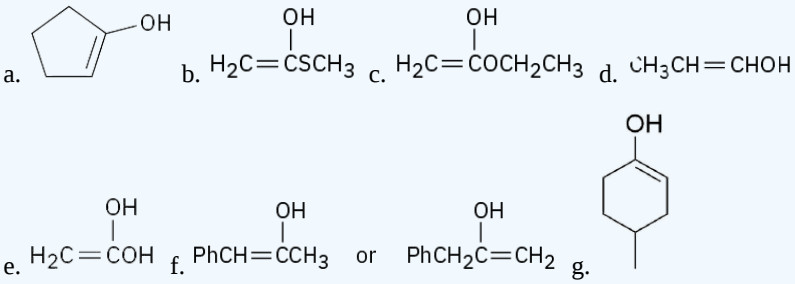
? Exercise 8.1.1

Draw structures for the enol tautomers of the following compounds:

a. Cyclopentanone **b.** Methyl thioacetate **c.** Ethyl acetate **d.** Propanal

e. Acetic acid **f.** Phenylacetone **g.** 4-methylcyclohexanone

Answer

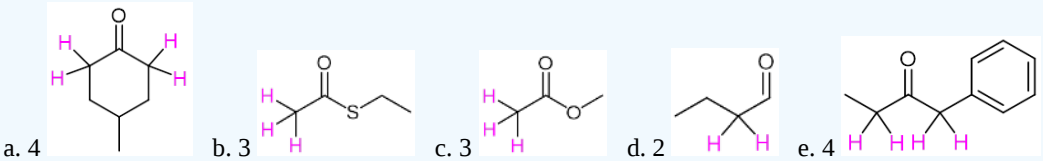


? Exercise 8.1.2

How many acidic hydrogens does each of the molecules listed below have? Identify them.

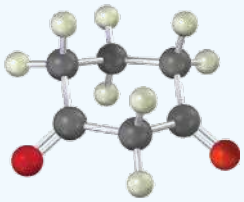
a. 4-methylcyclohexanone **b.** Ethyl thioacetate **c.** Methyl acetate **d.** Butanal **e.** 1-Phenyl-2-butanone

Answer

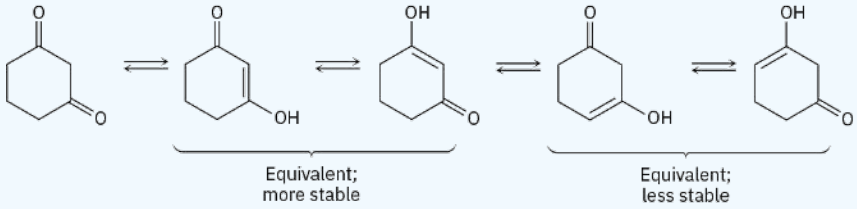


Exercise 8.1.3

Draw structures for all mono-enol forms of the following molecule **and** decide which mono-enol would be expected to be most stable. Explain.



Answer

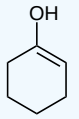


Exercise 8.1.4

Under normal conditions, cyclohexanone exists in the enol tautomer in a much higher percentage than acetone. Explain.

Answer

The enol tautomer of cyclohexanone has more alkyl substituents than the enol tautomer of acetone. This makes the double bond of the enol double bond of cyclohexanone more stable and easier to form.



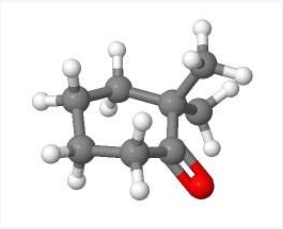
Enol of Cyclohexane



Enol of Acetone

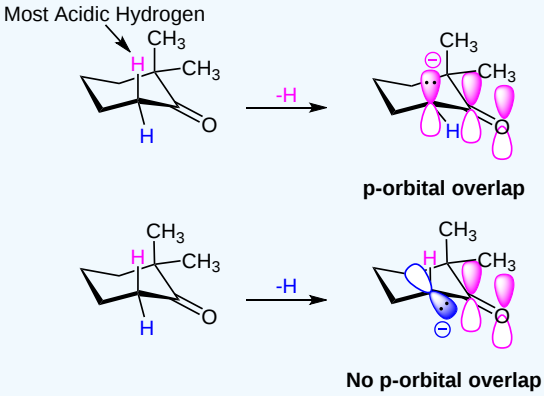
Exercise 8.1.5

For the following compound, please identify the most acidic hydrogen atom. Remember that for an enolate conjugate base to be stabilized through conjugation, the lone pair electrons must be contained in a p orbital parallel to the p orbitals, forming the C=O pi bond.



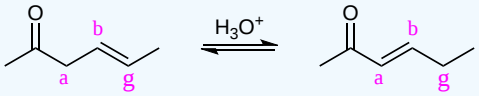
Answer

The presence of two methyl groups on one of the α-carbons of the carbonyl means that the two hydrogens on the other α-carbon may be deprotonated to form an enolate. When the indicated axial hydrogen is deprotonated the p-orbital formed is parallel with the carbonyl p-orbitals and can participate in overlap. If the equatorial hydrogen were to be deprotonated, the p-orbital formed would be perpendicular with the carbonyl p-orbitals and prevented from participating in overlap.

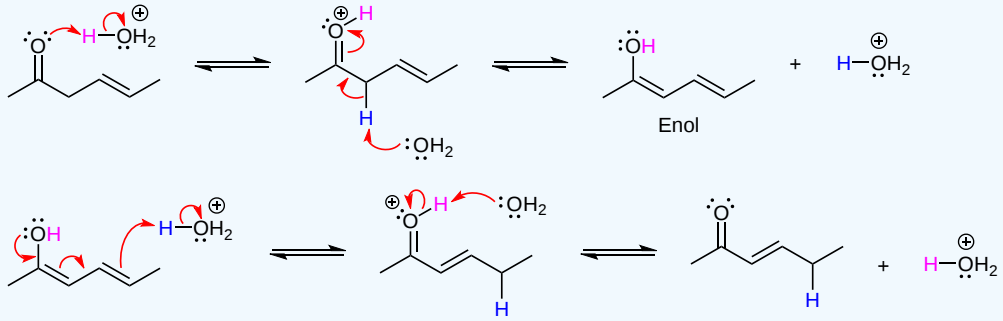


Exercise 8.1.6

Nonconjugated ß, gamma-unsaturated ketones, such as 2-hexen-4-one, can be converted to their α, ß-unsaturated isomers by treatment with an acid catalyst. Please propose a mechanism for this isomerization.



Answer



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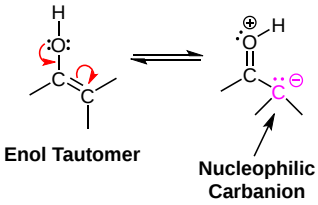
8.2: Reactivity of Enols- The Mechanism of Alpha-Substitution Reactions

Objectives

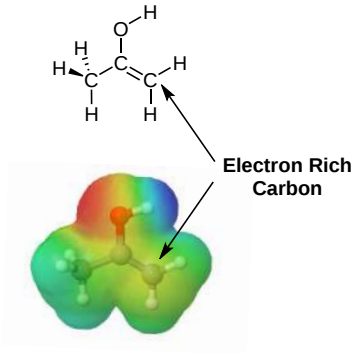
After completing this section, you should be able to write a detailed mechanism for an acid-catalyzed, alpha-substitution reaction of a carbonyl compound.

How Enols React

The oxygen of an enol can donate electron density into its double bond making it electron-rich and more reactive than typical alkenes.



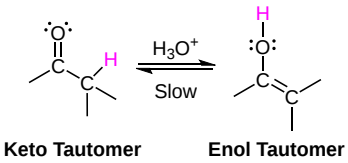
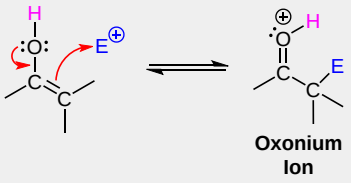
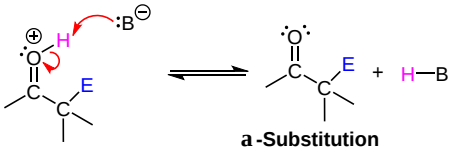
As seen in the electrostatic potential map for propen-2-ol ($CH_3COH=CH_2$), the enol tautomer of acetone, shows an increased electron density on the α-carbon (yellow) especially when compared to the -CH_3 carbon (blue/green). One of the resonance forms of an enol places a lone pair of electrons and a negative charge on the α-carbon forming a carbanion nucleophile. Enols react with electrophiles in a similar fashion as other carbanion nucleophiles, such as Grignard reagents.



Mechanism of Alpha Substitution Reactions Using an Enol

The mechanism begins with acid-catalyzed tautomerization to form an enol, as discussed in **Section 8.1**. Lone pair electrons on the enol oxygen move to become a C=O pi bond, thus creating a positively charged oxonium ion. This also causes electrons from the C=C enol pi bond to attack an electrophile, forming a C-E sigma bond. These two electron movements in concert represent the enol

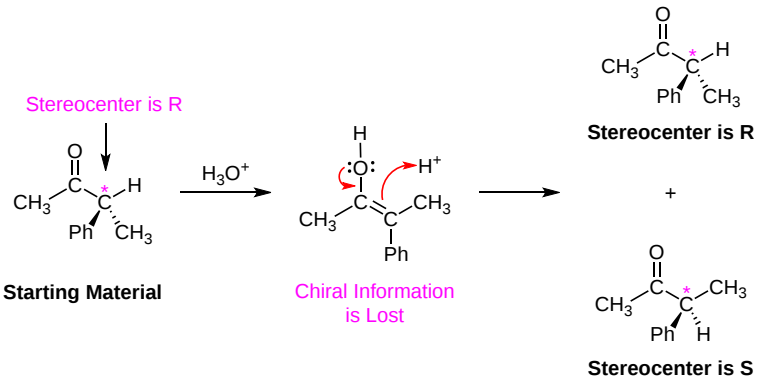
acting as a nucleophile. In the last step, an H^+ is removed from the carbonyl oxygen, regenerating the acid catalyst and forming an α-substituted carbonyl.

1) Acid catalyzed tautomerization to form an enol	
2) The nucleophilic enol attacks the electrophile	
3) Deprotonation of the carbonyl to produce an α-substituted product	

Stereochemical Implication of Enol Formation

During an acid-catalyzed enol formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond, which removes any chiral information from the original α-carbon. Because the enol alkene is planar, the incoming electrophile can attack from either the top or the bottom of the molecule. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter is formed during the reaction, the product will typically be a racemic mixture of enantiomers at the site of substitution.

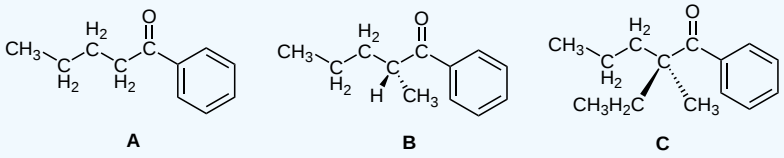
One of the easiest ways of displaying this process is through acid-catalyzed racemization. If a carbonyl compound has an α-carbon with a defined stereochemistry and an α-hydrogen, a racemic mixture can be formed simply through tautomerization. The addition of acid promotes the formation of the enol tautomer, which removes the chiral information of the α-carbon. The enol then attacks an H^+ electrophile to reform the keto tautomer, which then contains a racemic mixture of enantiomers.



Example of Acid-Catalyzed Racemization

? Exercise 8.2.1

Which of the following optically active ketones would undergo acid-catalyzed racemization? Explain.

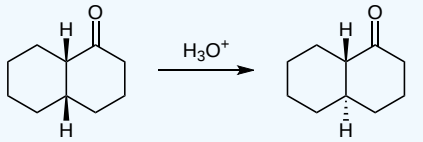


Answer

Molecule A would not because the alpha carbon is not a stereocenter. Molecule B would because the alpha carbon is a stereocenter and contains a hydrogen. Molecule C would not because it does not contain an alpha hydrogen.

? Exercise 8.2.2

When *cis*-Decalone is treated with an acid, it almost exclusively becomes *trans*-Decalone. Explain.



Answer

This change involves a process call epimerization. Epimers are diastereomers that differ at only one chiral carbon. Epimerization is a process where only one of multiple chiral carbons is changed. In this example, the stereocenter in question is a chiral carbon. The addition of an acid promotes this carbon becoming part of an enol, thereby losing its chiral information. When the enol tautomer converts back to the ketone tautomer, a mixture of both *cis* and *trans* epimers should form. However, as discussed in a previous section, the *trans* isomer of the decalin ring system is more stable than the *cis isomer*. Because there is a defined difference in stability, the trans isomer of decalone is preferred.

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8.3: Alpha Halogenation of Aldehydes and Ketones

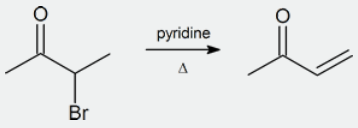
Objectives

After completing this section, you should be able to

1. write an equation to illustrate the alpha halogenation of aldehydes and ketones.
2. Identify the product formed from the alpha halogenation of a given aldehyde or ketone.
3. Identify the carbonyl compound, the reagents, or both, needed to prepare a given α-halogenated aldehyde or ketone.
4. illustrate the importance of the alpha halogenation of carbonyl compounds as an intermediate step in the synthesis of α,β-unsaturated aldehydes and ketones.
5. Write a detailed mechanism for the acid-catalyzed halogenation of a ketone.
6. Describe the evidence provided by kinetic experiments supporting the suggestion that the acid-catalyzed, alpha-halogenation of ketones proceeds via the rate-determining formation of an enol.

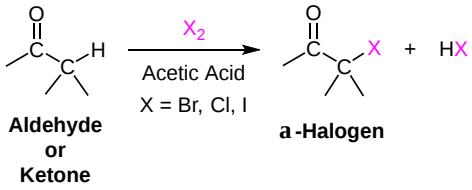
Study Notes

Note: α-bromo ketones are a good starting material to generate α,β-unsaturated ketones by dehydrobromination.



Aldehydes and ketones can substitute an α-hydrogen for a halogen atom in the presence of an acid. This reaction proceeds via acid-catalyzed tautomerization to form a nucleophilic enol, which then reacts with an electrophilic halogen (Cl_2, Br_2, or I_2). Because an enol intermediate is used, a racemic mixture of products can be produced. A particularly useful variation of this reaction uses bromine in acetic acid as the solvent. The α-bromo-substituted product can then be readily transformed into an α,β-unsaturated carbonyl by reaction with pyridine and heat.

General Reaction (α substitution)



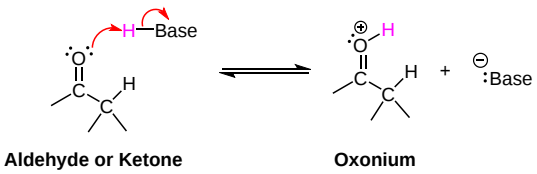
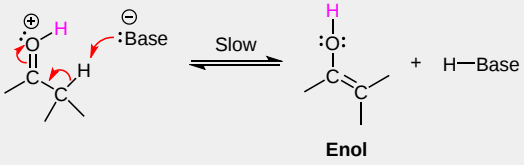
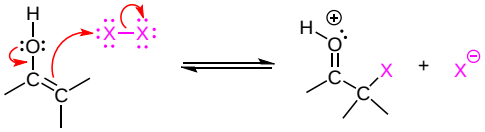
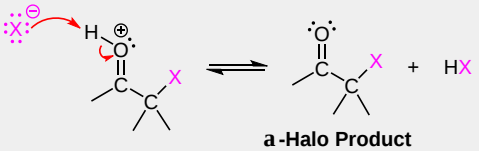
Example 8.3.1



Acid-Catalyzed Mechanism

The mechanism begins with protonation of the carbonyl oxygen, followed by removal of an α-hydrogen to form the enol. Lone pair electrons from the enol oxygen move to form a carbonyl, while the pi electrons from the double bond attack the halogen, forming

an oxonium ion intermediate with a C-X sigma bond in the α-position. Deprotonation of the oxonium ion intermediate provides the α-halogen-substituted product and regenerates the acid catalyst.

1) Protonation by the acid catalyst	
2) Removal of an α-hydrogen to form the enol. This step is slow and represents the rate-determining step.	
3) Nucleophilic attack on the halogen	
4) Deprotonation	

Experimental Evidence of the Enol Intermediate

This reaction was the focus of one of the first mechanistic investigations in organic chemistry. In the early 1900's chemist Arthur Lapworth showed that the rates of chlorination, bromination, and iodination of acetone were all the same. Also, it was shown that the rates for all three halogenation reactions were first-order with respect to acetone and the acid catalyst but independent of the halogen concentration (overall second-order for the mechanism). The rate law expression for the α-halogenation of a ketone can be given by:

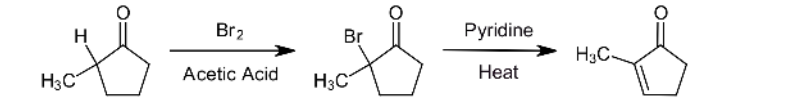
$$\text{rate} = k\,[\text{ketone}]\,[H^+]$$

This implies that the halogen participates in the mechanism through a fast step which occurs after the rate-determining step. These observations led Lapworth to theorize that the rate-determining step of the mechanism involves converting acetone to a more reactive form. The fact that the substitution occurs on the α-carbon led Lapworth to propose that the more reactive form was an enol tautomer of acetone.

Synthetic Uses for α-Halogenated Carbonyls

The product of an α-bromination can be converted to an α, β-unsaturated carbonyl by reaction with pyridine and heat which causes the elimination of H and Br. This reaction takes place by an E2 elimination mechanism and creates a C=C double bond which is conjugated with the carbonyl. In order to promote an E2 reaction, a sterically hindered base, pyridine, is often used.

An example of this reaction involves the α-bromination of 2-methylcyclopentanone to form 2-bromo-2-methylcyclopentanone. Because enol tautomers prefer to form on the more substituted α-carbon, α-bromination also occurs on the more substituted α-carbon. Although the enol intermediate causes a racemic mixture of the α-brominated compound to form, it is irrelevant because the chiral carbon is subsequently converted to an achiral alkene. Subsequent reaction with pyridine and heat forms the α,β-unsaturated ketone, 2-methyl-2-cyclopentenone.

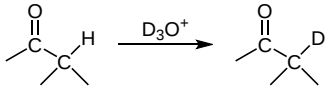


2-Methylcyclopentanone **(Racemic Mixture)** **2-Methyl-2-cyclopentenone**

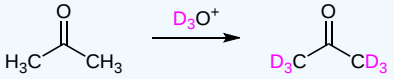
Deuterium Exchange

More evidence for the formation of an enol intermediate was provided by deuterium exchange. Deuterium is an isotope of hydrogen that contains one proton and one neutron. Due to the acidic nature of α-hydrogens, they can be exchanged with deuterium by reaction with the isotopic form of water, D_2O (deuterium oxide-heavy water). The process is accelerated by the addition of the deuterium equivalent of a strong acid, such as deuterium chloride (DCl), which quickly reacts with D_2O to form D_3O^+, the deuterium equivalent of hydronium (H_3O^+). If an excess of D_2O is used, the exchange process continues until all α-hydrogen atoms in a given compound are replaced with deuterium. Deuterium exchange is an effective method for introducing an isotopic label into a molecule. Also, deuterium does not appear in ^1H NMR, so deuterium exchange can help determine peak assignments.

General Reaction (Deuterium exchange)



Example 8.3.2

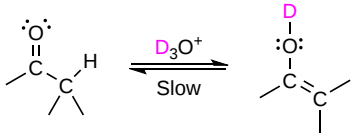
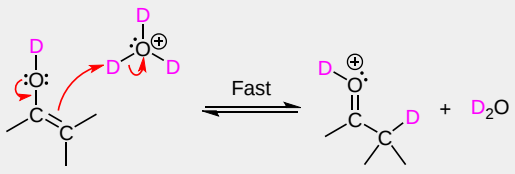
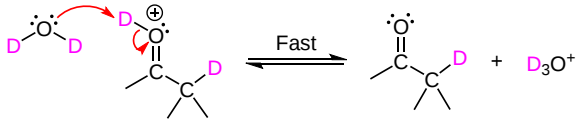


Acetone

Hexadeuteroacetone
Acetone-d6
Deuterated Acetone

Mechanism in Acidic Conditions

The mechanism for deuterium exchange is virtually the same as keto-enol tautomerism under acidic conditions, as shown in **Section 8.2**. The only difference is that when the keto tautomer is reformed, a deuterium is placed in the *α*-position.

1) Formation of an enol	 **Aldehyde or Ketone** **Enol**
2) *α*-Deuteration	
3) De-deuteration to form the keto tautomer	

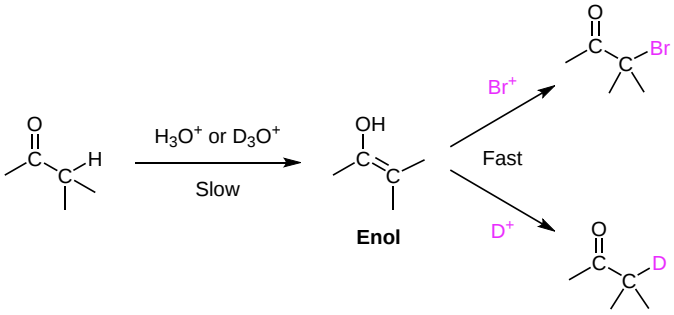
Example 8.3.3

A simple method for determining the number of α-hydrogen in a compound is through reaction of D_3O^+. The reaction product is then isolated, and its molecular weight is determined by mass spectrometry. For example, if cyclopentanone is reacted with D_3O^+, the isolated product has a molecular weight of 88 g/mol. Please explain how this method works and how many α-hydrogens cyclopentanone is predicted to have.

Solution

During acid-catalyzed deuterium exchange, each α-hydrogen in the compound is replaced with a deuterium. For each proton (AW = 1) replaced with a deuterium (AW = 2), the molecular weight of the compound is increased by one. Since cyclopentanone has a molecular weight of 84 g/mol and the isolated product has a molecular weight of 88 g/mol, it can be predicted that cyclopentanone has four α-hydrogens.

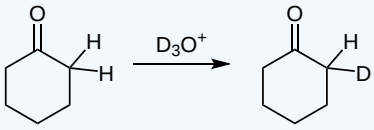
Kinetic investigations into the mechanism of this reaction provided further evidence for the formation of a reactive enol intermediate. It was shown that the rate of deuterium exchange was the same as the rate of halogenation for ketones. This implies that both reactions have a common intermediate involved in the rate-determining step of their mechanism, an enol.



Exercises

Exercise 8.3.1

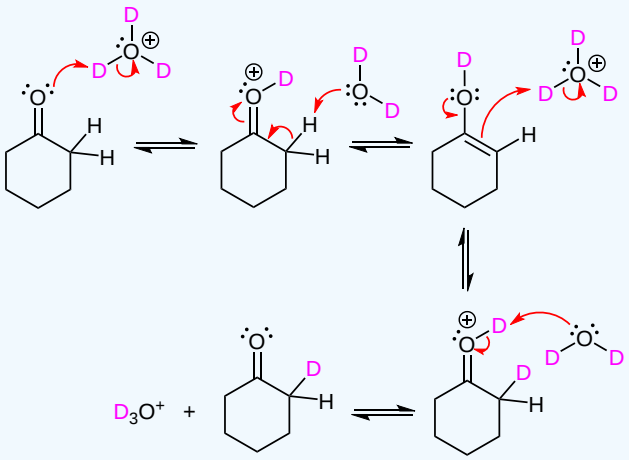
Write the complete mechanism for the deuteration of cyclohexanone on treatment with D_3O^+.



Answer

Acid-catalyzed formation of an enol is followed by deuteronation of the enol double bond and dedeuteronation of oxygen.

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Exercise 8.3.2

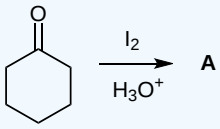
Show how you might prepare 1-penten-3-one from 3-pentanone.

Answer

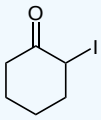
1) Br_2, H_3O^+; 2) Pyridine, Heat

Exercise 8.3.3

Draw the products of the following reaction:



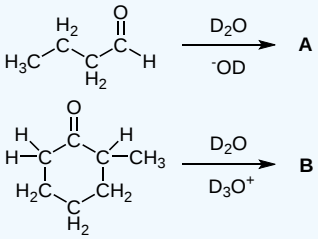
Answer



A

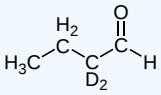
Exercise 8.3.4

Show the products of the following reactions:

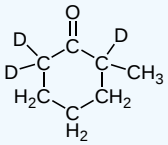


Answer

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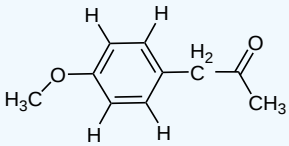
A



B

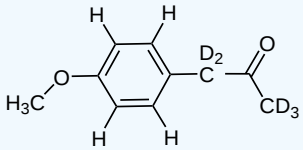
Exercise 8.3.5

The following compound was reacted with D_3O^+. The only signals that could be found in the 1H NMR spectrum of the product were at 3.9 ppm (3H) and 6.6-6.9 ppm (4H). Please explain the results of the NMR.



Answer

A deuterium exchange reaction occurred. All of the alpha-hydrogens in the molecule have been exchanged with deuterium. Because deuterium do not appear in a typical ^1H NMR, only the remaining hydrogens appear.



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8.4: Alpha Bromination of Carboxylic Acids

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the Hell-Volhard-Zelinskii reaction.
2. identify the product formed from the reaction of a given carboxylic acid with bromine and phosphorus tribromide.
3. identify the carboxylic acid, the reagents, or both, needed to synthesize a given α-bromo carboxylic acid.
4. outline the stereochemical implications of the fact that the Hell-Volhard-Zelinskii reaction proceeds through the formation of an acid bromide enol.

Study Notes

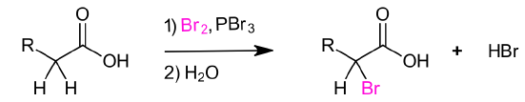
The reagents for the Hell-Volhard-Zelinskii reaction are given as bromine and phosphorus tribromide. In some questions, you may observe that only bromine and phosphorus are listed as reagents. Really there is no difference, as phosphorus tribromide would be formed *in situ* by the combination of bromine and red phosphorus:

$$3\,\mathrm{BR_2} + 2\,\mathrm{P} \longrightarrow 2\,\mathrm{PBr_3}$$

Excess bromine is required to ensure that enough reagent is available for the reaction with the enol.

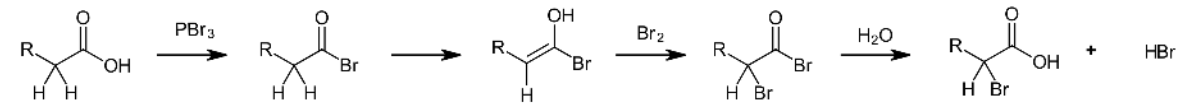
Hell-Volhard-Zelinskii Reaction

Although the α-bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, the reaction will generally not occur with carboxylic acids, esters, and amides. Carboxylic acids do not enolize to a sufficient extent since the carboxylic acid proton is preferably removed before an α-hydrogen. However, carboxylic acids, can be brominated in the α-position with a mixture of Br_2 and phosphorus tribromide (PBr_3) in what is called the Hell-Volhard-Zelinskii reaction.



Carboxylic Acid **α-Bromo Carboxylic Acid**

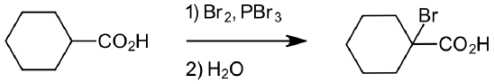
Mechanism

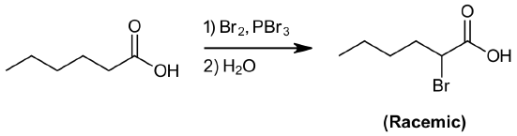


Carboxylic Acid **Acid Bromide** **Acid Bromide Enol** **α-Bromo Carboxylic Acid**

This reaction is the combination of three separate reaction mechanisms, all of which have been previously discussed. The mechanism starts with the reaction of the carboxylic acid with PBr_3 to form an acid bromide and HBr. Formation of an acid bromide is vital to this reaction because they lack the acidic carboxylic acid proton and can enolize much more readily making α-bromination possible. Next, HBr catalyzes the tautomerization of the acid bromide into its enol tautomer, acid bromide enol, which subsequently reacts with Br_2 to give α-bromination. Lastly, the product undergoes nucleophilic acyl substitution which cause the hydrolysis of the acid bromide to reform the carboxylic acid and the HBr catalyst. Because an enol intermediate is formed, this reaction will form a racemic mixture at the α-carbon.

Examples

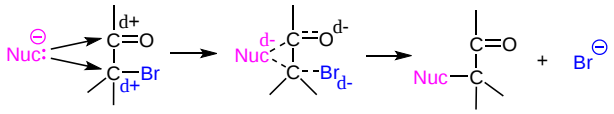




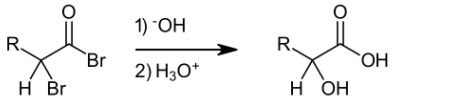
(Racemic)

Further Reactions of α-Bromo Carboxylic Acids

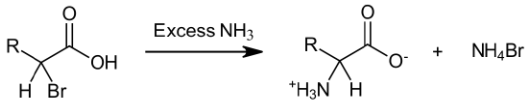
α-Bromo carboxylic acids are extremely useful synthetic intermediates because the halogen is highly reactive towards S_N2 reactions. Having the electrophilic carbon of the carbonyl adjacent to the electrophilic α-carbon attached to the bromine allows an incoming nucleophile to share its charge between the two. This stabilizes the transition state of the S_N2 reaction, lowering the energy of activation, and increasing reaction rates. Primary α-Halogenated carbonyls have S_N2 reaction rates that are much greater than the corresponding primary aliphatic halogens.



Because bromides are capable of reacting with a wide variety of nucleophiles, α-bromo carboxylic acids serve as important intermediates. Reaction of α-bromo carboxylic acids with an aqueous basic solution followed by an acidic work-up produces α-hydroxy carboxylic acids. Reaction of α-bromo carboxylic acids with an excess of ammonia provides α-amination, which provides a possible route to amino acids.

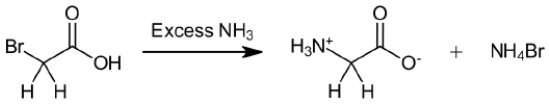


α-Bromo Carboxylic Acid **α-Hydroxy Carboxylic Acid**



α-Amino Carboxylic Acid

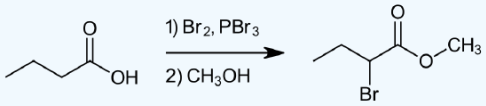
Example:



Bromoacetic acid **Glycine**

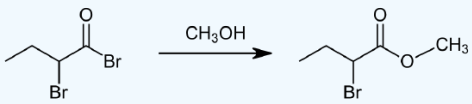
? Exercise 8.4.1

Explain why the following reaction occurs.



Answer

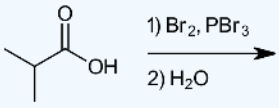
The first step represents the beginning of the Hell-Volhard-Zelinskii reaction which provides α-bromination and creates an acid bromide intermediate. The second step adds methanol which reacts with the acid bromide to produce an ester.

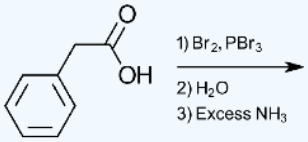


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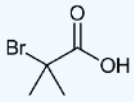
Exercise 8.4.2

Draw the products of the following reactions:

a- 

b- 

Answer

a- 

. b- α-hydroxy carboxylic acids

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8.5: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation

Objectives

After completing this section, you should be able to

1. explain why the alpha hydrogens of carbonyl compounds are more acidic than the hydrogens in a typical hydrocarbon.
2. list the properties that make lithium diisopropylamide a suitable reagent for converting a wide range of carbonyl compounds into their enolate anions.
3. arrange a given list of carbonyl compounds in order of increasing or decreasing acidity.
4. determine whether a given carbonyl-containing compound is more or less acidic than selected other compounds, such as water, ammonia, alcohols, alkanes, alkenes, alkynes and amines.
5. explain why dicarbonyl compounds, such as β-diketones, are more acidic than compounds that contain only a single carbonyl group.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- β-diketone
- β-keto ester

α-hydrogens are weakly acidic because their conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the adjacent carbonyl. Removal of an α-hydrogen creates an sp^2 hybridized carbon anion. The negative charge and lone pair electrons of the carbon anion are contained in an unhybridized p orbital. Orbital overlap between the p orbitals of the adjacent carbonyl pi bond and the lone pair electrons allows the negative charge to be shared with the electronegative Carbonyl oxygen, stabilizing the enolate ion. (Figure 8.5.1).

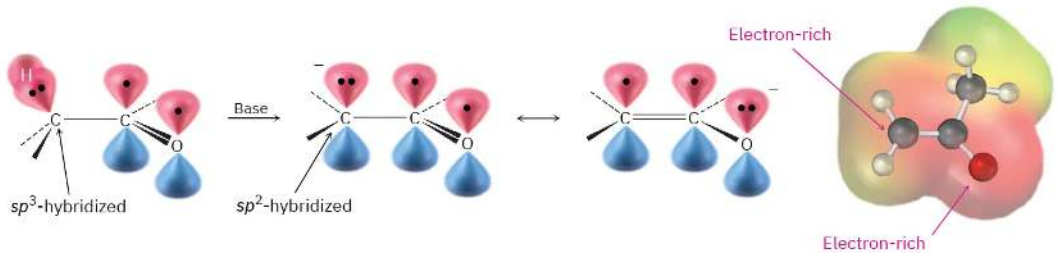
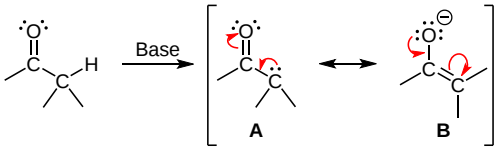


Figure 8.5.1: Mechanism of enolate-ion formation by abstraction of an α proton from a carbonyl compound. The enolate ion is stabilized by resonance, and the negative charge (red) is shared by the oxygen and the α carbon atom, as indicated in the electrostatic potential map.

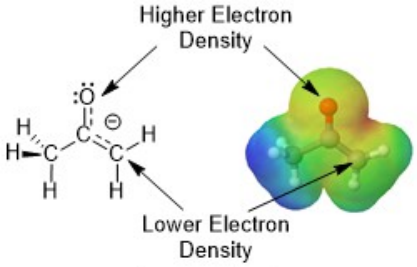
Enolate conjugation can be represent by two major resonance forms represented by structures A and B which share the negative charge (Shown Below). In resonance form A, the negative charge is on a carbon while in resonance form B the negative change is on an oxygen.



Enolate Ion

Resonance form B is preferred because oxygen is highly electronegative and better able to stabilize the negative charge. Both resonance form contribute to an overall resonance hybrid but not equally. Due to its stability, resonance form A makes a greater contribution to the resonance hybrid structure. Form A's increased contribution to the hybrid is seen when considering the electrostatic potential map of an acetone enolate. The red/yellow color shows there is a high electron density around the oxygen.

The yellow/green color around the enolate carbon shows that there is a lower but still significant electron density present. Notice that the electron density on the enolate carbon is much larger than the non-enolate carbon (blue color).



Acetone Enolate Resonance Hybrid

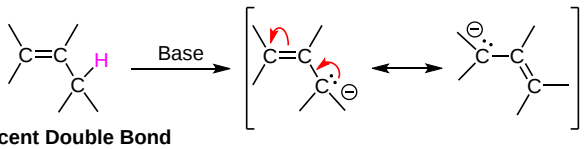
Acidity of α-hydrogens

The effect of an adjacent carbonyl on the acidity of α-hydrogens is seen when comparing the pK_a of aldehydes (~16-18) and ketones (~19-21) to the pK_a of an alkane (~50). The ability of the electronegative oxygen to stabilize a negative charge can be seen by considering the pK_a of an allyl C-H bond (~42).



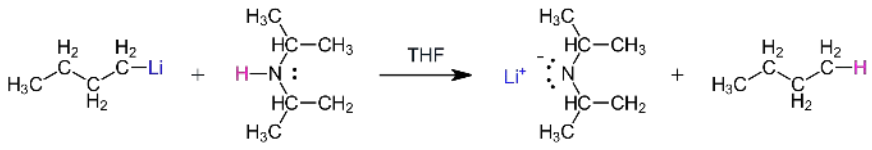
Aldehydes and Ketones (pK_a ~ 20) **Alkanes (pK_a ~ 50)**

Having a C-H bond adjacent to a C=C double bond allows the conjugate base created by deprotonating an allyl C-H bond to be stabilized by conjugation. However, the stability gained only provides a 10^8 increase in acidity when compared to an alkane. In comparison, the presence of an electronegative oxygen allows the acidity of an α-hydrogen to be 10^{20} times greater than that of an alkane.



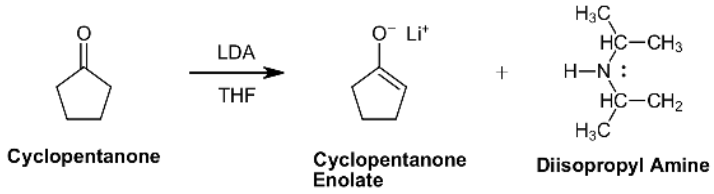
Adjacent Double Bond (pK_a ~ 42)

Although *α*-hydrogens are weakly acidic, typical strong bases such as a hydroxide or alkoxides are only capable of forming the enolate ion in very low concentrations. This can leave a significant concentration of the electrophilic carbonyl carbon remaining, which can react with the bases or the enolate. To achieve the complete deprotonation of aldehyde or ketone reactants to their enolate conjugate bases, a very strong base such as LDA (lithium diisopropylamide) must be used. Complete deprotonation removes the carbonyl groups of the starting material from the reaction mixture, preventing their formation of unwanted products. Also, the large alkyl substituents sterically hinder the ability of LDA and its corresponding amine (diisopropyl amine) to undergo nucleophilic addition to the carbonyl. In addition to aldehydes and ketones, LDA readily deprotonates a wide variety of carbonyl containing functional groups including esters, amides and nitriles. Ether solvents such as tetrahydrofuran (THF) are commonly used for enolate formation with LDA. Certain other strong bases, such as alkyl lithium and Grignard reagents, cannot be used to make enolate anions because they rapidly and irreversibly add to the carbonyl groups. Nevertheless, these very strong bases are useful for preparing LDA. By reacting *n*-butyllithium with diisopropylamine (pK_a 36), LDA can be easily formed.

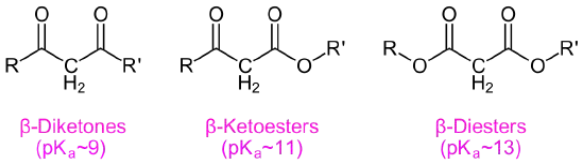


n-Butyllithium **Diisopropyl Amine** **Lithium Diisopropyl Amide (LDA)** **Butane**

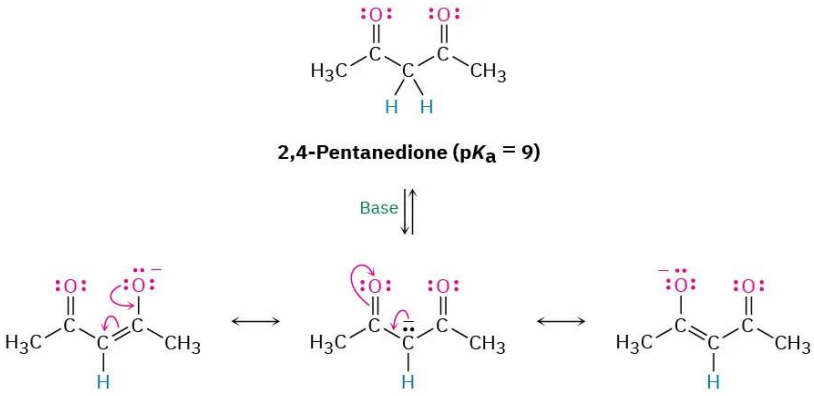
Example



Hydrogen atoms with two or more adjacent carbonyl groups are more acidic than typical α-hydrogens.



The enolate ions of compound such as *β*-diketones, *β*-keto-esters, and *β*-diesters are stabilized through additional resonance forms which share the negative charge with multiple carbonyl oxygens. The acidity of these compounds is increased to the point where weaker bases, such as sodium ethoxide ($NaOCH_2CH_3$) can be used to form the enolate.



The pK_a and acidic hydrogens of multiple functional groups are shown in the table below.

Table 8.5.1 Acidity Constants for Some Organic Compounds:

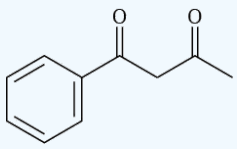
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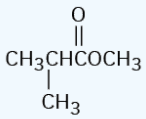
Functional Group	Structure	pK_a
carboxylic acid	HO–(C=O)R	5
nitro	$RCH_2–NO_2$	9
β-diketone *	$R(O=C)–CH_2–(C=O)R$	9
β-ketoester *	$R(O=C)–CH_2–(C=O)OR$	11
β-diester *	$RO(O=C)–CH_2–(C=O)OR$	13
amide	RNH–(C=O)R	15
alcohol	$RCH_2–OH$	16
aldehyde	$RCH_2–(C=O)H$	17
ketone	$RCH_2–(C=O)R$	20
thioester	$RCH_2–(C=O)SR$	21
ester	$RCH_2–(C=O)OR$	25
nitrile	$RCH_2–C≡N$	25
sulfone	$RCH_2–SO_2R$	25
amide	$RCH_2–(C=O)N(CH_3)_2$	30
alkane	$CH_3–R$	50

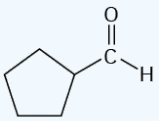
* = a functional group with two ketones.

Worked Example 8.5.1: Identifying the Acidic Hydrogens in a Compound

Identify the most acidic hydrogens in each of the following compounds, and rank the compounds in order of increasing acidity:

(a) 

(b) 

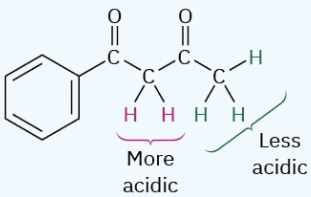
(c) 

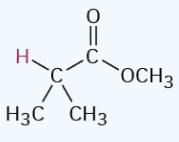
Strategy

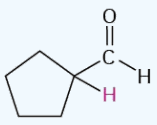
Hydrogens on carbon next to a carbonyl group are acidic. In general, a β-dicarbonyl compound is most acidic, a ketone or aldehyde is next most acidic, and a carboxylic acid derivative is least acidic. Remember that alcohols, phenols, and carboxylic acids are also acidic because of their –OH hydrogens.

Solution

The acidity order is (**a**) > (**c**) > (**b**). Acidic hydrogens are shown in red.

(a) 

(b) 

(c) 

Exercise 8.5.1

Identify the most acidic hydrogens in each of the following molecules:

a. CH_3CH_2CHO **b.** $(CH_3)_3C{-}COCH_3$ **c.** CH_3CO_2H **d.** Benzamide **e.** $CH_3CH_2CH_2CN$ **f.** $CH_3CON(CH_3)_2$

Answer

a. CH_3CH_2CHO **b.** $(CH_3)_3CCOCH_3$ **c.** CH_3CO_2H **d.** $PhCONH_2$ **e.** $CH_3CH_2CH_2CN$ **f.** $CH_3CON(CH_3)_2$

Exercise 8.5.2

Draw a resonance structure of the acetonitrile anion, $^{-}{:}CH_2C{\equiv}N$, and account for the acidity of nitriles.

Answer

$$^{-}{:}CH_2C{\equiv}N: \longleftrightarrow CH_2{=}C{=}{\ddot{}}N{:}^{-}$$

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8.6: Reactivity of Enolate Ions

Objectives

After completing this section, you should be able to

1. identify the two possible ways in which a given enolate anion could conceivably react with an electrophile.
2. write an equation to illustrate the haloform reaction.
3. identify the products formed from the reaction of a given methyl ketone with a halogen and excess base.
4. identify the methyl ketone, the reagents, or both, needed to obtain a specified carboxylic acid through a haloform reaction.

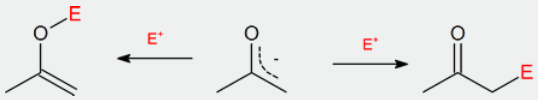
Key Terms

Make certain that you can define and use in context the key terms below.

- haloform
- haloform reaction

Study Notes

Because the negative charge on an enolate ion is delocalized, there are two reactive sites and therefore two potential products. The *α*-substituted product is much more common.



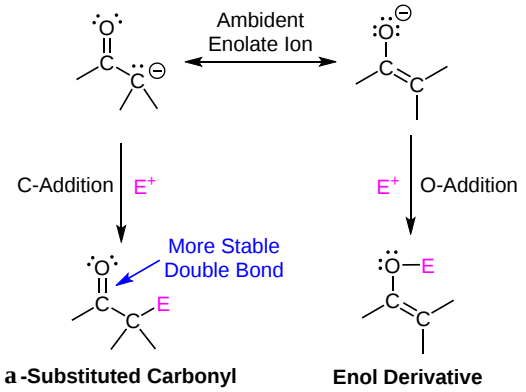
A "haloform" is any compound of the type CHX_3, where X = Cl, Br or I. Of these three compounds, chloroform is the most common.

The haloform reaction described in the reading is usually carried out with iodine. This reaction is called the "iodoform test," and is one of the reactions carried out in the laboratory as a simple qualitative test for methyl ketones.

How Enolates React

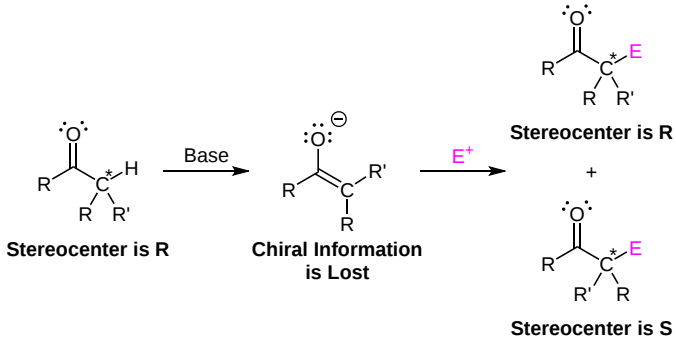
Due to their negative charges, enolates are better and more versatile nucleophiles than enols. The increased reactivity of enolates makes them capable of a wider range of reactions than enols. Also, α-hydrogen-containing compounds can be completely converted to an enolate by reaction with a strong base. Enols can only be created in small amounts by manipulating their equilibrium.

Since the negative charge of an enolate anion is delocalized between the α-carbon and an oxygen, electrophiles may bond to either atom. Reactants having two or more reactive sites are called ambident, so this term applies to enolate anions. Either the C of the O reactive site in an enolate may act as a nucleophile depending on the reaction conditions. Reactions with the oxygen would create a new O-E bond and produce an enol derivative. Reactions with the α-carbon creates a new C-E bond and creates an α-substituted carbonyl compound. Although reactions with the nucleophilic oxygen are possible, reactions involving the nucleophilic α-carbon are much more common, partially due to the thermodynamic stability of the C=O bonds in the final products. Also, the enolate counter ion, such as Li^+ or Na^+, is more tightly associated with the negatively charged enolate oxygen, which can then block incoming electrophiles, reducing their chance of reaction at the oxygen.



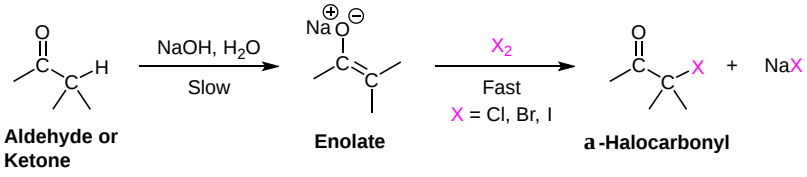
Stereochemical Implication of Enolate Formation

During enolate formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond, which removes any chiral information from the original α-carbon. Because the enol alkene is planar, the incoming electrophile can attack from either the top or the bottom. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter is formed during the reaction, the product will be a racemic mixture of enantiomers.



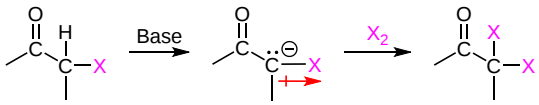
Base Promoted α-Halogenation

An enolate reacts rapidly with a halogen to produce α-halogenated carbonyl products. This reaction tends to overreact and form polyhalogenated products. If a monohalogenated product is sought, the acid-catalyzed halogenation reaction discussed in section 8.4 is preferred. Because complete formation to the enolate is not necessary, weak bases, such as the hydroxide anion, are sufficient to produce this reaction. Once a small amount of enolate is formed, it quickly reacts with the halogen. This removes the enolate and shifts the equilibrium toward the formation of more enolate, in accordance with Le Chatelier's principle.



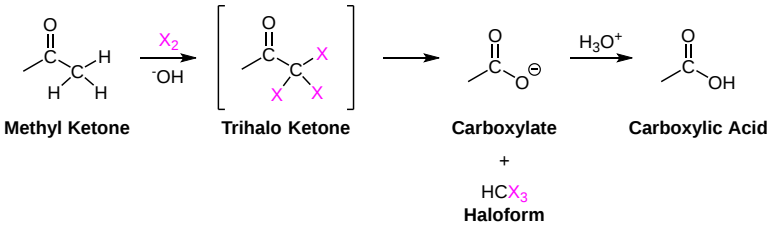
Overreaction During Base Promoted α-Halogenation

The α-hydrogens of halogenated carbonyl products are usually more acidic than the corresponding non-halogenated compounds. The inductive electron-withdrawing effect of the electronegative halogen stabilizes the negative charge of the enolate ion. This promotes further enolate formation and also further halogenation of the α-carbon. Monohalogenated carbonyls form an enolate over 100 times faster than their non-halogenated counterparts, making multiple halogenations of the α-carbon frequent. This effect is exploited to cause the haloform reaction.

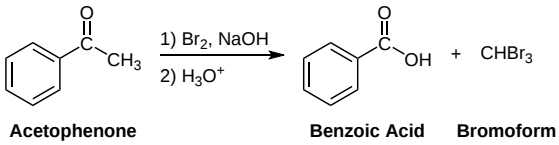


The Haloform Reaction

Overall, the haloform reaction represents a method for the conversion of methyl ketones to carboxylic acids. Due to the increased reactivity of α-halogenated products, methyl ketones typically undergo base promoted halogenation three times to give a trihalo-ketone. A halomethyl ion leaving group is then substituted with a hydroxide ion during nucleophilic acyl substitution. The resulting carboxylate can then be protonated to form a carboxylic acid.



Example

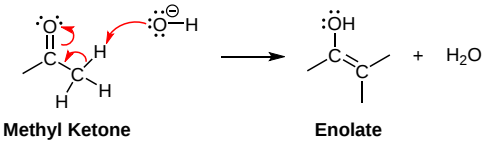
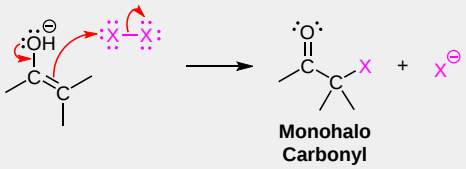
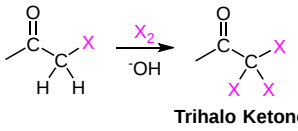
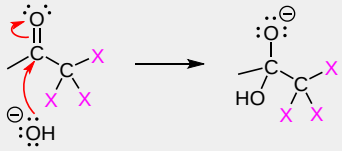
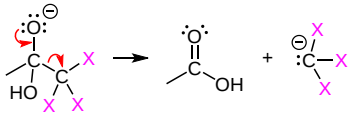
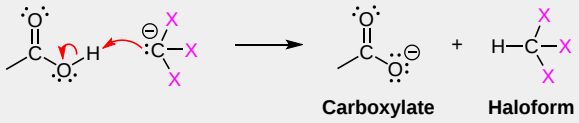
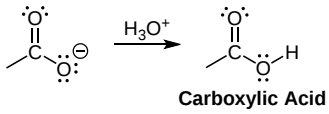


Mechanism

Note! This reaction is considered to be base-promoted and not base-catalyzed because an entire equivalent of base is required for each α-halogenation. Deprotonation of an α-hydrogen with hydroxide produces the nucleophilic enolate ion, which subsequently reacts with the halogen. The increasing acidity of the α-halogenated ketone causes this reaction to occur two more times. Once formed, the $-CX_3$ group attached to the carbonyl can act as a leaving group. Nucleophilic acyl substitution with a hydroxide anion causes C-C bond cleavage and eventually produces a haloform ($CHCl_3$, $CHBr_3$, CHI_3) and a carboxylate anion. The carboxylate ion is easily protonated with acid to form a carboxylic acid functional group. Often, this reaction is performed using iodine (I_2) because the subsequent iodoform (CHI_3) side-product is a bright yellow solid which is easily filtered off.

This reaction represents one of the few examples of a carbanion leaving group. The trihalomethyl ion ($^{-}:CX_3$) is particularly stabilized due to the inductive electron-withdrawing effects of the three halogens. The stability of the carbanion can be seen when

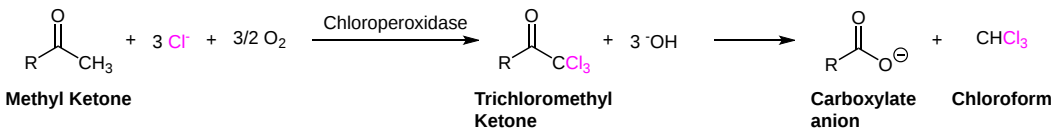
considering the pK_a corresponding to the conjugate acid. In particular, bromoform ($CHBr_3$) has a pK_a of 13.7, which is more than 10^{20} times more acidic than a typical alkane C-H bond.

1) Enolate formation	
2) Nucleophilic attack on the halogen	
3) Repeat the halogenation two more times	
4) Nucleophilic attack on the electrophilic carbonyl carbon	
5) Nucleophilic acyl substitution	
6) Deprotonation	
7) Protonation of the carboxylate	

Biological Haloform Reaction

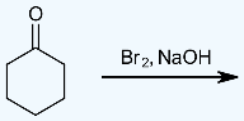
Interest in the haloform reaction has increased since the discovery that certain plants and marine algae can biosynthesize chloroform, bromoform, and other small halocarbons through an analogous process. Previously, it was assumed that these toxic compounds were present in the environment as man-made pollutants.

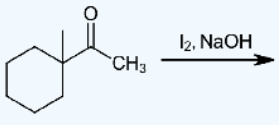
The likely starting material of the biosynthesis are biogenic methyl ketones, a halogen anion, and oxygen. The enzyme, chloroperoxidase, catalyzes the polyhalogenation of the methyl groups. As in the haloform reaction, the final biosynthesis step involves a nucleophilic acyl substitution with a hydroxide anion to create a haloform and a carboxylate anion.



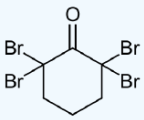
Exercise 8.6.1

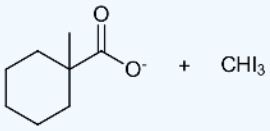
Please predict the expected products of the following reactions:

a) 

b) 

Answer

a) 

b) 

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8.7: Alkylation of Enolate Ions

Objectives

After completing this section, you should be able to

1. write a general mechanism for the attack of an enolate anion on an alkyl halide.
2. write a reaction sequence to illustrate the preparation of carboxylic acids via the malonic ester synthesis.
3. identify the product formed, and all the intermediates, in a given malonic ester synthesis.
4. identify all of the compounds needed to prepare a given carboxylic acid by a malonic ester synthesis.
5. write a detailed mechanism for each of the steps involved in a malonic ester synthesis.
6. write a reaction sequence to illustrate the preparation of ketones through the acetoacetic ester synthesis.
7. identify the product formed, and all the intermediates, in a given acetoacetic ester synthesis.
8. identify all of the compounds needed to prepare a given ketone by an acetoacetic ester synthesis.
9. write a detailed mechanism for each of the steps involved in an acetoacetic ester synthesis.
10. identify the product or products formed when a given lactone, ester, nitrile or ketone is treated with lithium diisopropylamide followed by an alkyl halide.
11. identify the compounds needed to prepare a given α-substituted ketone, ester, lactone or nitrile by a method involving the alkylation of an enolate anion.

Key Terms

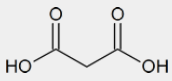
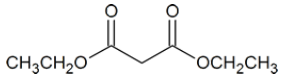
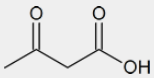
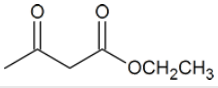
Make certain that you can define, and use in context, the key terms below.

- alkylation
- malonic ester synthesis

Study Notes

The two syntheses discussed in this section provide routes to a wide variety of carboxylic acids and methyl ketones. You may wish to review the factors influencing S_N2 reactions in conjunction with this section.

You should try to memorize the structures of malonic ester and ethyl acetoacetate. The IUPAC names of these compounds are shown in the table below.

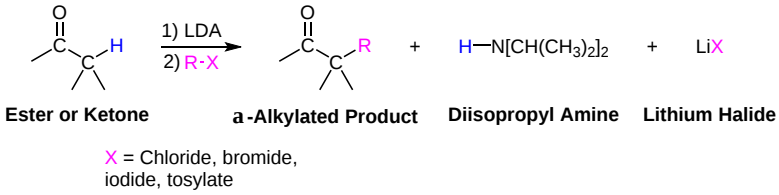
Structure	Common name	IUPAC name
	malonic acid	propanedioic acid
	malonic ester or diethyl malonate	diethyl propanedioate
	acetoacetic acid	3-oxobutanoic acid
	ethyl acetoacetate or acetoacetic ester	ethyl 3-oxobutanoate

Alkylation of Enolates

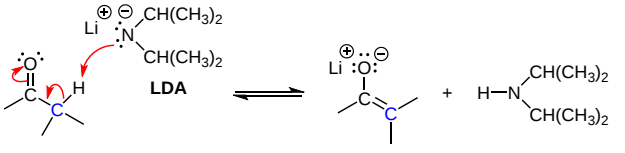
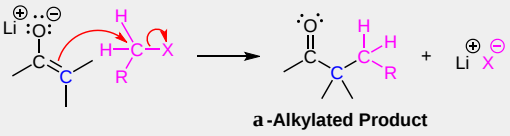
Enolates can be alkylated in the alpha position through an S_N2 reaction with alkyl halides. During this reaction an α-hydrogen is replaced with an alkyl group and a new C-C bond is formed. The limitations of S_N2 reactions still apply. This includes preferring a good primary or secondary leaving group, X = chloride, bromide, iodide, tosylate. Tertiary leaving groups cannot be used in this

reaction and typically give undesired E2 elimination products. A very strong base, such as LDA, is often used because of its ability to form the enolate completely. Removal of the carbonyl starting material from the reaction mixture prevents it from participating in nucleophilic addition by the enolate. Aldehydes are usually not directly alkylated because their enolates prefer to undergo the carbonyl condensation reactions discussed later in **Section 9.2**. In addition, the acidic hydrogen on carboxylic acids inhibits the formation of an enolate, and makes their direct alkylation difficult. Esters, including lactones, and symmetrical ketones readily undergo direct alkylation. However, direct alkylations, like all enolate-based reactions, can form a racemic mixture if the alkylated α-carbon produced is chiral.

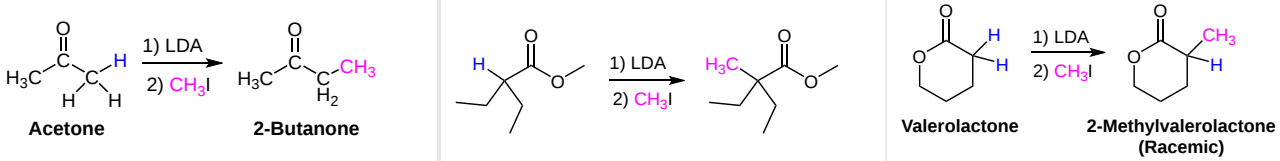
General Reaction



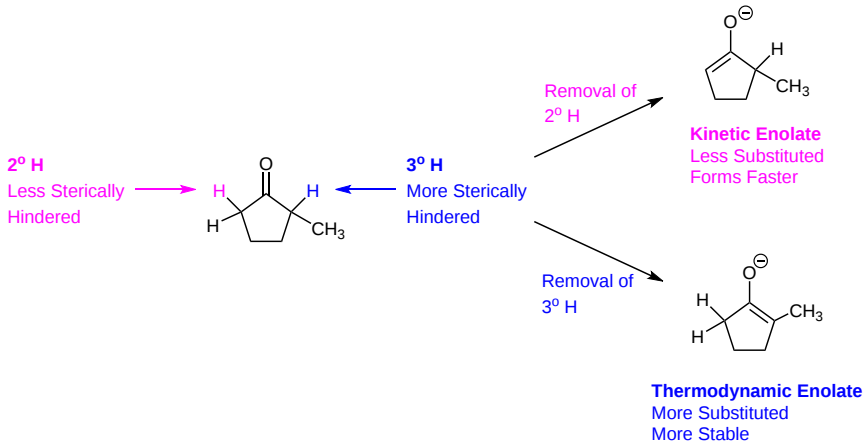
Mechanism

1) Enolate formation	
2) S_N2 attack	

Examples

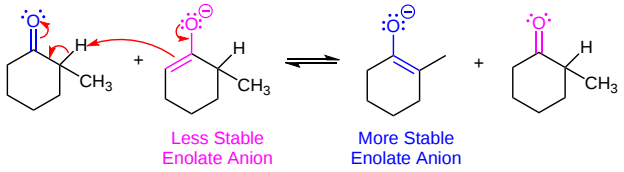


When an unsymmetrical ketone with two sets of non-equivalent α-hydrogens is treated with a base, two possible enolates can form. Regioselective enolate formation is possible under the proper conditions. The main determinant is whether the reaction is under kinetic control (rate) or thermodynamic control (equilibrium). Although a predominant product can be obtained, a mixture of products is usually formed, reducing product yield.

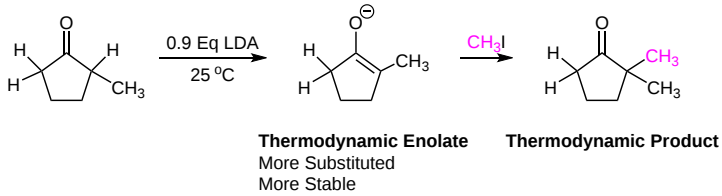


Thermodynamic Enolates

The thermodynamic enolate is formed when the more substituted α-hydrogen is removed. This leads to the more alkyl substituted, therefore the more stable, enolate to be formed. The presence of additional alkyl groups hinders the formation of the thermodynamic enolate and makes it kinetically slow, especially when a bulky base like LDA is used. Thermodynamic enolates are favored by conditions which allow for equilibration between the possible enolates. When the ketone starting material is not completely deprotonated, equilibrium between the possible enolates and the α-hydrogens of the ketone can occur. During equilibrium, interconversion between enolates allows the thermodynamic enolate to dominate. Other conditions can also promote the formation of the thermodynamic enolate, such as higher reaction temperatures, or using a smaller, less sterically hindered base such as sodium hydride (NaH). Weaker bases, such as sodium ethoxide, do not completely deprotonate the ketone starting material, allowing enolate equilibration to occur.

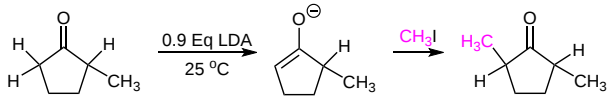


Example of enolate equilibration



Kinetic Enolates

Kinetic enolates are favored under conditions which do not allow for equilibration between the enolates, such as the use of a strong bulky base, like LDA, in a molar equivalent to the ketone starting material. Kinetic enolates are formed when the less substituted α-hydrogen is deprotonated. Being less sterically hindered allows this α-hydrogen to be deprotonated faster even though it forms a less thermodynamically stable enolate. Using a molar equivalent of LDA completely converts the ketone starting material to an enolate, removing it from the reaction mixture and preventing equilibration between the possible enolates. Low reaction temperatures (-78 °C) prevent enolate equilibration and promote the formation of the kinetic enolate.

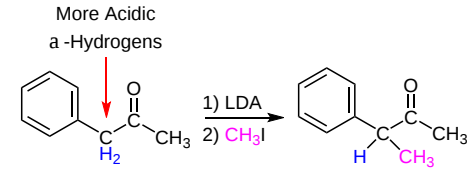


Kinetic Enolate
Less Substituted
Forms Faster

Kinetic Product
(Racemic)

When and enolate of an asymmetric ketone is stabilized through additional resonance forms there is no competition between possible enolates despite kinetic or thermodynamics conditions. The resonance stabilized enolate will be preferentially alkylated to the point that formation of the alkylated products of other possible enolates will be minimal.

Example



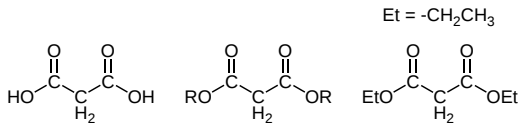
1-Phenyl-2-propanone

1-Methyl-1-phenyl-2-propanone (Racemic)

Malonic Ester Synthesis

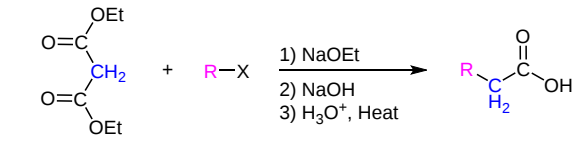
Malonic ester synthesis is a series of reactions that convert an alkyl halide to a carboxylic acid with two additional carbons. One important use of this synthesis pathway is that it allows for the creation of α-alkylated carboxylic acids which cannot be created by direct alkylation.

The starting material of this reaction is a malonic ester: a diester derivative of malonic acid. Diethyl propanedioate, also known as diethyl malonate, is the malonic ester most commonly used in pathway. Since it is a 1,3-dicarbonyl compound, diethyl malonate has relatively acidic α-hydrogens (pK_a = 12.6) and can be transformed to its enolate using sodium ethoxide as a base. Other alkoxide bases are not typically used given the possibility of a transesterification reaction.



Malonic Acid **Malonic Ester** **Diethyl Malonate**

General Reaction

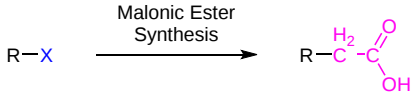


Diethyl malonate **Alkyl Halide**

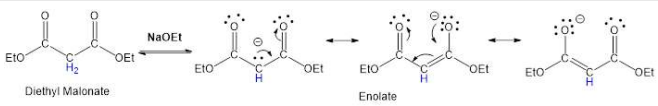
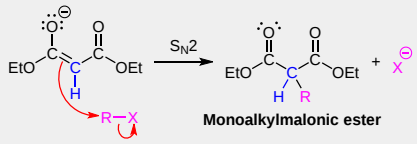
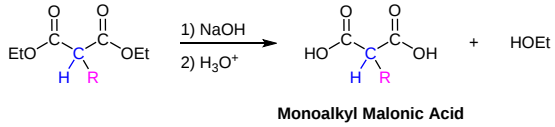
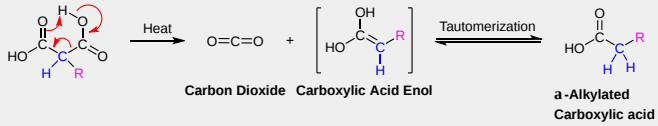
a-Alkyl Carboxylic Acid

Predicting the Product of a Malonic Ester Synthesis

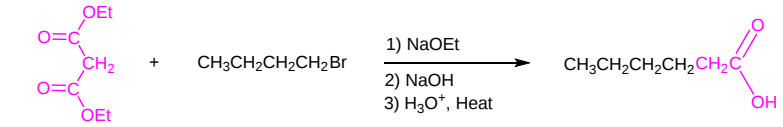
The product of a Malonic Ester Synthesis can be created by simply replacing the halogen on the alkyl halide with a $-CH_2CO_2H$ group.



Malonic Ester Synthesis takes place in four steps:

1) Enolate Formation Reacting diethyl malonate with sodium ethoxide (NaOEt) forms a resonance-stabilized enolate.	
2) Alkylation The enolate is alkylated via an S_N2 reaction to form a monoalkylmalonic ester.	
3) Ester hydrolysis and protonation After alkylation, the diester undergoes hydrolysis with sodium hydroxide to form a dicarboxylate. Subsequent protonation with acid forms a monoalkyl malonic acid.	
4) Decarboxylation & Tautomerization Monoalkyl malonic acids decarboxylate when heated, forming an α-alkyl carboxylic acid and carbon dioxide (CO_2). Decarboxylation can only occur in compounds with a second carbonyl group two atoms away from carboxylic acid, such as in malonic acids and β-keto acids. The mechanism occurs via a concerted mechanism involving a proton transfer between the carboxylic acid hydrogen and the nearby carbonyl group to form the enol of a carboxylic acid and CO_2. The enol undergoes tautomerization to form the carboxylic acid.	

Example



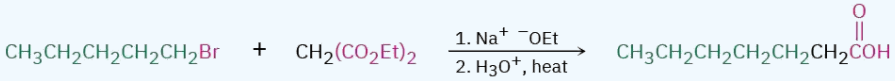
Worked Example 8.7.1: Using Malonic Ester Synthesis to Prepare a Carboxylic Acid

How would you prepare heptanoic acid using a malonic ester synthesis?

Strategy

A malonic ester synthesis converts an alkyl halide into a carboxylic acid having two more carbons. Thus, a seven-carbon acid chain must be derived from the five-carbon alkyl halide 1-bromopentane.

Solution

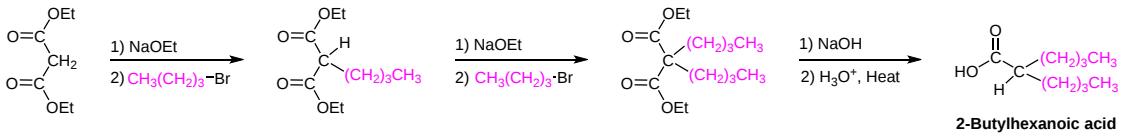


Dialkylation

The presence of two α-hydrogens in malonic esters allows for a second alkylation to be performed prior to decarboxylation. This leads to dialkylated carboxylic acids. Due to the lack of stereochemical control inherent in enolate based reactions, if the two added alkyl groups are different, a racemic mixture of products will result.

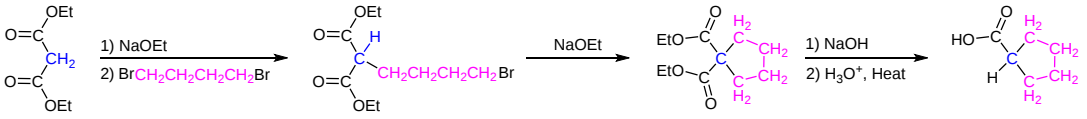
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Examples



2-Butylhexanoic acid

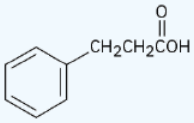
In a variation of the dialkylation reaction - if one molar equivalent of malonic ester is reacted with one molar equivalent of a dihaloalkane and two molar equivalents of sodium ethoxide, a cyclization reaction occurs. By changing the dihaloalkane, three, four, five, and six-membered rings can be created.

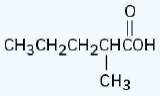


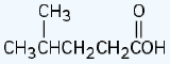
Cyclopentanecarboxylic acid

Exercise 8.7.1

How could you use a malonic ester synthesis to prepare the following compounds? Show all steps.

a. 

b. 

c. 

Answer

a. 1. $Na^+ {}^-OEt$; 2. $PhCH_2Br$; 3. H_3O^+

b. 1. $Na^+ {}^-OEt$; 2. $CH_3CH_2CH_2Br$; 3. $Na^+ {}^-OEt$; 4. CH_3Br; 5. H_3O^+

c. 1. $Na^+ {}^-OEt$; 2. $(CH_3)_2CHCH_2Br$; 3. H_3O^+

Exercise 8.7.2

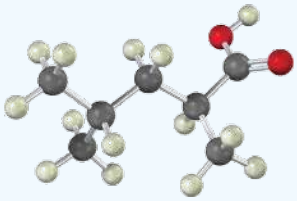
Monoalkylated and dialkylated acetic acids can be prepared by malonic ester synthesis, but trialkylated acetic acids ($R_3C–CO_2H$) can't be prepared. Explain.

Answer

Malonic ester has only two acidic hydrogens to be replaced.

Exercise 8.7.3

How could you use a malonic ester synthesis to prepare the following compound?



Answer

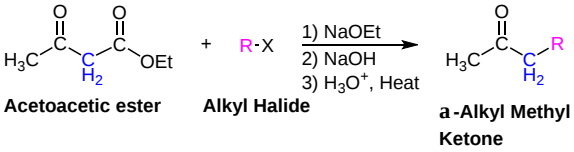
1. $Na^+ {}^-OEt$; 2. $(CH_3)_2CHCH_2Br$; 3. $Na^+ {}^-OEt$; 4. CH_3Br; 5. H_3O^+

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The Acetoacetic Ester Synthesis

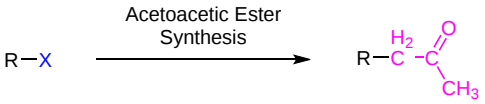
The acetoacetic ester synthesis is a series of reactions which converts alkyl halides into a methyl ketone with three additional carbons. This reaction creates an α-substituted methyl ketone without side-products. The starting reagent for this pathway is ethyl 3-oxobutanoate, also called ethyl acetoacetate, or acetoacetic ester. Like other 1,3-dicarbonyl compounds, ethyl acetoacetate is more acidic than ordinary esters, being almost completely converted to an enolate by sodium ethoxide.

General Reaction



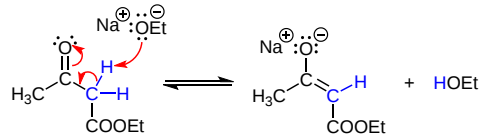
Predicting the Product of an Acetoacetic Ester Synthesis

The product of an acetoacetic ester synthesis can be created by replacing halogen on the alkyl halide with a $-CH_2COCH_3$ group.

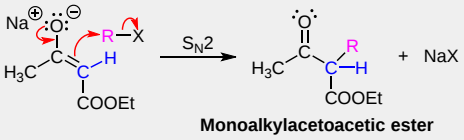


Acetoacetic Ester Synthesis Reaction Steps

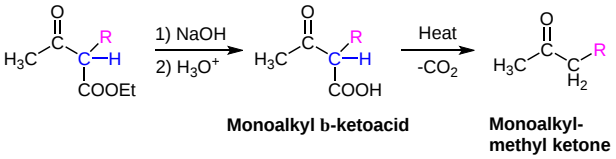
1) Formation of the enolate
As previously described, the α-hydrogens of acetoacetic ester are rather acidic (pK_a = 10.7), allowing the enolate to be easily formed when sodium ethoxide is used as a base.



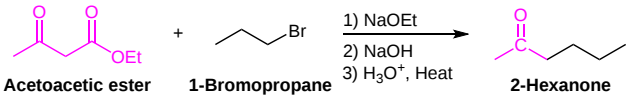
2) Alkylation via an S_N2 Reaction
Subsequent reaction with an alkyl halide produces a mono-alkylacetoacetic ester.



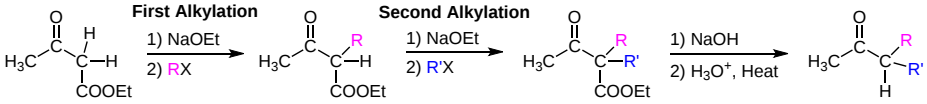
3) Ester hydrolysis and decarboxylation
Hydrolysis with NaOH followed by protonation produces an alkylated beta-ketoacid. β-ketoacids are easily decoboxylated to form an α-alkyl substituted methyl ketone and carbon dioxide (CO_2) using a similar mechanism as the malonic ester synthesis.



Examples



Much like the malonic ester synthesis, a second alkyl group can be added before the decarboxylation step.



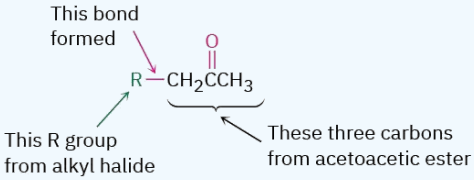
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Worked Example 8.7.2: Using Acetoacetic Ester Synthesis to Prepare a Ketone

How would you prepare 2-pentanone by an acetoacetic ester synthesis?

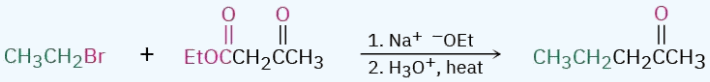
Strategy

An acetoacetic ester synthesis yields a methyl ketone by adding three carbons to an alkyl halide.



Thus, the acetoacetic ester synthesis of 2-pentanone must involve reaction of bromoethane.

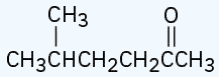
Solution

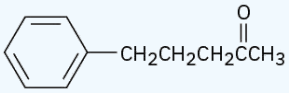


2-Pentanone

Exercise 8.7.4

What alkyl halides would you use to prepare the following ketones by an acetoacetic ester synthesis?

a. 

b. 

Answer

a. $(CH_3)_2CHCH_2Br$ b. $PhCH_2CH_2Br$

Exercise 8.7.5

Which of the following compounds can't be prepared by an acetoacetic ester synthesis? Explain.

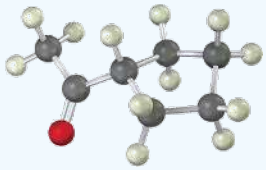
(a) Phenylacetone **(b)** Acetophenone **(c)** 3,3-Dimethyl-2-butanone

Answer

None can be prepared.

Exercise 8.7.6

How would you prepare the following compound using an acetoacetic ester synthesis?

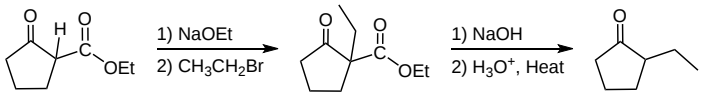


Answer

1. 2 $Na^+ {}^-OEt$; 2. $BrCH_2CH_2CH_2CH_2Br$; 3. H_3O^+

Direct Alkylation of other β-keto esters

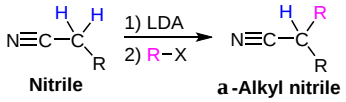
The reaction steps of the acetoacetic ester synthesis can also be applied to other β-keto esters with acidic α-hydrogens. Because the α-hydrogens between the two carbonyls are the most acidic, they are preferentially deprotonated, allowing for a single enolate to be formed. Even cyclic beta-keto esters can be alkylated and subsequently decarboxylated to give an α-alkylated cyclic ketone.



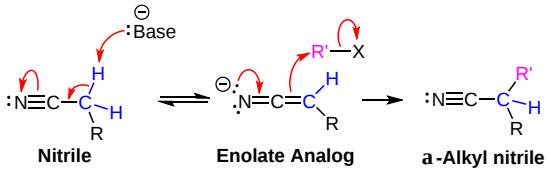
Direct Alkylation of Nitriles

The presence of acidic α-hydrogens in nitriles gives them the ability to form an enolate equivalent which can be also be directly alkylated.

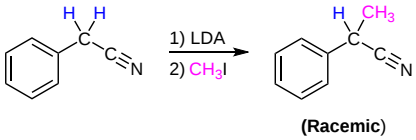
General Reaction



Mechanism



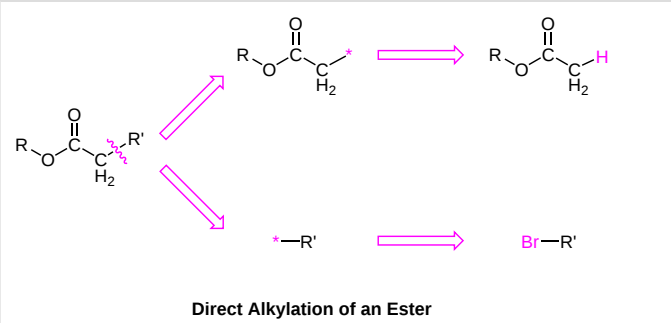
Example



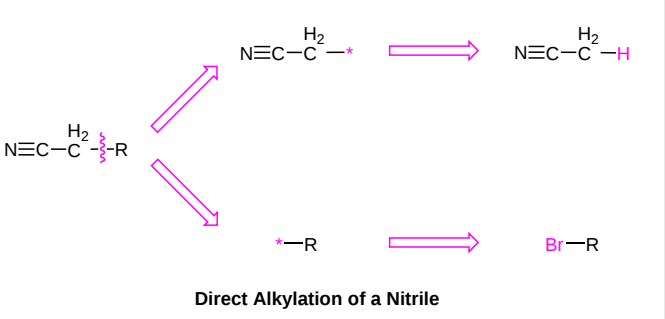
Planning a Synthesis Using Enolate Alkylations

When planning a synthesis involving enolates, the key is to recognize the functionality that can form an enolate. During retrosynthetic analysis a C-C bond is broken between the α-carbon and the β-carbon away from this functionality. It is also important to be able to identify specific groups of atoms, which indicate if a malonic ester or an acetoacetic ester synthesis can be used. Having multiple C-C bonds which can be broken allows for multiple synthetic pathways.

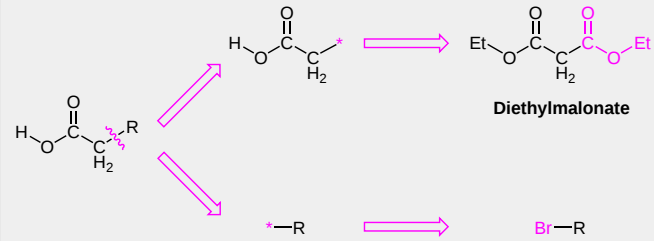
After retrosynthetically breaking the C-C bond, the fragment with the functionality will gain a hydrogen and the other fragment will gain a halogen. Sometimes the fragment with the functionality will become diethyl malonate or acetoacetic ester.



Direct Alkylation of an Ester

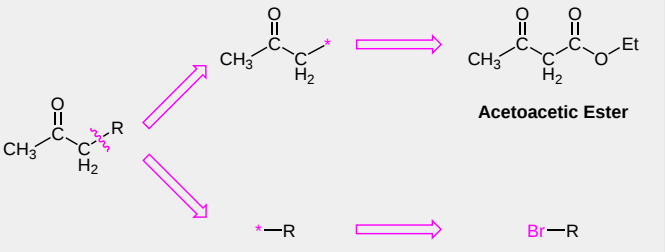


Direct Alkylation of a Nitrile



Diethylmalonate

Malonic Ester Synthesis

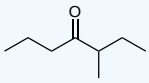


Acetoacetic Ester

Acetoacetic Ester Synthesis

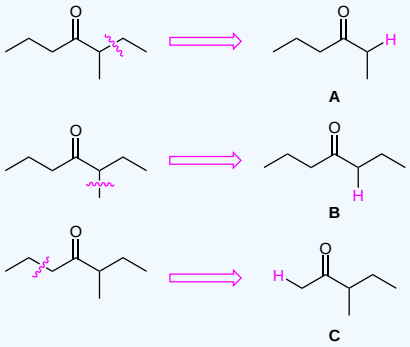
Worked Example 8.7.2

Plan a synthesis of the following molecule using an alkylation of an enolate. Consider multiple pathways and explain which is preferable.



Solution

The target molecule does not contain the appropriate fragments to utilize either the malonic ester or acetoacetic acid synthesis so direct alkylation of a ketone will likely be used. When analyzing this molecule, there are three α-β C-C bonds which could be cleaved to create a possible starting material. When looking at the possible starting materials, A and C are asymmetrical ketones and therefore can create multiple products during alkylation. B is a symmetrical ketone and should be the most likely to create the target molecule in high yield.

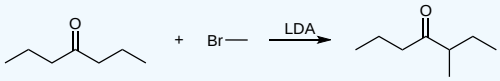


A

B

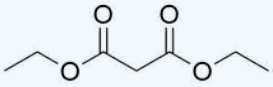
C

Possible Synthesis



? Exercise 8.7.4

Propose a synthesis for each of the following molecules from this malonic ester.



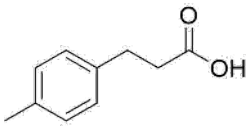
Answer

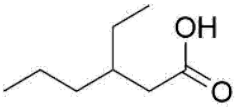
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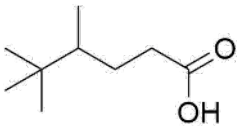
Exercises

Questions

1)

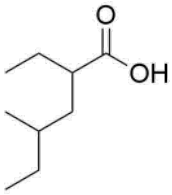
(a) 

(b) 

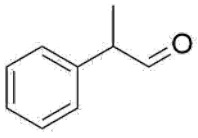
(c) 

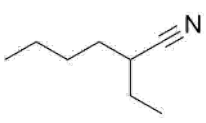
2) Why can't you prepare tri-substituted acetic acids from a malonic ester?

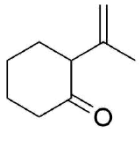
3) Propose a synthesis for the following molecule via a malonic ester.

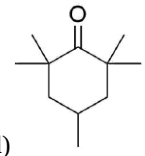


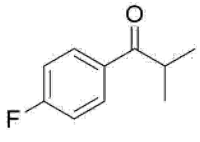
4) How might you prepare the following compounds from an alkylation reaction?

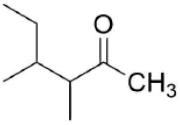
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

Solutions

1

(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

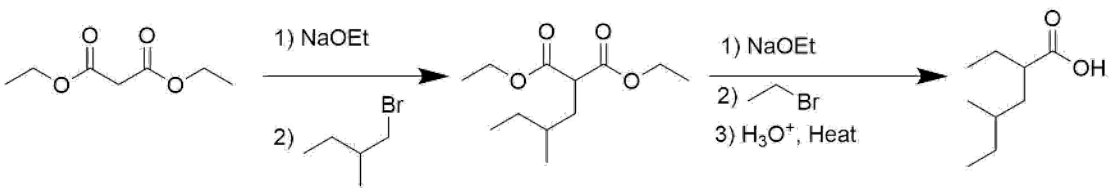
(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

(c) 1) Malonic Ester, NaOEt, 2) 1-Bromo-2,3,3-trimethylbutane, 3) Base, 4) Acid, Heat

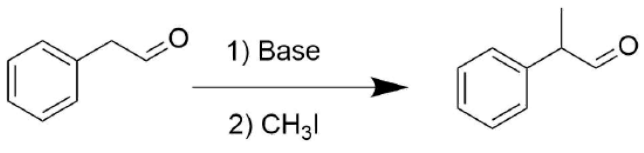
2

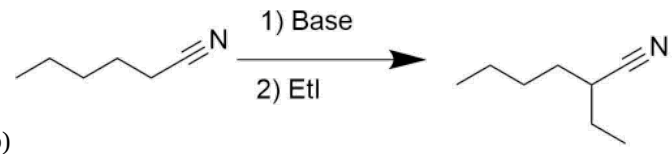
Malonic esters only contain two acid protons.

3

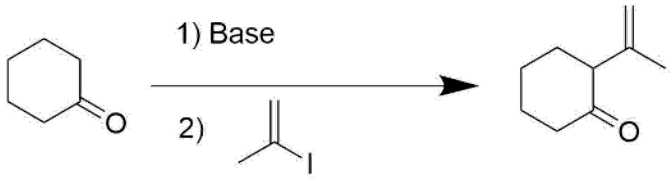


4

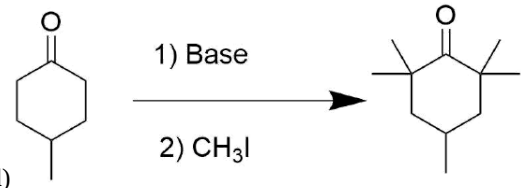
(a) 

(b) 

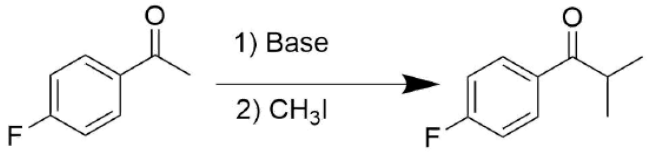
(c)



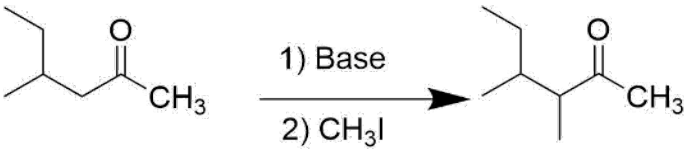
(d)



(e)



(f)



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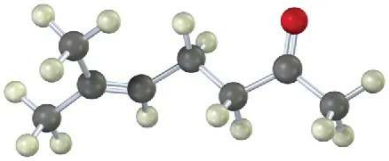
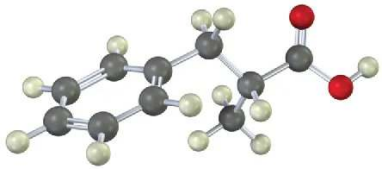
- **22.7: Alkylation of Enolate Ions** by Dietmar Kennepohl, Layne Morsch, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.
- **22.7: Alkylation of Enolate Ions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.8: Additional Problems

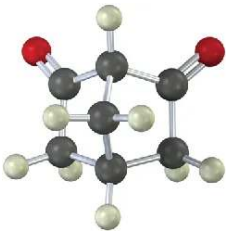
8 • Additional Problems

Visualizing Chemistry

PROBLEM 8-17 Show the steps in preparing each of the following substances using either a malonic ester synthesis or an acetoacetic ester synthesis:

(a)  (b) 

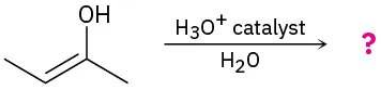
PROBLEM 8-18 Unlike most β-diketones, the following β-diketone has no detectable enol content and is about as acidic as acetone. Explain.

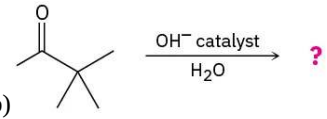


PROBLEM 8-19 For a given α-hydrogen atom to be acidic, the C–H bond must be parallel to the p orbitals of the C=O double bond (that is, perpendicular to the plane of the adjacent carbonyl group). Identify the most acidic hydrogen atom in the conformation shown for the following structure. Is it axial or equatorial?

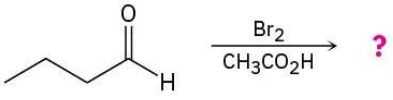
Mechanism Problems

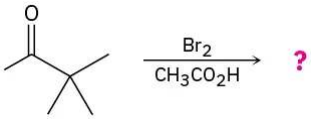
PROBLEM 8-20 Draw the corresponding keto or enol tautomer for each of the following molecules.

(a) 

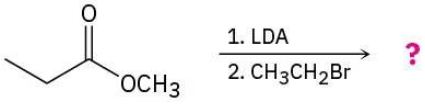
(b) 

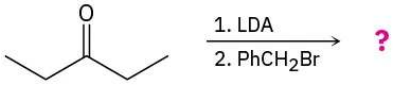
PROBLEM 8-21 Predict the product(s) and show the mechanism for each of the following reactions:

(a) 

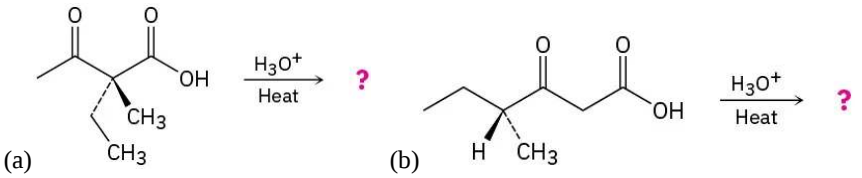
(b) 

PROBLEM 8-22 Predict the product(s) and show the mechanism for each of the following reactions:

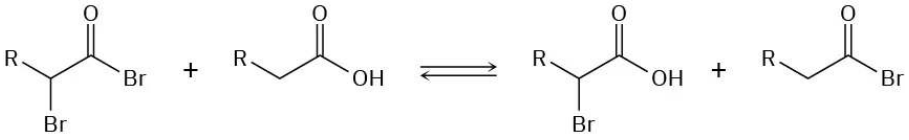
(a) 

(b) 

PROBLEM 8-23 The following two optically active β-keto acids were decarboxylated under the conditions typically used for the acetoacetic ester synthesis. Will the ketone products be optically active? Explain.

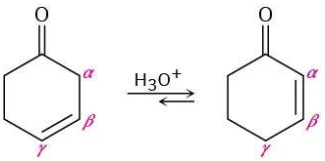


PROBLEM 8-24 In the Hell–Volhard–Zelinskii reaction, only a catalytic amount of PBr_3 is necessary because of the following equilibrium. Propose a mechanism for formation of the equilibrium.

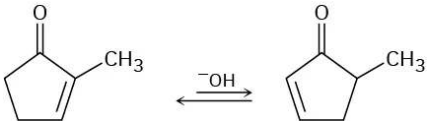


PROBLEM 8-25 When a ketone is treated with a halogen under acidic conditions, the α-monohalogenated product can be obtained in high yield. Under basic conditions, however, it is difficult to isolate the monohalogenated product. Explain.

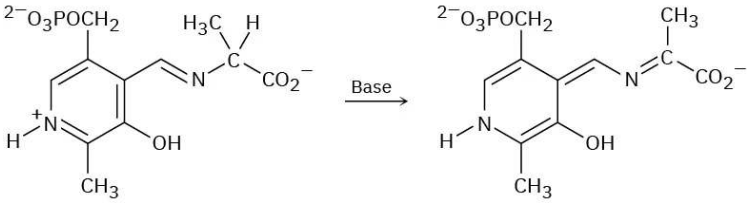
PROBLEM 8-26 Nonconjugated β,γ-unsaturated ketones, such as 3-cyclohexenone, are in an acid-catalyzed equilibrium with their conjugated α,β-unsaturated isomers. Propose a mechanism for the isomerization.



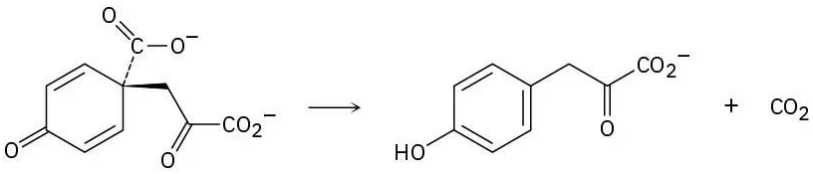
PROBLEM 8-27 2-substituted 2-cyclopentenones can be interconverted with 5-substituted 2-cyclopentenones under basic conditions. Propose a mechanism for this isomerization.



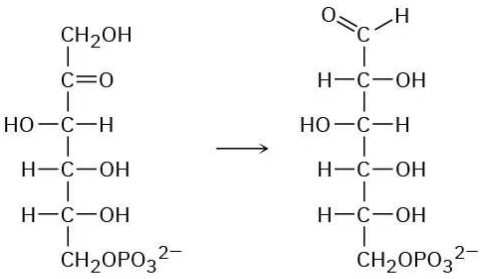
PROBLEM 8-28 Using curved arrows, propose a mechanism for the following reaction, one of the steps in the metabolism of the amino acid alanine.



PROBLEM 8-29 Using curved arrows, propose a mechanism for the following reaction, one of the steps in the biosynthesis of the amino acid tyrosine.

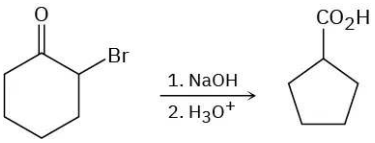


PROBLEM 8-30 One of the later steps in glucose biosynthesis is the isomerization of fructose 6-phosphate to glucose 6-phosphate. Propose a mechanism, using acid or base catalysis as needed.



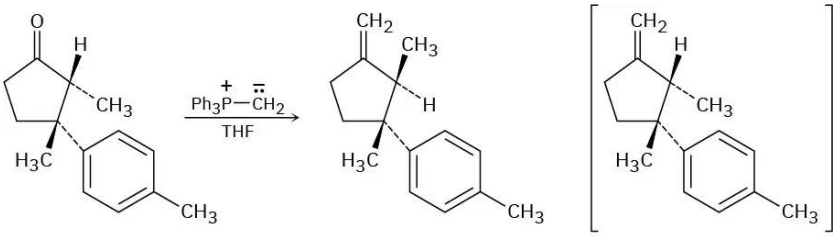
Fructose 6-phosphate **Glucose 6-phosphate**

PROBLEM 8-31 The *Favorskii reaction* involves treatment of an α-bromo ketone with base to yield a ring-contracted product. For example, reaction of 2-bromocyclohexanone with aqueous NaOH yields cyclopentanecarboxylic acid. Propose a mechanism.



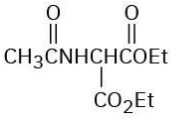
PROBLEM 8-32 Treatment of a cyclic ketone with diazomethane is a method for accomplishing a ring-expansion reaction. For example, treatment of cyclohexanone with diazomethane yields cycloheptanone. Propose a mechanism.

PROBLEM 8-33 The final step in an attempted synthesis of laurene, a hydrocarbon isolated from the marine alga *Laurencia glandulifera*, involved the Wittig reaction shown. The product obtained, however, was not laurene but an isomer. Propose a mechanism to account for the unexpected results.



Laurene
(Not formed)

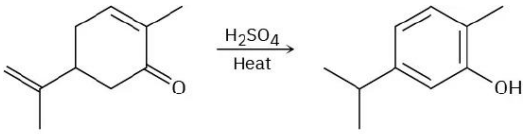
PROBLEM 8-34 Amino acids can be prepared by reaction of alkyl halides with diethyl acetamidomalonate, followed by heating the initial alkylation product with aqueous HCl. Show how you would prepare alanine, $CH_3CH(NH_2)CO_2H$, one of the twenty amino acids found in proteins, and propose a mechanism for acid-catalyzed conversion of the initial alkylation product to the amino acid.



Diethyl acetamidomalonate

PROBLEM 8-35 Amino acids can also be prepared by a two-step sequence that involves Hell–Volhard–Zelinskii reaction of a carboxylic acid followed by treatment with ammonia. Show how you would prepare leucine, $(CH_3)_2CHCH_2CH(NH_2)CO_2H$, and identify the mechanism of the second step.

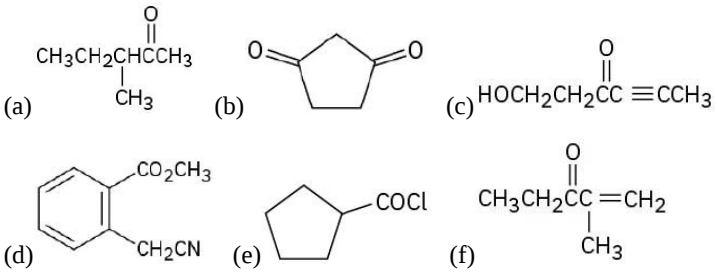
PROBLEM 8-36 Heating carvone with aqueous sulfuric acid converts it into carvacrol. Propose a mechanism for the isomerization.



Carvone **Carvacrol**

Acidity of Carbonyl Compounds

PROBLEM 8-37 Identify all the acidic hydrogens (p<i">K_a < 25) in the following molecules:

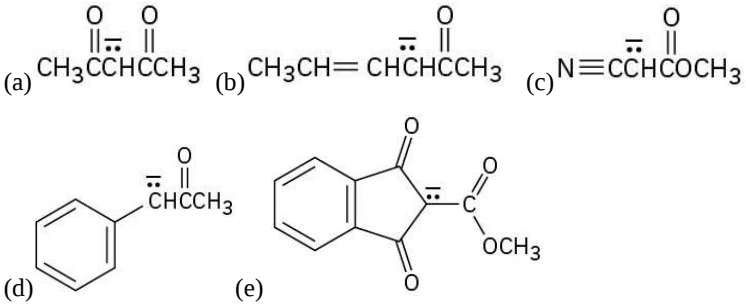


PROBLEM 8-38 Rank the following compounds in order of increasing acidity:

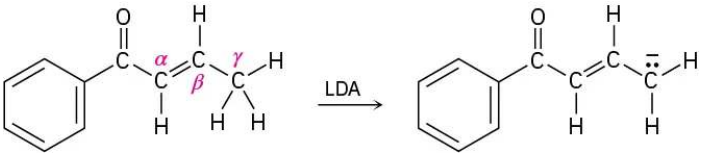
(a) $CH_3CH_2CO_2H$ **(b)** CH_3CH_2OH **(c)** $(CH_3CH_2)_2NH$

(d) CH_3COCH_3 **(e)** $CH_3CCH_2CCH_3$ **(f)** CCl_3CO_2H

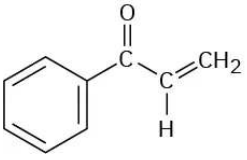
PROBLEM 8-39 Write resonance structures for the following anions:



PROBLEM 8-40 Base treatment of the following α,β-unsaturated carbonyl compound yields an anion by removal of H^+ from the γ carbon. Why are hydrogens on the γ carbon atom acidic?



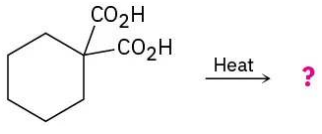
PROBLEM 8-41 Treatment of 1-phenyl-2-propenone with a strong base such as LDA does not yield an anion, even though it contains a hydrogen on the carbon atom next to the carbonyl group. Explain.

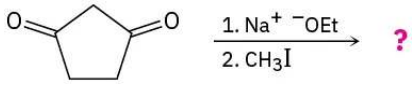


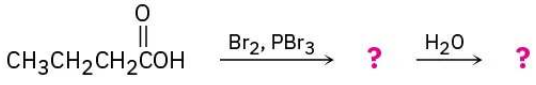
1-Phenyl-2-propenone

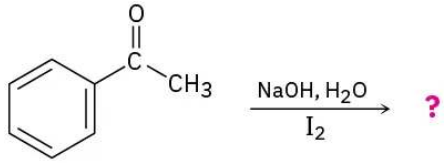
α-Substitution Reactions

PROBLEM 8-42 Predict the product(s) of the following reactions:

(a) 

(b) 

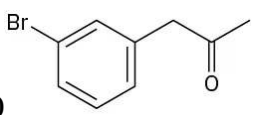
(c) 

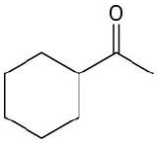
(d) 

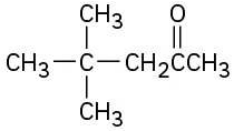
PROBLEM 8-43 Which, if any, of the following compounds can be prepared by a malonic ester synthesis? Show the alkyl halide you would use in each case.

(a) Ethyl pentanoate **(b)** Ethyl 3-methylbutanoate **(c)** Ethyl 2-methylbutanoate **(d)** Ethyl 2,2-dimethylpropanoate

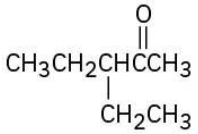
PROBLEM 8-44 Which, if any, of the following compounds can be prepared by an acetoacetic ester synthesis? Explain.

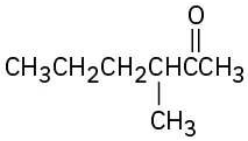
(a) 

(b) 

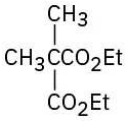
(c) 

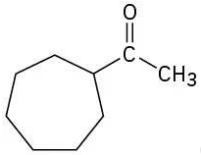
PROBLEM 8-45 How would you prepare the following ketones using an acetoacetic ester synthesis?

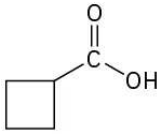
(a) 

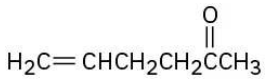
(b) 

PROBLEM 8-46 How would you prepare the following compounds using either an acetoacetic ester synthesis or a malonic ester synthesis? (a)

(a) 

(b) 

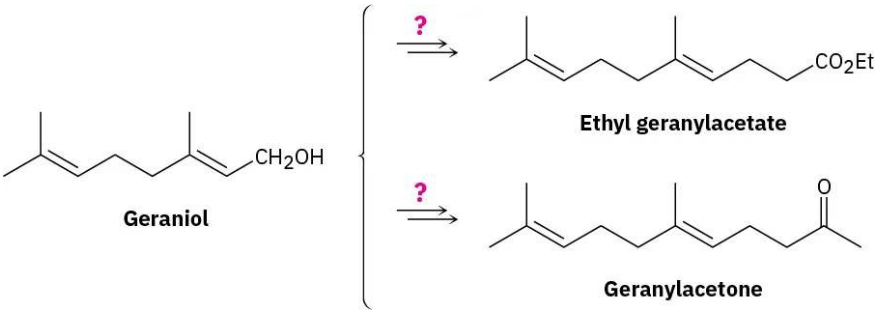
(c) 

(d) 

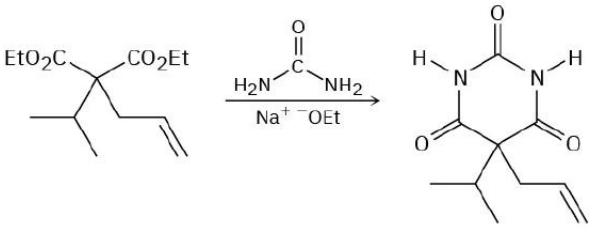
PROBLEM 8-47 Which of the following substances would undergo the haloform reaction?

(a) CH_3COCH_3 **(b)** Acetophenone **(c)** CH_3CH_2CHO **(d)** CH_3CO_2H **(e)** $CH_3C{\equiv}N$

PROBLEM 8-48 How might you convert geraniol into either ethyl geranylacetate or geranylacetone?



PROBLEM 8-49 Aprobarbital, a barbiturate once used in treating insomnia, is synthesized in three steps from diethyl malonate. Show how you would synthesize the necessary dialkylated intermediate, and then propose a mechanism for the reaction of this intermediate with urea to give aprobarbital.



General Problems

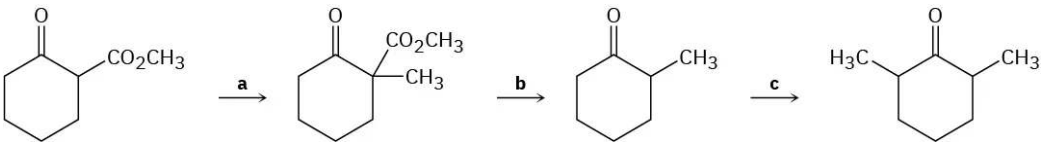
PROBLEM 8-50 One way to determine the number of acidic hydrogens in a molecule is to treat the compound with NaOD in D_2O, isolate the product, and determine its molecular weight by mass spectrometry. For example, if cyclohexanone is treated with NaOD in D_2O, the product has MW = 102. Explain how this method works.

PROBLEM 8-51 When optically active (*R*)-2-methylcyclohexanone is treated with either aqueous base or acid, racemization occurs. Explain.

PROBLEM 8-52 Would you expect optically active (*S*)-3-methylcyclohexanone to be racemized on acid or base treatment in the same way as 2-methylcyclohexanone (PROBLEM 8-51)? Explain.

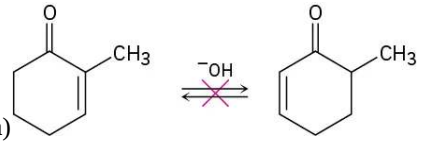
PROBLEM 8-53 When an optically active carboxylic acid such as (*R*)-2-phenylpropanoic acid is brominated under Hell–Volhard–Zelinskii conditions, is the product optically active or racemic? Explain.

PROBLEM 8-54 Fill in the reagents **a**–**c** that are missing from the following scheme:

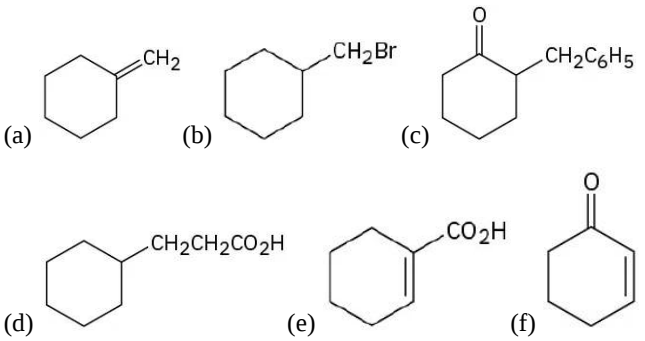


PROBLEM 8-55 Although 2-substituted 2-cyclopentenones are in a base-catalyzed equilibrium with their 5-substituted 2-cyclopentenone isomers, the analogous isomerization is not observed for 2-substituted 2-cyclohexenones. Explain.

(a)

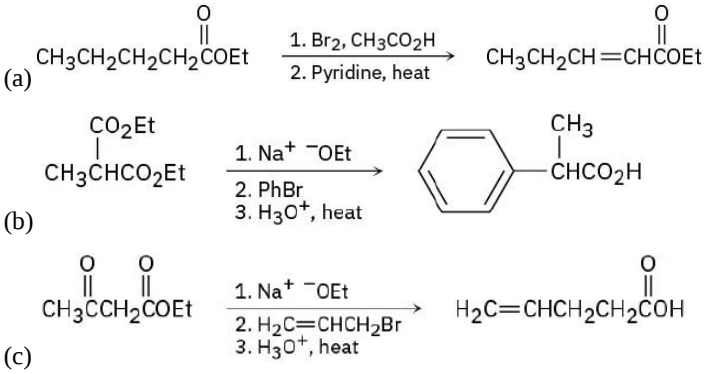


PROBLEM 8-56 How would you synthesize the following compounds from cyclohexanone? More than one step may be required.

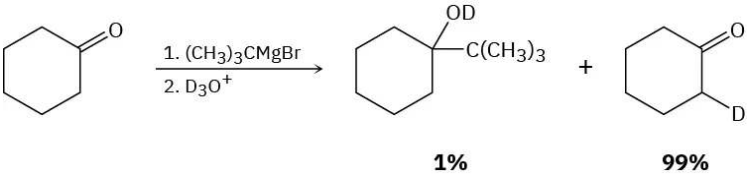


PROBLEM 8-57 The two isomers *cis*- and *trans*-4-*tert*-butyl-2-methylcyclohexanone are interconverted by base treatment. Which isomer do you think is more stable, and why?

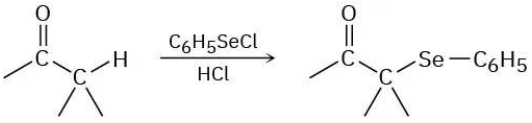
PROBLEM 8-58 The following synthetic routes are incorrect. What is wrong with each?



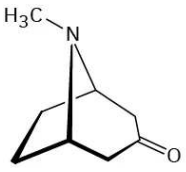
PROBLEM 8-59 Attempted Grignard reaction of cyclohexanone with *tert*-butylmagnesium bromide yields only about 1% of the expected addition product along with 99% unreacted cyclohexanone. If D_3O^+ is added to the reaction mixture after a suitable period, however, the "unreacted" cyclohexanone is found to have one deuterium atom incorporated into it. Explain.



PROBLEM 8-60 Ketones react slowly with benzeneselenenyl chloride in the presence of HCl to yield *α*-phenylseleno ketones. Propose a mechanism for this acid-catalyzed *α*-substitution reaction.



PROBLEM 8-61 South American Incas chewed the leaves of the coca bush, *Erythroxylon coca*, to combat fatigue. Chemical studies of *Erythroxylon coca* by Friedrich Wöhler in 1862 resulted in the discovery of *cocaine*, $C_{17}H_{21}NO_4$, as the active component. Basic hydrolysis of cocaine leads to methanol, benzoic acid, and another compound called *ecgonine*, $C_9H_{15}NO_3$. Oxidation of ecgonine with CrO_3 yields a keto acid that readily loses CO_2 on heating, giving tropinone.



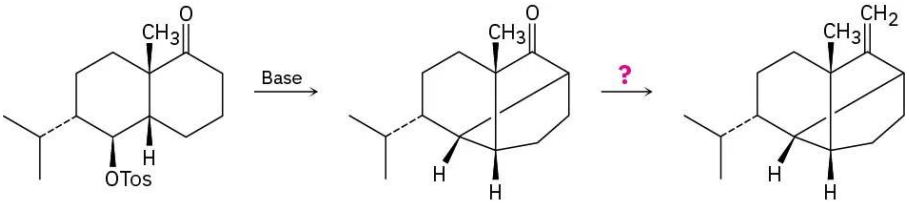
Tropinone

(a) What is a likely structure for the keto acid?

(b) What is a likely structure for ecgonine, neglecting stereochemistry?

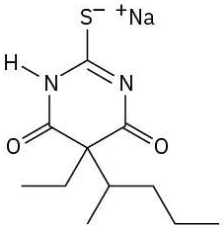
(c) What is a likely structure for cocaine, neglecting stereochemistry?

PROBLEM 8-62 The key step in a reported laboratory synthesis of sativene, a hydrocarbon isolated from the mold *Helminthosporium sativum*, involves the following base treatment of a keto tosylate. What kind of reaction is occurring? How would you complete the synthesis?



A keto tosylate **Sativene**

PROBLEM 8-63 Sodium pentothal is a short-acting barbiturate derivative used as a general anesthetic and known in popular culture as a truth serum. It is synthesized like other barbiturates (see the *Chemistry Matters* at the end of this chapter), using thiourea, $(H_2N)_2C$Math input error



Sodium pentothal

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8.S: Carbonyl Alpha-Substitution Reactions (Summary)

Concepts & Vocabulary

- Four common types of reactions involving carbonyl reactions: 1) nucleophilic addition; 2) nucleophilic acyl substitution; 3) alpha substitution; 4) carbonyl condensations. The first two were previously discussed and the second two involve the properties of the carbon directly adjacent to the carbonyls, **α carbons**.
- Alpha-substitution reactions results in the replacement of an H attached to the alpha carbon with an electrophile.
- The nucleophile in these reactions are new and called enols and enolates.
- In this chapter, the focus is on α substitutions reactions with aldehydes and ketones.

22.1 Keto-Enol Tautomerization

- Greek letters are used to denote the carbon atoms near carbonyls.
- The carbon in the carbonyl is the reference point and the alpha carbon is adjacent to the carbonyl carbon.
- Hydrogen atoms attached the these carbons denoted with Greek letters will have the same designation, so an alpha hydrogen is attached to an alpha carbon.
- Aldehyde hydrogens not given Greek leters.
- α hydrogens display unusual acidity, due to the resonance stabilization of the carbanion conjugate base, called an enolate.
- Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group, which is different than resonance.
- The tautomerization in this chapter focuses on the carbonyl group with alpha hydrogen, which undergo keto-enol tautomerism.
- Keto refers to the tautomer containing the carbonyl while enol implies a double bond and a hydroxyl group present in the tautomer.
- The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer, though the keto form is typically favored for simple carbonyl compounds.
- The 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium.
- The positioning of the carbonyl groups in the 1,3 arrangement allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen as well as the alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization.
- Aromaticity can also stabilize the enol tautomer over the keto tautomer.
- Under neutral conditions, the tautomerization is slow, but both acid and base catalysts can be utilized to speed the reaction up.
- Biological enol forming reactions use isomerase enzymes to catalyze the shifting of a carbonyl group in sugar molecules, often converting between a ketose and an aldose in a process called carbonyl isomerization.

22.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions

- The oxygen of the enol donates electron density to the double bond making it more electron rich and thus more reactive than a typical alkene.
- The mechanism starts with an acid-catalyzed tautomerization to form an enol.
- The double bond is then able to act as a nucleophile and attack an electrophile.
- The final product is an alpha-substituted carbonyl after the deprotonation of the carbonyl to also regenerate the acid-catalyst.
- The enol formed has planar geometry, which means the electrophile can attach on the top or bottom of the alpha-carbon.
- A racemic mixture can result if a sterocenter is created at the site of substitution.

22.3 Alpha Halogenation of Aldehydes and Ketones

- Aldehydes and ketons can undergo a substitution of an alpha hydrogen to a halogen.
- An acid-catalyzed tautomerization starts the mechanism followed by the enol attacking molecular halogens.
- The nucleophile in this reaction is the enol and the electrophile is the halogen.
- Mechanistic studies showed that the reaction was a first-order in the ketone.
- The halogen is part of a fast step after the rate-determing step.
- The formation of an enol intermediate was provided using a reaction called deuterium exchange.

- Due to the acidic nature of α hydrogens they can be exchanged with deuterium by reaction with the isotopic form of water, D_2O.
- The mechanism for deuterium exchange is virtually the same as that of keto-enol tautomerism under acidic conditions, the difference being a deuterium is placed in the *α*-position.
- Both alpha halogenation and deuterium exhange reactions were found to have a common intermediate involved in the rate determining step of their mechanism, an enol.

22.4 Alpha Bromination of Carboxylic Acids

- The *α*-bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, but the reaction will generally not occur with more stable carboxylic acid derivatives.
- Carboxylic acids do not enolize to a sufficient extent since the carboxylic acid proton is preferably removed before an *α*-hydrogen.
- Carboxylic acids, can be brominated in the *α* position with a mixture of Br_2 and phosphorus tribromide (PBr_3) in what is called the Hell-Volhard-Zelinskii reaction.
- *α*-Bromo carboxylic acids are extremely useful synthetic intermediates because the halogen is highly reactive towards S_N2 reaction.
- Reaction of a *α*-bromo carboxylic acids with an excess of ammonia provides *α*-amination, which is a possible route to amino acids.

22.5 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation

- α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the adjacent carbonyl.
- The enolate has two resonance structures to contribute to the resonance hybrid.
- While α-hydrogens are weakly acidic, typical strong bases such as hydroxide or alkoxide are only capable of forming the enolate ion in very low concentrations.
- To achieve complete deprotonation of aldehyde or ketone reactants to their enolate conjugate bases, a very strong base such as LDA (lithium diisopropylamide) must be used.
- Hydrogen atoms with two or more adjacent carbonyl groups are more acidic than typical α hydrogens, such as *β*-diketones, *β*-keto-esters, and *β*-diesters, which create enolates that are stabilized through additional resonance forms which share the negative charge with multiple carbonyl carbons.
- The acidity of these compounds is increased to the point where typical strong bases such as hydroxide and alkoxide can be used to form the enolate.

22.6 Reactivity of Enolate Ions

- Enolates are better nucleophlies than enols.
- α-hydrogen containing compounds can be completely converted to an enolate by reaction with a strong base whereas enols can only be created in small amounts through manipulating their equilibrium.
- Either the C of the O reactive site in an enolate may act as a nucleophile depending on the reaction conditions, but reactions involving the nucleophilic α-carbon are more common, partially due to the thermodynamic stability of the C=O bonds in the final products.
- An enolate reacts rapidly with a halogen to produce α-halogenated carbonyl products.
- The α-hydrogens of halogenated carbonyl products are usually more acidic than the corresponding non-halogenated compounds, which promotes polyhalogenated products.
- The Haloform reaction represents a method for the conversion of methyl ketones to carboxylic acids.
- This reaction is considered a base promoted and not base catalyzed because an entire equivalent of base is required for each α-halogenation.
- Deprotonation of an α-hydrogen with hydroxide produces the nucleophilic enolate ion which subsequently reacts with the halogen.
- The increasing acidity of α-halogenated ketone causes this reaction to occur two more times.
- Once formed, the CX_3 group attached to the carbonyl can act as a leaving group, eventually produces a haloform ($CHCl_3$, $CHBr_3$, CHI_3) and a carboxylate anion.

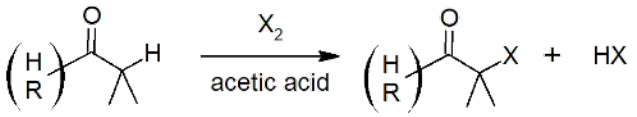
22.7 Alkylation of Enolate Ions

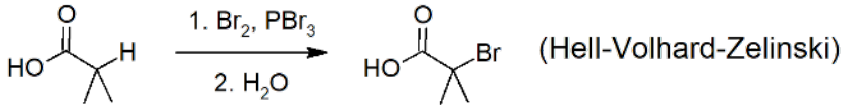
- Enolates can be alkylated in the alpha position through an S_N2 reaction with alkyl halides.
- An α hydrogen is replaced with an alkyl group and a new C-C bond is formed.
- Very strong bases like LDA are often used to fully deprotonate the carbonyl and completely form the enolate.
- Direct alkylations, like all enolate-based reactions, will form a racemic mixture if the alkylated alpha carbon is chiral.
- When an unsymmetrical ketone with two sets of nonequivalent alpha hydrogens is treated with a base, two possible enolates can form.
- The main determinant for which enolate is formed is whether the reaction is under kinetic control (rate) or thermodynamic (equilibrium) control.
- The thermodynamic enolate is formed when the more substituted alpha hydrogen is removed, yielding the more alkyl substituted, therefore the most stable, enolate.
- Formation of the thermodynamic enolate is sterically hindered and is kinetically slow, especially with a bulky base like LDA.
- Kinetic enolates are formed when the less substituted alpha hydrogen is deprotonated, being less sterically hindered allows this alpha hydrogen to be deprotonated faster even though it forms a less thermodynamically stable enolate.
- The malonic ester synthesis is a series of reactions which converts an alkyl halide to a carboxylic acid with two additional carbons.
- The importance of this synthesis pathways is that it allows for the creation of alpha alkylated carboxylic acids which cannot be created by direct alkylation.
- The acetoacetic ester synthesis is a series of reaction which converts alkyl halides into a methyl ketone with three additional carbons.
- This reaction creates an alpha substituted methyl ketone without side-products.
- In retrosynthetic analysis, a C-C bond is broken between the alpha carbon and the beta carbon away from this functionality.

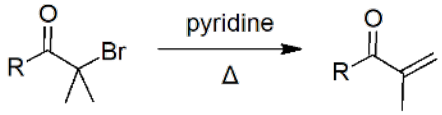
Skills to Master

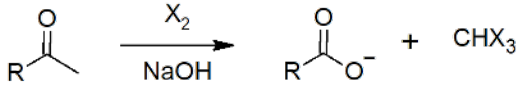
- Skill 22.1 Determine alpha carbons and alpha hydrogens.
- Skill 22.2 Draw the enols formed from carbonyl derivatives.
- Skill 22.3 Provide the mechanism for the keto-enol tautomerization under neutral, acidic and basic conditions.
- Skill 22.4 Provide the mechanism for the enol-keto tautomerization under neutral, acidic and basic conditions.
- Skill 22.5 Draw the products of halogenation reactions.
- Skill 22.6 Provide the mechanism for halogenation reactions.
- Skill 22.7 Write an equation to illustrate the Hell-Volhard-Zelinskii reaction.
- Skill 22.8 Identify the product formed from the reaction of a given carboxylic acid with bromine and phosphorus tribromide.
- Skill 22.9 Explain why the alpha hydrogen of carbonyl compounds are more acidic than a typical hydrogen.
- Skill 22.10 Explain why dicarbonyl protons are more acidic than compounds that contain a single carbonyl.
- Skill 22.11 Provide a mechanism for the haloform reaction.
- Skill 22.12 Provide a mechanism for an alkylation reaction with an enolate.
- Skill 22.13 Provide a mechanism for malonic ester synthesis.
- Skill 22.14 Propose synthesis for alkylated carboxylic acids.
- Skill 22.15 Provide a mechanism for acetoacetic acid synthesis.
- Skill 22.16 Propose a synthesis for alkylated methyl ketones.

Summary of Reactions

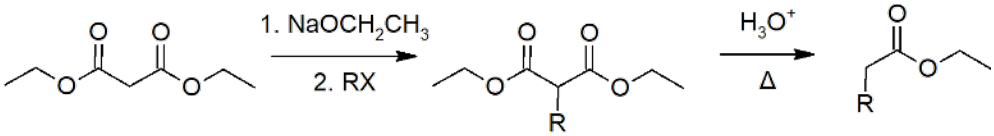


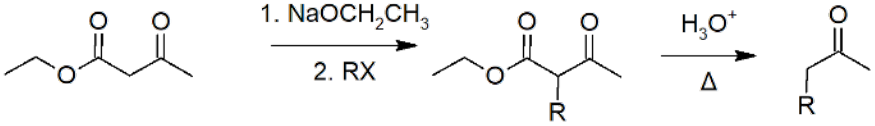


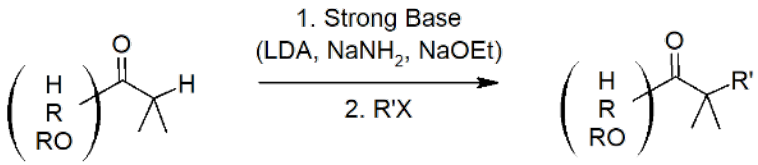




Alkylation







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CHAPTER OVERVIEW

9: Carbonyl Condensation Reactions

Learning Objectives

When you have completed Chapter 9, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- solve road-map problems that require a knowledge of carbonyl condensation reactions.
- define, and use in context, any of the key terms introduced.

In this chapter, we consider the fourth and final general type of reaction that carbonyl compounds undergo—the carbonyl condensation reaction. Carbonyl condensation reactions take place between two carbonyl-containing reactants, one of which must possess an alpha-hydrogen atom. The first step of the reaction involves the removal of an alpha-hydrogen atom by a base. In the second step, the enolate anion that results from this removal attacks the carbonyl-carbon of the second reacting molecule. In the final step of the reaction, a proton is transferred to the tetrahedral intermediate formed in the second step, although in some cases the product that results may subsequently be dehydrated.

9.0: Chapter Objectives
9.1: Carbonyl Condensations - The Aldol Reaction
9.2: Carbonyl Condensations versus Alpha Substitutions
9.3: Aldol Condensation - Dehydration of Aldol Products
9.4: Using Aldol Reactions in Synthesis
9.5: Mixed Aldol Reactions
9.6: Intramolecular Aldol Reactions
9.7: The Claisen Condensation Reaction
9.8: Mixed Claisen Condensations
9.9: Intramolecular Claisen Condensations - The Dieckmann Cyclization
9.10: Conjugate Carbonyl Additions - The Michael Reaction
9.11: Carbonyl Condensations with Enamines - The Stork Reaction
9.12: The Robinson Annulation Reaction
9.13: Some Biological Carbonyl Condensation Reactions
9.14: Additional Problems
9.S: Carbonyl Condensation Reactions (Summary)

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9.0: Chapter Objectives

The importance of carbonyl condensation reactions to synthetic organic chemistry arises from the large number of combinations of carbonyl compounds that can be used in such reactions. Aldehydes or ketones can be used in a simple aldol condensation to produce β-hydroxy aldehydes, β-hydroxy ketones, or their dehydration products. Mixtures of aldehydes, ketones, or both, can be used in a mixed aldol condensation. Internal aldol condensations can occur in compounds containing two suitable carbonyl groups. Aldol-like condensations can be brought about between aldehydes and a variety of compounds containing acidic alpha-hydrogen atoms, including diethyl malonate, acetic anhydride, nitriles and nitro compounds. Esters can be used in Claisen condensations and 1,6- and 1,7-diesters can give rise to internal condensations, called Dieckmann cyclizations. Related reactions include the Michael reaction, in which an α,β-unsaturated carbonyl compound is reacted with an enolate anion; and the Stork enamine reaction, where an enamine adds to an α,β-unsaturated ketone.

The chapter concludes with a look at how condensation reactions can be used in the synthesis of complex ring-containing organic compounds, and at the role played by carbonyl condensation reactions in biological systems. Carbonyl condensation reactions occur in a large number of metabolic pathways. In fact, almost all classes of biomolecules—carbohydrates, lipids, proteins, nucleic acids, and many others—are biosynthesized through pathways that involve carbonyl condensation reactions. As with the α-substitution reaction discussed in the previous chapter, the great value of carbonyl condensations is that they are one of the few general methods for forming carbon–carbon bonds, thereby making it possible to build larger molecules from smaller precursors. In this chapter, we'll see how and why these reactions occur.



Figure 9.0.1: Many of the molecules needed by all growing organisms are biosynthesized using carbonyl condensation reactions. (credit: modification of work "Newborn Sea Lion" by Steven Bedard/Flickr, CC BY 2.0)

We've now studied three of the four general kinds of carbonyl-group reactions and have seen two general kinds of behavior. In nucleophilic addition and nucleophilic acyl substitution reactions, a carbonyl compound behaves as an electrophile when an electron-rich reagent adds to it. In α-substitution reactions, however, a carbonyl compound behaves as a nucleophile when it is converted into its enol or enolate ion. In the carbonyl condensation reactions that we'll study in this chapter, the carbonyl compound behaves *both* as an electrophile and as a nucleophile.



Electrophilic carbonyl group reacts with nucleophiles. **Nucleophilic enolate ion reacts with electrophiles.**

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9.1: Carbonyl Condensations - The Aldol Reaction

Objectives

After completing this section, you should be able to

1. write a general mechanism for carbonyl condensation reactions.
2. write an equation to illustrate the aldol condensation reaction.
3. identify the product formed when an aldehyde or ketone having an alpha-hydrogen atom is treated with base in a protic medium.
4. identify the aldehyde or ketone, and other reagents required to produce a given *β*-hydroxy carbonyl compound by an aldol reaction.
5. determine whether a given aldehyde or ketone will undergo an aldol reaction.
6. write the detailed mechanism of the aldol reaction.

Key Terms

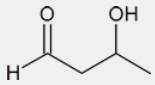
- aldol
- aldol reaction
- carbonyl condensation reaction

Study Notes

It is important that you understand the general mechanism of carbonyl condensation described in this section: once you grasp this mechanism, you will see that all the reactions that follow are very similar.

The aldol reaction is sometimes referred to as the aldol condensation. However, a condensation reaction is often regarded as a reaction in which two molecules join together with the elimination of a molecule of water (or some other compound of low molar mass). Thus, the aldol reaction described here is not a true condensation; the true aldol condensation is described later, in Section 9.3. It is perhaps unfortunate that the reactions discussed in this unit are all described as condensation reactions whether or not water is eliminated.

The term “aldol” (from "aldehyde alcohol") is used both to describe the specific compound 3-hydroxybutanal:

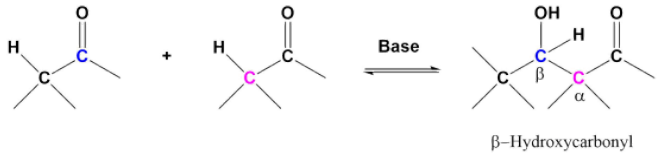


and to describe *β*-hydroxy aldehydes in general.

A useful carbon-carbon bond-forming reaction known as the Aldol Reaction is another example of electrophilic substitution at the alpha carbon in enolate anions. This reaction requires the formation of an enolate so at least one of the reactants must have an α-hydrogen. Due to the carbanion-like nature of enolates, they can add to carbonyls through nucleophilic addition much like Grignard reagents.

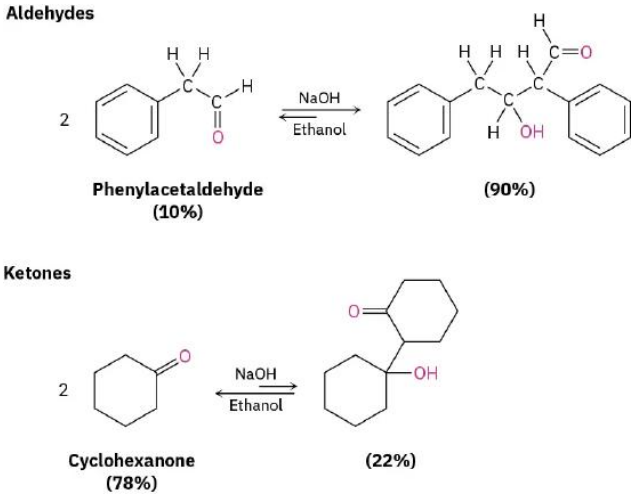
The aldol reaction takes advantage of a carbonyl compound’s ability to undergo both alpha substitution and nucleophilic addition reactions. The fundamental transformation in the aldol reaction is a dimerization of an aldehyde (or ketone) to form a beta-hydroxy aldehyde (or ketone). A C-C bond is formed between the alpha carbon of one reactant molecule and the carbonyl carbon of a second reactant molecule. In the reaction’s product, the formed C-C bond links a carbon in the alpha position and a carbon in the beta position away from the carbonyl.

General Aldol reaction



A typical example involves two molecules of acetaldehyde (ethanal) reacting to form beta-hydroxybuteraldehyde (3-hydroxybutanal). This product and other beta-hydroxy aldehydes are generically called “aldols” because they contain both an aldehyde and an alcohol functional group.

An aldol reaction, like many carbonyl addition reactions, is an equilibrium reaction and is reversible. The presence of an equilibrium means weaker bases, such a hydroxides or alkoxides, can be used to perform this reaction. The reaction equilibrium favors the products when aldehydes with little steric hindrance around the carbonyl are used. However, the reaction equilibrium for ketones and sterically hindered aldehydes favors the reactants.



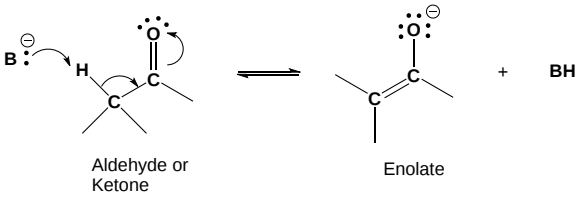
To provide good reaction yields when using these reactants, the equilibrium must be pushed towards the products. Typically, this is done by utilizing a method to remove the product as it is formed during the reaction.

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Mechanism of Aldol Reaction

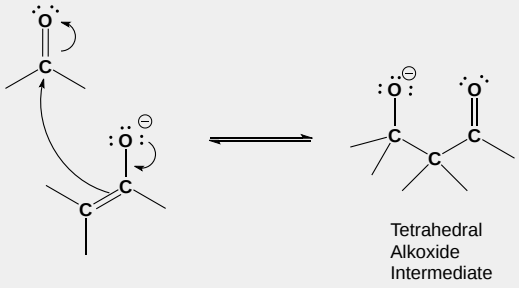
1) Enolate formation

The reaction starts with a base removing an alpha hydrogen to form a nucleophilic enolate.



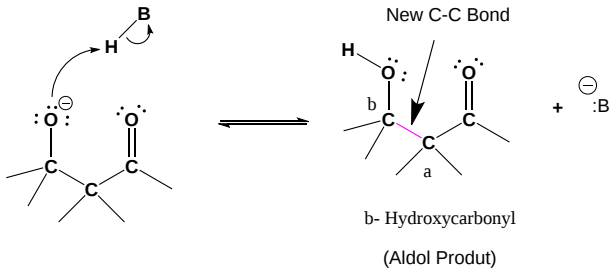
2) Nucleophilic attack by the enolate

Through nucleophilic addition, the enolate adds to the electrophilic carbonyl group on a second molecule. As with other nucleophilic addition reaction a tetrahedral alkoxide intermediate is formed.



3) Protonation

Protonation of the alkoxide forms the neutral aldol product and regenerates the base.



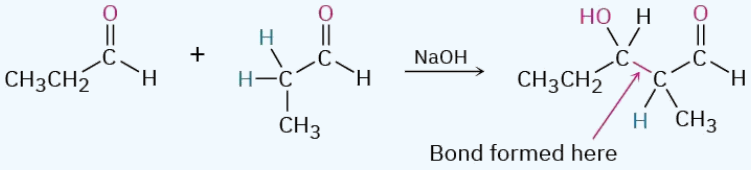
Worked Example 9.1.1: Predicting the Product of an Aldol Reaction

What is the structure of the aldol product from propanal?

Strategy

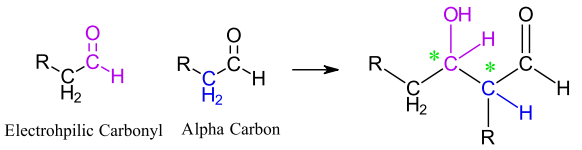
An aldol reaction combines two molecules of reactant by forming a bond between the α carbon of one molecule and the carbonyl carbon of the second molecule. The product is a β-hydroxy aldehyde or ketone, meaning that the two oxygen atoms in the product have a 1,3 relationship.

Solution



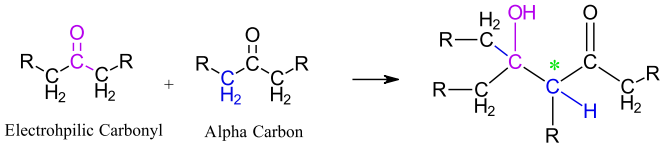
Stereochemical Ramifications of the Aldol Reaction

As previously discussed, both nucleophilic addition and alpha-substitution reactions have the possibility of creating chiral carbons. The alpha carbon and the electrophilic carbon of the reactants should be identified in the aldol product to assess their possible chirality. Most aldehydes produce chirality in both of these carbons. Most symmetrical ketones create a chiral carbon from the alpha-carbon of the reactant.



Aldehyde Reactants

Aldol Product with two Chiral Carbons

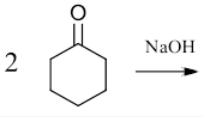


Symmetrical Ketone Reactants

Aldol Product with one Chiral Carbon

Worked Example 9.1.2: Predicting the Product of an Aldol Reaction

What would be the expected product of the following aldol reaction?

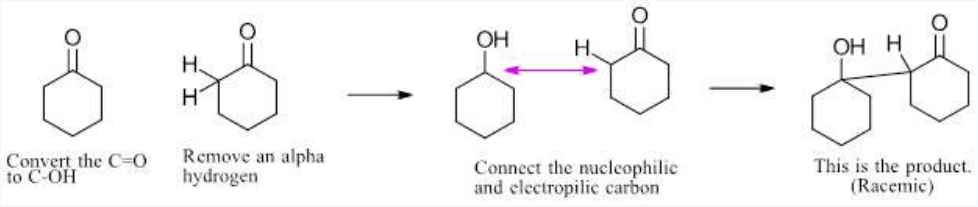


Strategy

An aldol reaction combines two molecules of reactant by forming a bond between the α carbon of one molecule and the carbonyl carbon of the second molecule. When considering the product of an aldol reaction, it is vital to consider each reactant molecule separately. Also, identify electrophilic carbonyl carbon and any alpha hydrogen present.

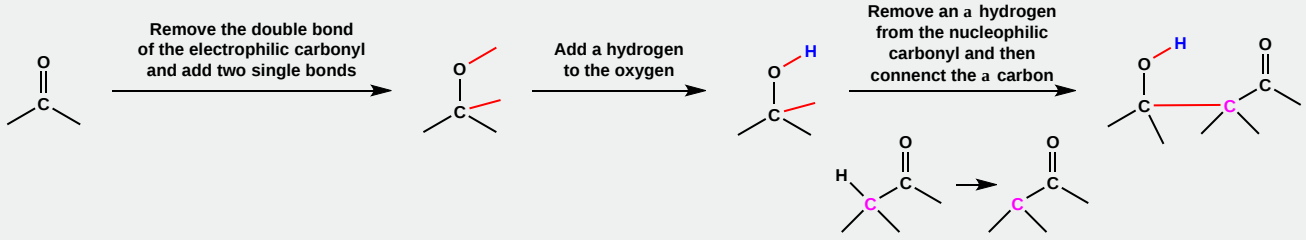
The product is a β-hydroxy aldehyde or ketone, meaning that the two oxygen atoms in the product have a 1,3 relationship.

Solution



Note

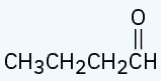
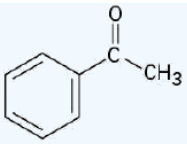
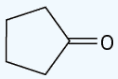
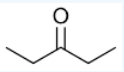
Predicting the Product of an Aldol Reaction



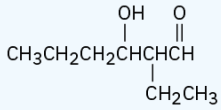
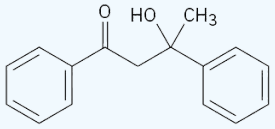
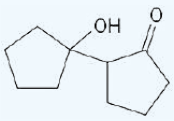
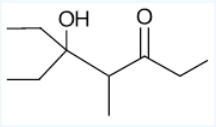
Exercise 9.1.1

Predict the aldol reaction product of the following compounds:

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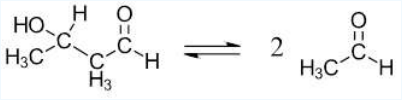
a.  b.  c.  d. 

Answer

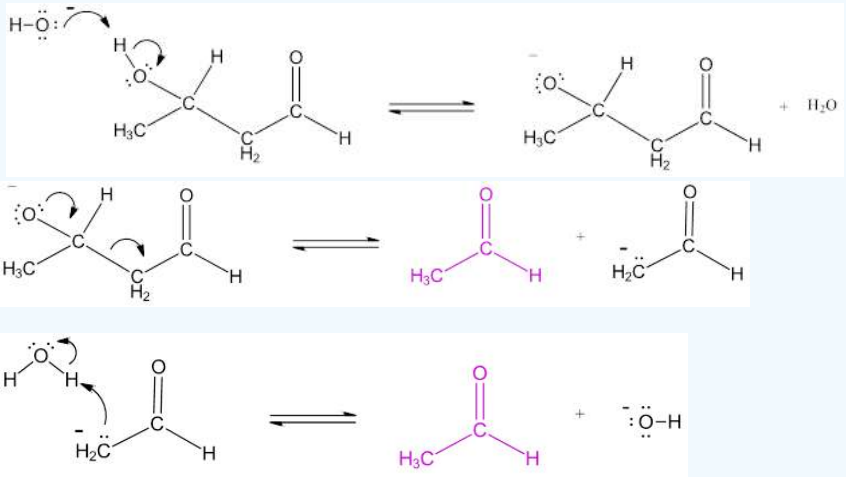
a.  b.  c.  d. 

Exercise 9.1.2

Because the aldol reaction is reversible, it is possible for a beta-hydroxy carbonyl compound to undergo a retro-aldol reaction. Using curved arrows to indicate the electron flow in each step, show how the base-catalyzed reverse-aldol reaction of 3-hydroxybutanal takes place to yield 2 equivalents of Ethanal.



Answer



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9.2: Carbonyl Condensations versus Alpha Substitutions

Objectives

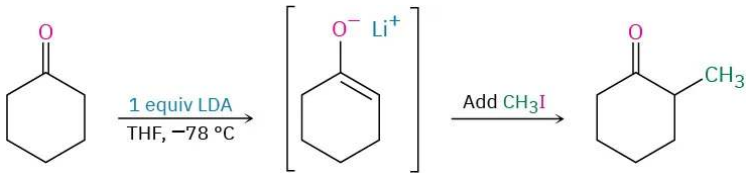
After completing this section, you should be able to describe the difference between a carbonyl condensation reaction and an alpha-substitution reaction, and determine which of these two types of reaction is most likely to occur, given the appropriate experimental data.

Study Notes

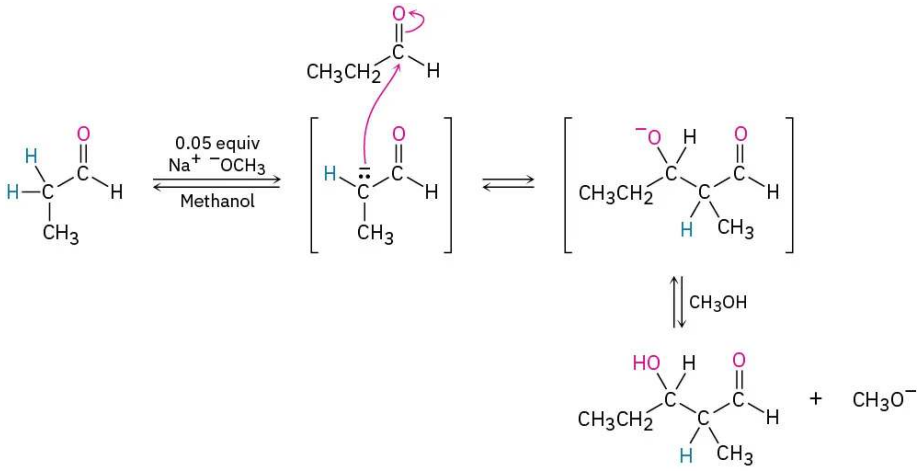
So far we have discussed three of the four general reactions of carbonyl compounds: nucleophilic additions of aldehydes and ketones (Chapter 19), nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21) and alpha-substitution reactions (Chapter 22). The fourth general reaction, carbonyl condensation, is similar to the alpha-substitution reaction, so you need to appreciate how it differs from the other three and the conditions under which it occurs.

Two of the four general carbonyl-group reactions—carbonyl condensations and α substitutions—take place under basic conditions and involve enolate-ion intermediates. Because the experimental conditions for the two reactions are similar, how can we predict which will occur in a given case? When we generate an enolate ion with the intention of carrying out an α alkylation, how can we be sure that a carbonyl condensation reaction won't occur instead?

There is no simple answer to this question, but the exact experimental conditions usually have much to do with the result. Alpha-substitution reactions require a full equivalent of strong base and are normally carried out so that the carbonyl compound is rapidly and completely converted into its enolate ion at a low temperature. An electrophile is then added rapidly to ensure that the reactive enolate ion is quenched quickly. In a ketone alkylation reaction, for instance, we might use 1 equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran solution at –78 °C. Rapid and complete generation of the ketone enolate ion would occur, and no unreacted ketone would remain, meaning that no condensation reaction could take place. We would then immediately add an alkyl halide to complete the alkylation reaction.



On the other hand, carbonyl condensation reactions require only a catalytic amount of a relatively weak base, rather than a full equivalent, so that a small amount of enolate ion is generated in the presence of unreacted carbonyl compound. Once a condensation occurs, the basic catalyst is regenerated. To carry out an aldol reaction on propanal, for instance, we might dissolve the aldehyde in methanol, add 0.05 equivalent of sodium methoxide, and then warm the mixture to give the aldol product.



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9.3: Aldol Condensation - Dehydration of Aldol Products

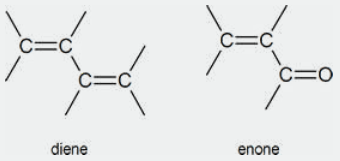
Objectives

After completing this section, you should be able to

1. write an equation to illustrate the formation of a conjugated enone from a *β*-hydroxy aldehyde or ketone.
2. write a detailed mechanism for the basic or acidic elimination of water from a *β*-hydroxy aldehyde or ketone.
3. explain why *β*-hydroxy aldehydes and ketones undergo elimination reactions much more readily than most other alcohols.
4. identify the enone products from the aldol condensation of a given aldehyde or ketone.

Study Notes

Conjugated enones, like conjugated dienes, have more inherent stability compared with their non-conjugated counterparts. You may wish to review Sections 2.2 on dienes, which gives a molecular orbital description showing π electron distribution over four atomic centres.

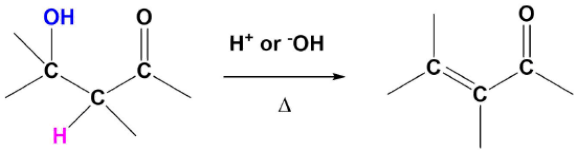


Note that both of the elimination mechanisms described here (acidic and basic) involve either the enol form or the enolate anion of the *β*-hydroxy carbonyl compound.

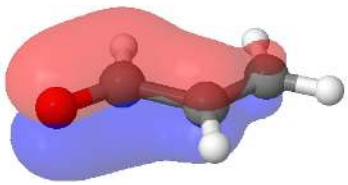
Aldol Dehydration

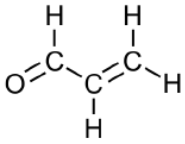
Dehydration of Aldol Products to Synthesize α, β Unsaturated carbonyl (enones)

The products of aldol reactions, with heating, often undergo a subsequent elimination of water, made up from an alpha-hydrogen and the beta-hydroxyl group. The product of this acid or base-catalyzed E1cB elimination reaction (Section 11-11) reaction is an α,β-unsaturated aldehyde or ketone (Enones). Although there may be multiple position where the alkene may form, it will always prefer to be in conjugation with the carbonyl.



Conjugated enone products are more stable than non-conjugated due to extended P orbital overlap. Conjugation of the p electrons of the alkene and carbonyl bonds provide a molecular-orbital description showing the interaction of p electrons of all four atoms. The additional stability provided by the conjugated carbonyl system of the product makes many aldol reactions thermodynamically factorable.

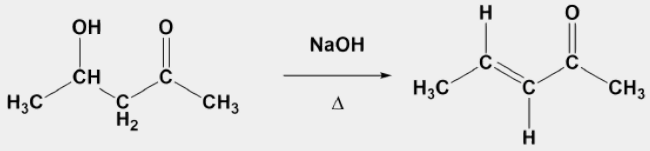
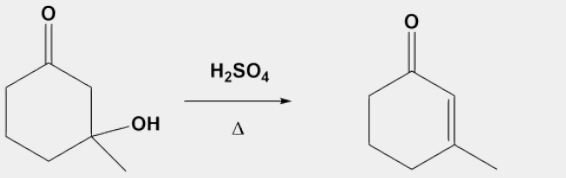




Propenal

A representation of pi bonding molecular orbitals of the conjugated enone, propenal, are delocalized through p-orbital overlap

The elimination of water from the reaction mixture can be used to drive the equilibrium towards the products by Le Chatelier's principal. This coupled with the thermodynamic stability of the conjugated product allow for good reaction yields when the formation of the initial aldol intermediate is unfavorable (ketones & sterically hindered aldehydes).

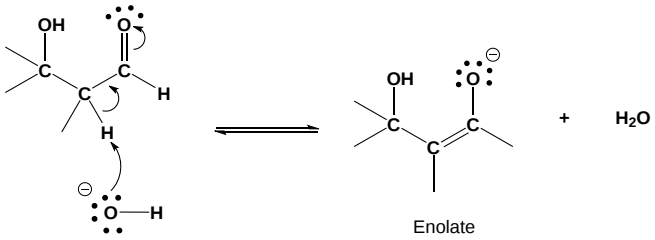
Basic Conditions	Acidic Conditions
	
4-Hydroxy-2-Pentanone → 3-Penten-2-one	3-Hydroxy-3-methylcyclohexanone → 3-Methyl-2-Cyclohexenone

Mechanism

Base Catalyzed Mechanism

1) Form an enolate

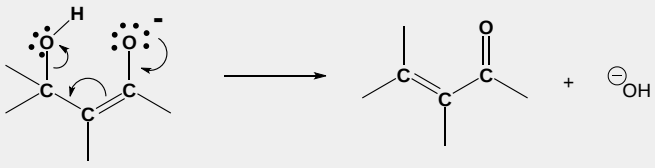
The mechanism starts with the base removing an alpha-hydrogen to form an enolate ion.



Enolate

2) Form the enone

The alkoxide reforming the carbonyl C=O bond promotes the elimination of alcohol OH as a leaving group which reforms the base catalyst. Although the base catalyzed elimination of alcohols is rare, it happens in this case in part due to the stability of the conjugated enone product.

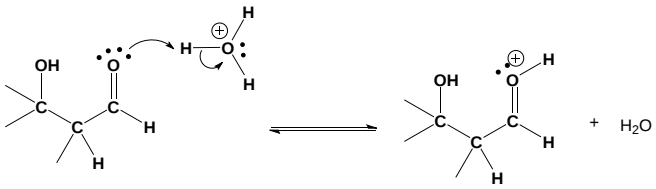


Enone

Mechanism in Acidic Conditions

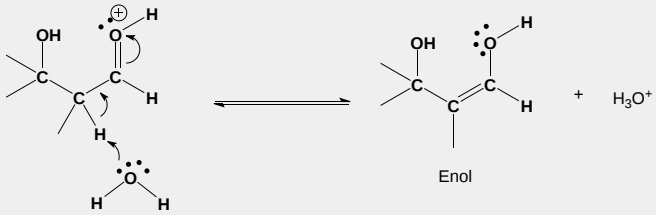
1) Protonation

The mechanism starts with the two-step tautomerization process to form an enol.



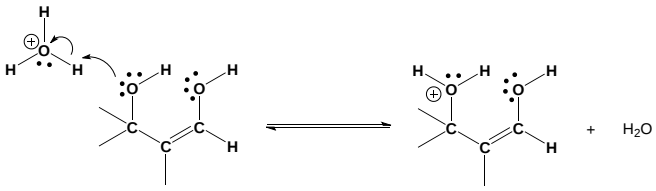
2) Deprotonation of the a- Carbon

Form an enol



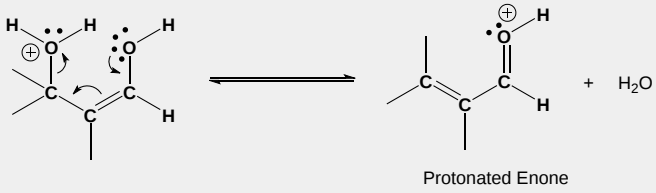
3) Protonation

Protonation of the alcohol OH increases its ability to act as a leaving group.



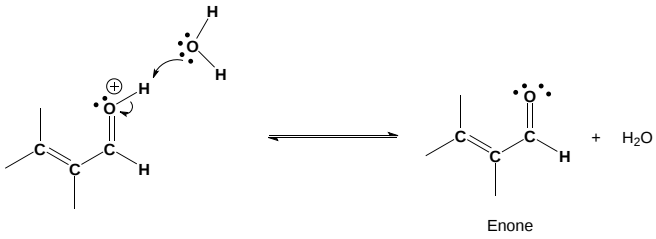
4) Elimination

Lone pair electrons from the enol reform the carbonyl C=O bond and promoted the elimination of water as a leaving group.



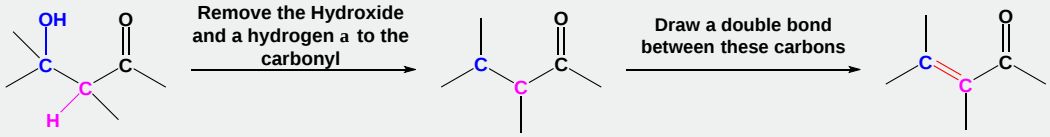
5) Deprotonation

Deprotonation by water in the final step creates the neutral enone product and regenerates the acid catalyst.



Note

Predicting the Product of an Enone Formation



Aldol Condensation

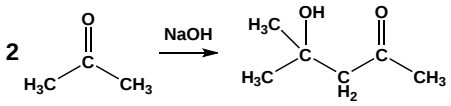
Reactions in which a larger molecule is formed from smaller components, with the elimination of a very small by-product such as water, are termed Condensations. Hence, the following examples are properly referred to as aldol condensations.

Whether an aldol reaction or an aldol condensation product is formed during a reaction largely depends on the reaction conditions. Typically, a reaction with a base at room temperature provides the aldol reaction product. However, if the reaction mixture is

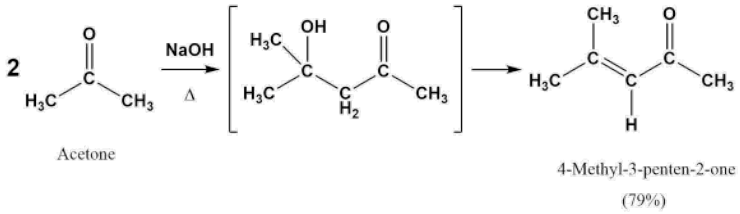
heated, the aldol product is quickly converted into the aldol condensation product. If the condensation product is desired, the aldol intermediate is usually not isolated.

Examples

Aldol Reaction

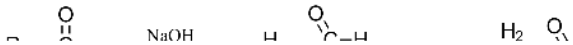
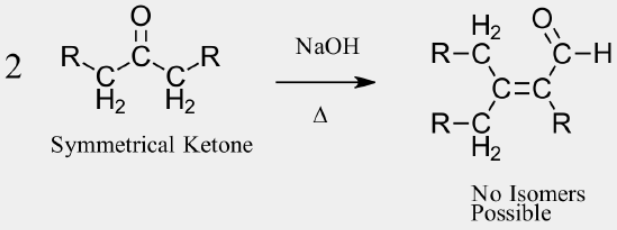


Aldol Condensation



Stereochemical Considerations

When aldehyde starting materials are used for an aldol condensation, there is the possibility of forming both E and Z alkene isomers. When symmetrical ketones are used, the alkene formed lacks the ability to form isomers so a single product is made.

Aldehyde	
Symmetrical Ketone	

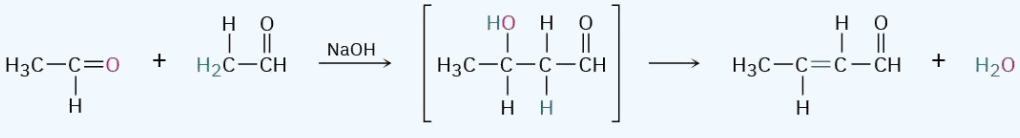
Worked Example 9.3.1: Predicting the Product of an Aldol Condensation

What is the structure of the enone obtained from aldol condensation of acetaldehyde?

Strategy

In the aldol reaction, H_2O is eliminated and a double bond is formed by removing two hydrogens from the acidic α position of one partner and the carbonyl oxygen from the second partner. The product is thus an α,β-unsaturated aldehyde or ketone.

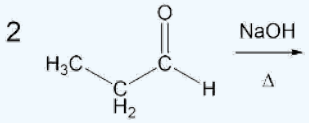
Solution



2-Butenal

Worked Example

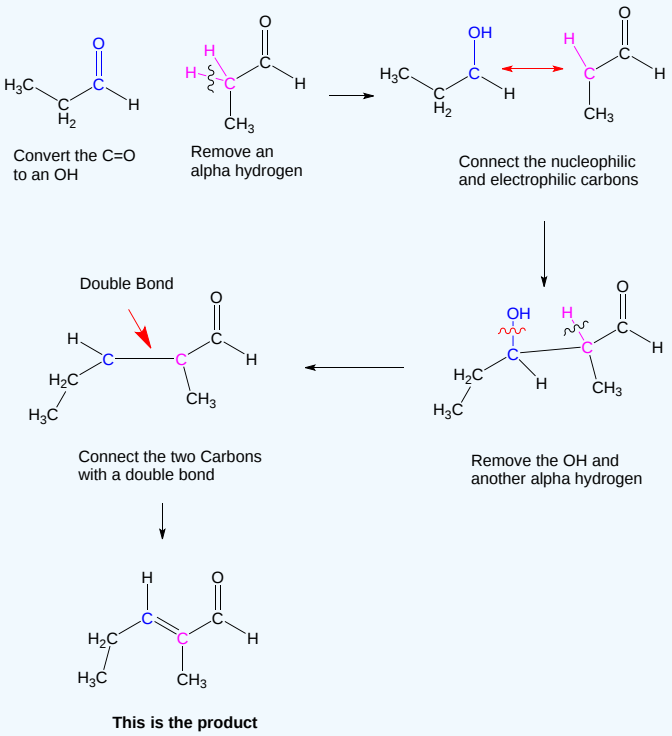
Draw the product of an aldol condensation with the following molecule:



Strategy

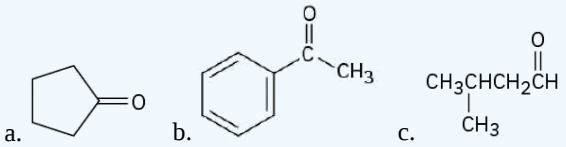
The overall reaction is a combination of two major steps, an aldol reaction followed by a dehydration to form the enone. In this situation it is best to consider the aldol product first (as discussed in Section 9.2), then convert it to the enone. Note! The double bond always forms in conjugation with the carbonyl.

Solution

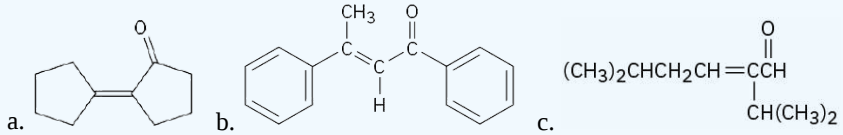


Exercise 9.3.1

What enone product would you expect from aldol condensation of each of the following compounds?



Answer

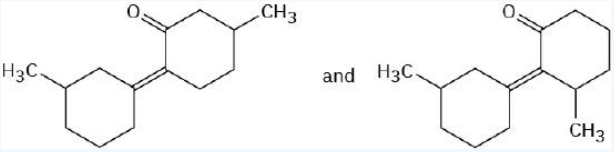


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Exercise 9.3.2

Aldol condensation of 3-methylcyclohexanone leads to a mixture of two enone products, not counting double-bond isomers. Draw them.

Answer



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9.4: Using Aldol Reactions in Synthesis

Objectives

After completing this section, you should be able to identify the aldehyde or ketone and other necessary reagents that should be used to prepare a given enone by an aldol condensation.

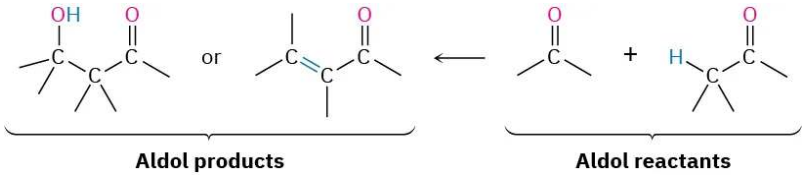
Study Notes

This section stresses the importance of being able to think logically.

The experience that you have already gained through designing multi-step syntheses and solving road-map problems should help you to recognize when an aldol reaction may have been one of the steps in the synthesis of a given compound.

It is important that you recognize that the aldol condensation is an important part of a synthetic chemist's repertoire, both because it involves the formation of a new carbon-carbon bond, and also because it yields a product containing two functional groups.

Aldol reactions are excellent methods for the synthesis of many enones or beta-hydroxy carbonyls. Because of this, being able to predict when an aldol reaction might be used in a synthesis in an important skill. This can be accomplished by identifying these combinations of atoms and bonds and then, working backwards, theoretically breaking the target molecule apart into possible reactants.

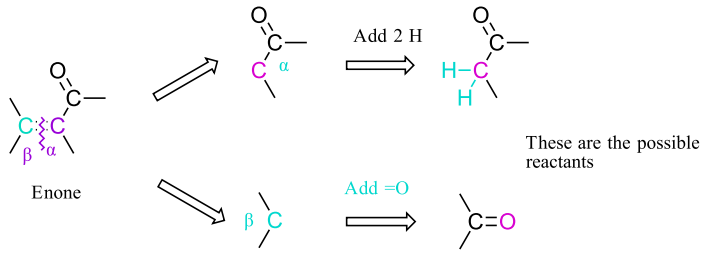


Products that are easily formed by an aldol reaction

Retro-synthetic Analysis

Determining the Reactants for an Aldol Condensation

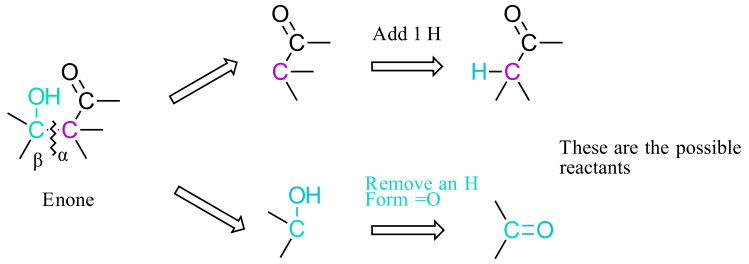
During an aldol condensation a C-C sigma and a C-C pi bond are formed. This makes the key bond cleavage in the target molecule the C=C bond between the carbons alpha and beta away from the carbonyl. After the cleavage, the carbon that was in the alpha position (on the fragment with the carbonyl) gains two hydrogens. The carbon that was in the beta gains a =O to form a carbonyl.



Determining the Reactants for an Aldol Reaction

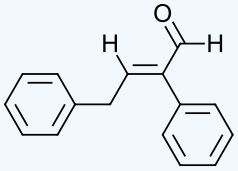
During an aldol condensation a C-C sigma bond is formed. This makes the key bond cleavage in the target molecule the C-C bond between the carbons alpha and beta away from the carbonyl. After the cleavage, the carbon that was in the alpha position (the

fragment with the carbonyl) gains one hydrogen. The fragment loses a hydrogen from the OH and then forms a C=O carbonyl bond.



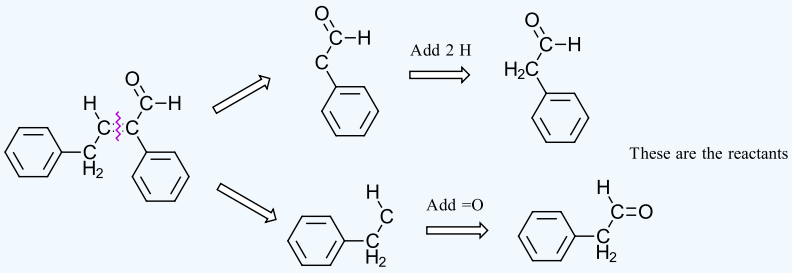
Worked Example

Show how the following molecule could be made using an aldol condensation.

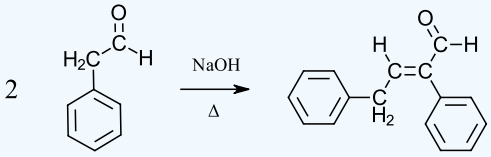


Answer

Analysis: The C=C bond in the target molecule is cleaved to form two fragments. The fragment with the carbonyl gains two alpha hydrogens. The other fragment gains a =O to form a carbonyl. Both fragments end up producing the same reactant which is typical for an aldol condensation.

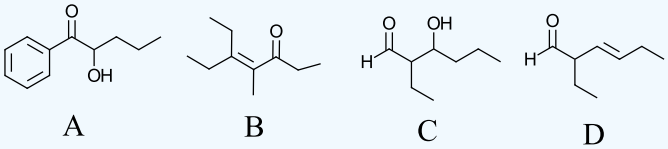


Solution



Exercises 9.4.1

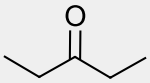
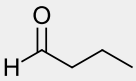
Which of the following molecules could be made using an aldol reaction or condensation? Please show the starting material for the reactions that are possible.



Answers

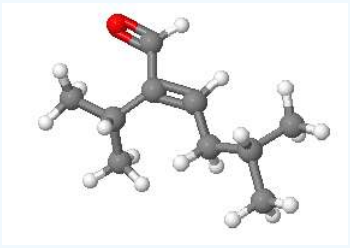
https://chem.libretexts.org/@go/page/500458

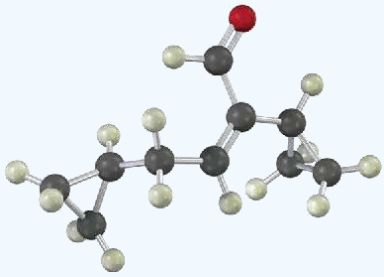
An aldol reaction makes molecule C, and Molecule B is made by Aldol condensation.

Solution for molecule B (5-Ethyl-4-methyl-4-hepten-3-one)	Solution for molecule C (3-Hydroxy-2-ethylhexanal)
 (3-Pentanone)	 (Butanal)

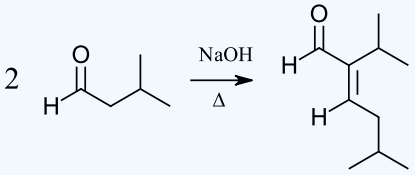
Exercises 9.4.2

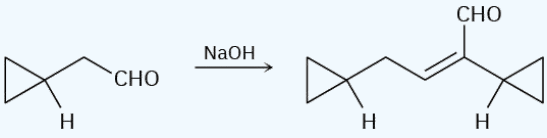
Please design a synthesis for the following molecules: Red = Oxygen, Grey = Carbon, White = Hydrogen

a. 

b. 

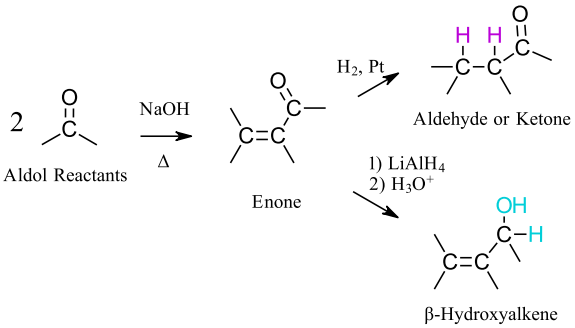
Answers

a. 

b. 

Additional Synthetic Considerations

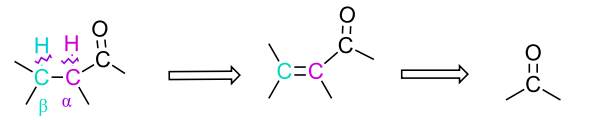
The enone product of an aldol condensation is versatile because it contains two functional groups (alkene & carbonyl) which can be subject to further reactions. Among many possible reactions, an enone can undergo hydrogenation to produce an aldehyde or ketone. Also, the carbonyl group can undergo hydride reduction to produce a beta-hydroxyalkene.



These additional reactions can be applied with the consideration of using an aldol reaction in the synthesis of a target molecule. A similar analysis can be extrapolated to the other reactions possible with the alkene and carbonyl present in an enone.

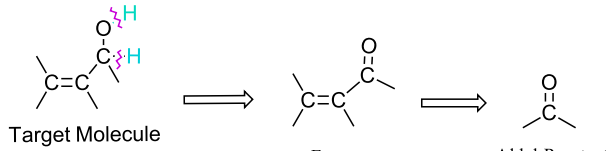
Analysis for Hydrogenation

To consider a hydrogenation, remove a hydrogen from a carbon in both the alpha and beta positions relative to the carbonyl. Then connect these two carbons with a C=C double bond. This create a possible enone which can be broken apart further using the analysis described above. Target molecules can have often have multiple alkyl chains which can be used to form a double bond.



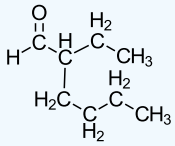
Analysis for Hydride Reduction

To consider a hydride reduction remove a hydrogen from the alcohol oxygen then a hydrogen from the adjacent carbon. Connect the oxygen and carbon with a double bond to form a C=O carbonyl. This provides an enone which can undergo further analysis.



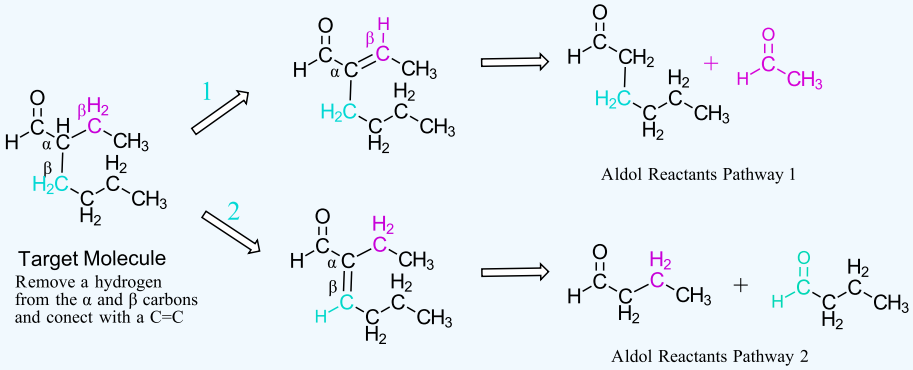
Worked Example 9.4.2

Please devise a synthesis pathway for the following molecule using an aldol reaction:

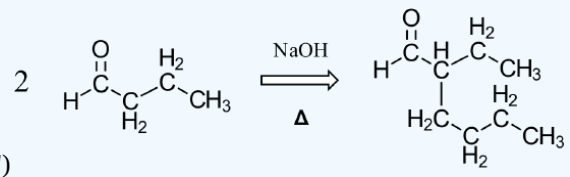


Answer

Analysis: Because the target molecule has two beta-carbons with hydrogens there are two possible synthesis pathways. Both should be considered for their effectiveness. Because a carbonyl is already present fragmentations will first be performed to create two possible enone intermediates. These enones will both be broken into their aldol reactants. When looking a possible aldol reactants produced by each pathway it is clear that pathway 2 is preferred. Because both fragments are the same they will react to form on major product.



Solution

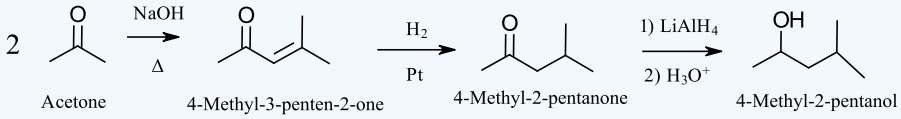


(Error in the figure, step 2 is missing: "2. hydrogenation")

Exercises 9.4.3

Please show the reaction steps required to make 4-methyl-2-pentanol from an aldol condensation.

Answer



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9.5: Mixed Aldol Reactions

Objectives

After completing this section, you should be able to

1. write an equation to illustrate a mixed aldol reaction.
2. identify the structural features necessary to ensure that two carbonyl compounds will react together in a mixed aldol reaction to give a single product rather than a mixture of products.
3. determine whether a given mixed aldol reaction is likely to produce a single product or a mixture of products.
4. identify the product or products formed in a given mixed aldol reaction.
5. identify the carbonyl compounds needed to produce a given enone or *β*-hydroxy aldehyde or ketone by a mixed aldol reaction.

Mixed Aldol Reaction and Condensations

The previous examples of aldol reactions and condensations used a common reactant as both the enolate donor and the electrophilic acceptor. The product, in such cases, is always a dimer of the reactant carbonyl compound. Aldol condensations between different carbonyl reactants are called crossed or mixed reactions, and under certain conditions, such crossed aldol condensations can be effective.

Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols. Because of this, most mixed aldol reactions are usually not performed unless one reactant has no a H's

The following abbreviated formulas illustrate the possible products in such a case, red letters representing the acceptor component and blue the donor. If all the reactions occurred at the same rate, equal quantities of the four products would be obtained. Separation and purification of the components of such a mixture would be difficult.

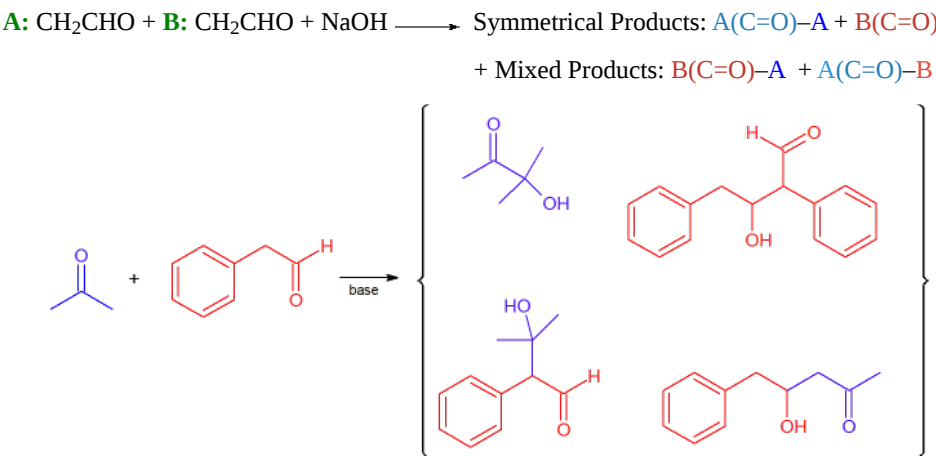


Figure 9.5.1: Products of a Mixed Aldol Reaction.

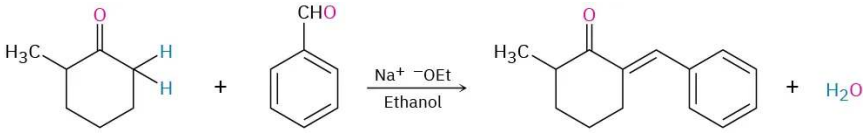
To avoid complex reaction mixtures the reactants should be chosen to favor one particular donor/acceptor reaction. Successful mixed aldol reactions usually use one of two combinations of factors.

1- Lacking alpha-hydrogens

A reaction of an aldehyde with no alpha-hydrogens with a ketone with alpha hydrogens: Aldehydes lacking alpha-hydrogens cannot form an enolate so they can only function as electrophilic acceptor reactants. This reduces the number of possible products by half. Although it would be possible for the ketone to react with itself it is unlikely. Aldehydes are more reactive acceptor electrophiles than ketones. This makes the preferred reaction one with the ketone as an enoloate donor and the aldehyde as an electrophilic acceptor.

The aldol condensation between an aromatic aldehyde with no α-hydrogens and an aliphatic aldehyde or ketone with α-hydrogen is called a **Claisen–Schmidt condensation**. The reaction product is a highly conjugated α,β-unsaturated aldehyde, or ketone, which

forms in the more stable (E)-alkene isomer.

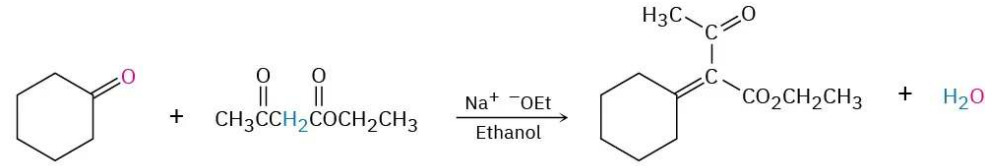


2-Methylcyclohexanone (donor) **Benzaldehyde (acceptor)**

Figure 9.5.2: Claisen–Schmidt Condensation.

2- Highly acidic alpha-hydrogens

One of the reactants has alpha-hydrogens which are highly acidic: The acidic compound will be preferably converted into an enolate donor which removes the possibility of its carbonyl acting as an electrophilic acceptor. An example is the aldol condensation of ethylacetoacetate and cyclopentanone. Ethylacetoacetate has α-hydrogens which are particularly acidic due to their conjugate base being stabilized by two carbonyl bonds (**Section 8.6**). Upon reaction with base, ethylacetoacetate is converted to the enolate donor leaving cyclopentanone as the electrophilic acceptor. This provides one predominant aldol condensation product. In this reaction, sodium ethoxide is used as a base to prevent hydrolysis side-reactions with the ester of ethyl acetoacetate.

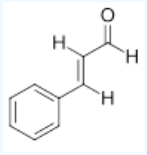
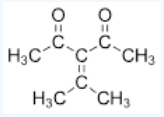
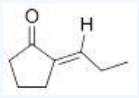


Cyclohexanone (acceptor) **Ethyl acetoacetate (donor)**

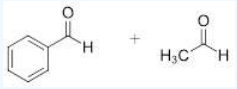
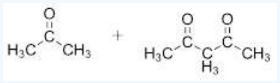
Figure 9.5.3: α,β-unsaturated ketoester (Aldol Condensation Product)

? Exercises 9.5.1

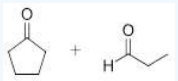
Show the reactants required to make the following using a mixed aldol condensation. Indicate those which would be likely to produce a mixture of products.

a)  b)  c) 

Answers

a)  b) 

c) Because both reactants have α-hydrogens and neither are particularly acidic, the reaction probably will produce a mixture of condensation products.



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9.6: Intramolecular Aldol Reactions

Objectives

After completing this section, you should be able to

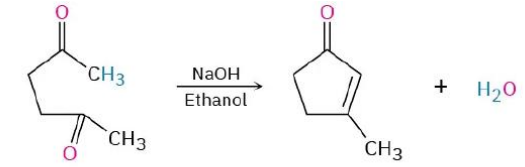
1. write an equation to illustrate an intramolecular aldol reaction.
2. identify the product formed when a given dicarbonyl compound undergoes an intramolecular aldol condensation.
3. identify the dicarbonyl compound which, when treated with a suitable base, could be used to prepare a given cyclic enone by an intramolecular aldol condensation.

Study Notes

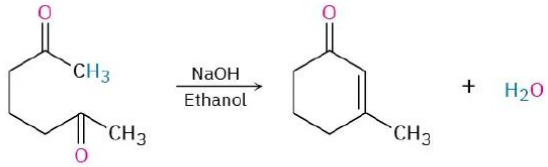
"Intramolecular " means "within the same molecule." You have already seen some examples of intramolecular reactions in previous chapters. Another term for intramolecular aldol reaction is "internal aldol reaction."

Intramolecular aldol reaction

Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction. The term "Intramolecular" means "within the same molecule." In this case, it means that the enolate donor and the electrophilic acceptor of an aldol reaction are contained in the same molecule such as dialdehydes, keto aldehydes, or diketones. In these cases, the small distance between the donor and acceptor leads to faster reaction rates for intramolecular condensations making intermolecular condensations (which require two molecules to collide in solution) less favorable. For example, base treatment of a 1,4-diketone such as 2,5-hexanedione yields a cyclopentenone product, and base treatment of a 1,5-diketone such as 2,6-heptanedione yields a cyclohexenone.



2,5-Hexanedione (a 1,4-diketone) **3-Methyl-2-cyclopentenone**



2,6-Heptanedione (a 1,5-diketone) **3-Methyl-2-cyclohexenone**

The mechanism of intramolecular aldol reactions is similar to that of intermolecular reactions. The only difference is that both the nucleophilic carbonyl anion donor and the electrophilic carbonyl acceptor are now in the same molecule. One complication, however, is that intramolecular aldol reactions might lead to a mixture of products, depending on which enolate ion is formed. For example, 2,5-hexanedione might yield either the five-membered-ring product 3-methyl-2-cyclopentenone or the three-membered-ring product (2-methylcyclopropenyl) ethanone (Figure 9.6.1). In practice, though, only the cyclopentenone is formed.

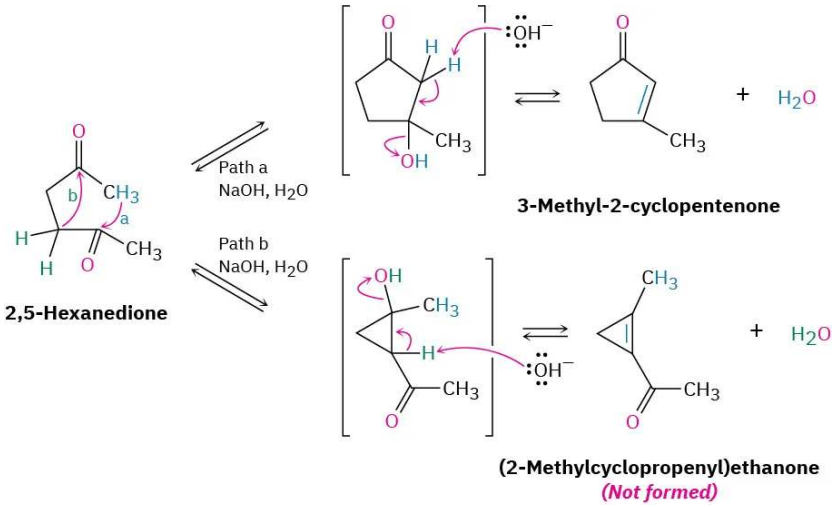
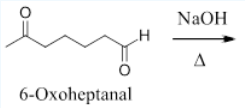


Figure 9.6.1: Intramolecular aldol reaction of 2,5-hexanedione yields 3-methyl-2-cyclopentenone rather than the alternative cyclopropene.

The selectivity observed in the intramolecular aldol reaction of 2,5-hexanedione is due to the fact that all steps in the mechanism are reversible, so an equilibrium is reached. Thus, the relatively strain-free cyclopentenone product is considerably more stable than the highly strained cyclopropene alternative. For similar reasons, intramolecular aldol reactions of 1,5-diketones lead only to cyclohexenone products rather than to the more strained acylcyclobutenes.

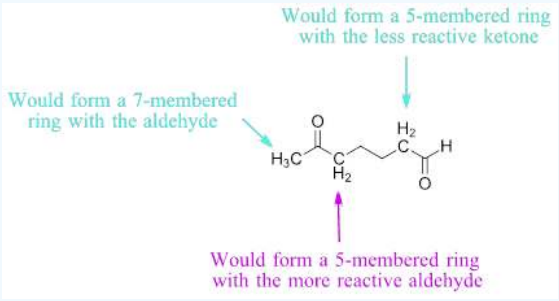
? Worked Example

Please draw the expected product of an intramolecular aldol condensation with the following molecule:

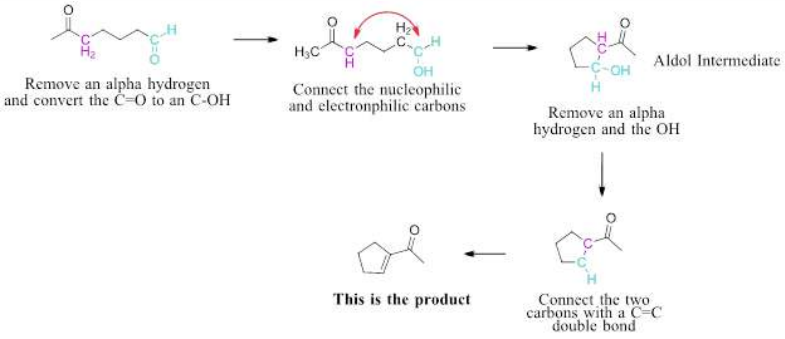


Answer

Analysis: 6-Oxoheptanal has three unique sets of alpha-hydrogens which could be deprotonated to form an enolate. Selecting the correct set involves analyzing the carbonyl reactivity's along with the possible ring sizes of the products.



Solution: Once the preferred alpha-hydrogens are determined go through the steps discussed in the previous sections to determine the aldol condensation product. Remember to form the aldol intermediate first.



Exercise 9.6.1

Treatment of a 1,3-diketone such as 2,4-pentanedione with base does not give an aldol condensation product. Explain.

Answer

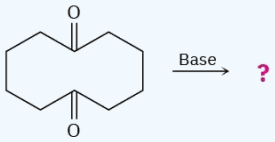
2,4-Pentanedione like other 1,3-Diketones have particularly acidic alpha-hydrogens between the two carbonyl. When base is applied these will be the first to deprotonate and form an enolate. For an intramolecular aldol condensation to occur an alpha-hydrogen one of the methyl groups would have to be removed which would be difficult.



The CH_2 position between the two carbonyl groups is so acidic that it is completely deprotonated to give a stable enolate ion.

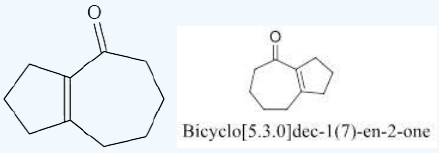
Exercise 9.6.2

What product would you expect to obtain from base treatment of 1,6-cyclodecanedione?



1,6-Cyclodecanedione

Answer



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9.7: The Claisen Condensation Reaction

Objectives

After completing this section, you should be able to

1. write an equation to illustrate a Claisen condensation reaction.
2. write a detailed mechanism for a Claisen condensation reaction or its reverse.
3. identify the product formed in a given Claisen condensation reaction.
4. identify the ester and other reagents needed to form a given β-keto ester by a Claisen condensation reaction.

Key Terms

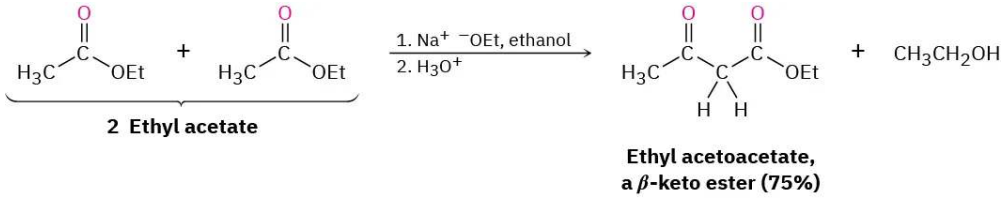
- Claisen condensation reaction

Study Notes

You have already seen that ethyl acetoacetate-type compounds are very useful in organic syntheses. Any reaction which results in the formation of these compounds will also be of importance. In the next section, you will see how the range of β-keto esters that can be prepared by this method is extended through the use of two different esters as starting materials.

Claisen Condensation

Because esters commonly contain both α-hydrogens and a carbonyl bond, they can undergo a reversible condensation similar to the aldol reaction called a Claisen Condensation. In a fashion similar to the aldol reaction, one ester acts as a Claisen enolate donor (nucleophile) while a second ester acts as the Claisen acceptor (electrophile). During the reaction, a new carbon-carbon is formed to produce a β-keto ester product. This reaction is considered a condensation because it eliminates a small alcohol as an unwanted side-product.



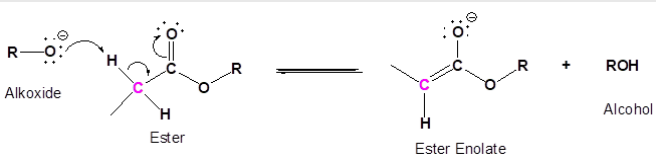
Although they may appear similar, there are a number of fundamental differences between an aldol and Claisen condensation. During the mechanism of the reaction, the formed tetrahedral alkoxide intermediate is not protonated to from an “aldol” type product. Rather, the alkoxide intermediate will reform the C=O carbonyl bond and eliminate a (-OR) leaving group to produce a nucleophilic acyl substitution product.

Mechanism

The Claisen condensation mechanism is analogous to the ester saponification reaction seen in *Section 21.6*.

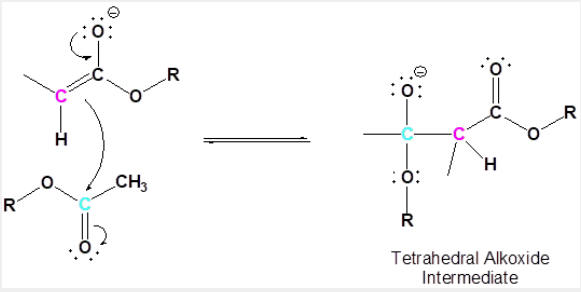
1) Enolate formation

The mechanism starts with the alkoxide base removing an alpha-hydrogen from the ester to form a nucleophilic ester enolate ion.



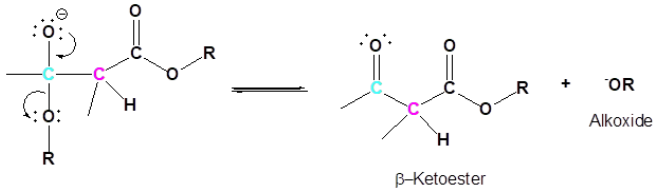
2) Nucleophilic attack

The enolate nucleophile adds to carbonyl carbon of a different ester, forming a tetrahedral alkoxide intermediate.



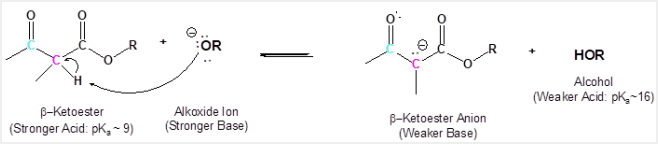
3) Removal of leaving group

The alkoxide then reforms the carbonyl, eliminating the –OR leaving group to form a beta-ketoester.



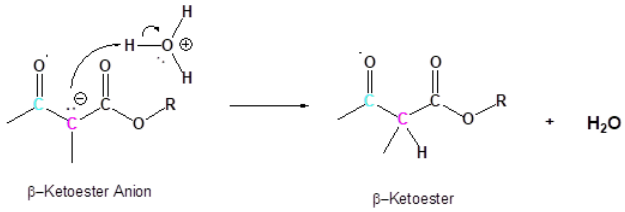
4) Deprotonation

The acidity of beta-ketoesters (pK_a ~9) is high enough to allow them to be completely deprotonated by alkoxide bases (pK_a of an alcohol ~16) to form a second enolate. This make the equilibrium of this step very favorable, which is enough to drive the whole reaction towards the product.



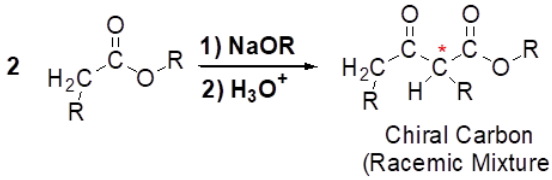
5) Protonation

The enolate is protonated in an acid work-up to form the neutral beta-ketoester product.



Stereochemical Considerations

The alpha-carbon gains a substituent during the reaction, which means it will most likely form a chiral carbon. The fact that the alpha-carbon is temporarily converted to an enolate in the last step of the mechanism means that a racemic mixture of enantiomers will form.

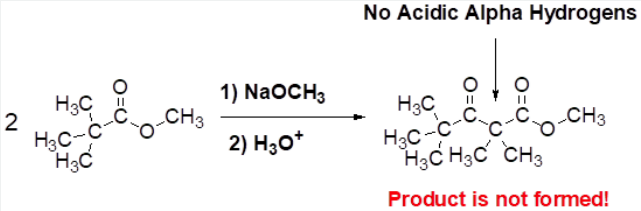


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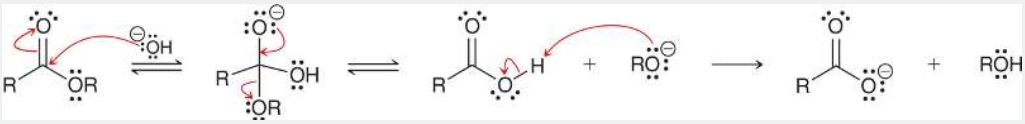
Note

Claisen Condensation Limitations

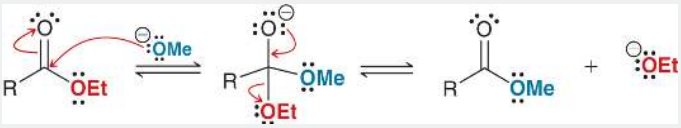
1- the β-keto ester products of Claisen condensation can be acidic enough to be deprotonated by the reaction's base during the final steps of the mechanism. This means the base is not catalytically regenerated during the reaction and a full equivalent of base is required. The β-keto ester condensation products are removed from the equilibrium by this deprotonation, which causes the reaction to be driven forward by Le Chatelier's principle. This concept is so important that a Claisen product will not form unless it contains an alpha hydrogen acidic enough to react completely with the reaction base. This requires that the ester starting materials have at least two alpha-hydrogens for a Claisen condensation product to form. One is removed to form an ester enolate, and the second is removed to drive the reaction forward.



2- Claisen Condensations cannot use a hydroxide for the reaction base due to the possibility of ester hydrolysis.

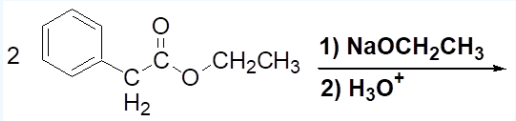


3- Also, to prevent transesterification side products, the alkoxide base typically has the same alkyl group as alkoxy group present in the ester starting material.



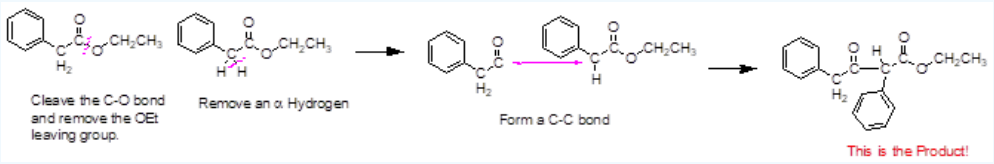
Worked Example

Draw the products of the following reaction:



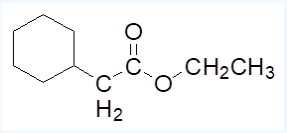
Answer

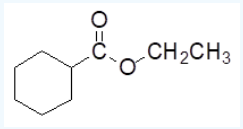
Analysis: Remember to consider each start ester separately.

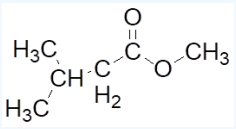


Exercise 9.7.1

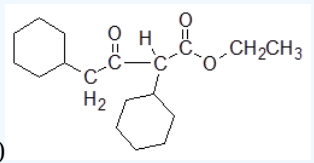
Please draw the products if the following molecules were to undergo a Claisen condensation.

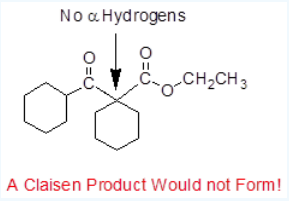
a) 

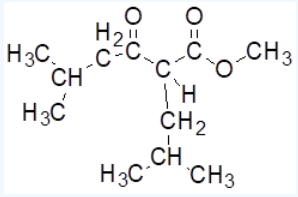
b) 

c) 

Answers

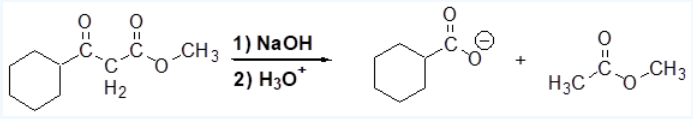
a) 

b) 

c) 

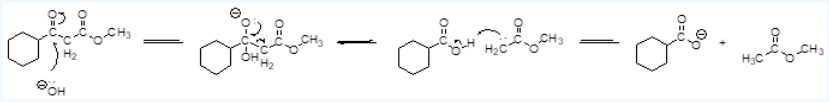
Exercise 9.7.2

The beta-keto ester product of a Claisen condensation can be under hydrolysis with Sodium Hydroxide, as shown in the reaction below. Please draw a curved arrow mechanism to explain how the products are formed. Also, explain why the ketone functional group preferably reacts with hydroxide instead of the ester.



Answers

The carbonyl of the ketone is more likely to be attacked by the hydroxide nucleophile because is more reactive than the ester's



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9.8: Mixed Claisen Condensations

Objectives

After completing this section, you should be able to

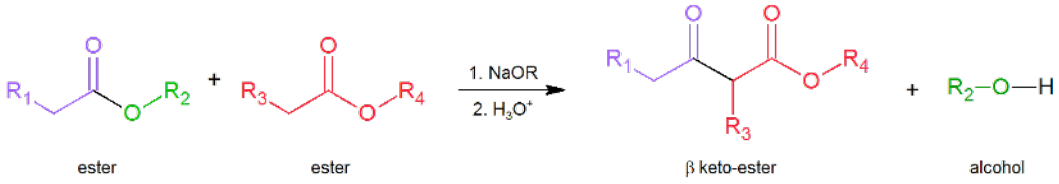
1. write an equation to illustrate a mixed Claisen condensation.
2. identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
3. determine whether a given pair of esters is likely to produce a good yield of a single product when subjected to a mixed Claisen condensation.
4. identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
5. identify the esters that should be used to produce a given β-keto ester by a mixed Claisen condensation.
6. write an equation to illustrate the formation of a β-diketone through a mixed Claisen-type condensation between an ester and a ketone.
7. identify the β-diketone formed as the result of a mixed Claisen-type condensation between a given ester and a given ketone.
8. identify the reagents necessary to synthesize a given β-diketone by a mixed Claisen-type condensation between an ester and a ketone.
9. write detailed mechanisms for mixed Claisen reactions and reactions that are related to the mixed Claisen reaction, including those in which both reacting moieties are present in the same compound.

Study Notes

Just as we can react together two different aldehydes or ketones in a mixed aldol condensation, so can we react together two different esters in a mixed (or "crossed") Claisen condensation. Again, by carefully selecting our substrates we can obtain a good yield of the desired product and minimize the number of possible by-products. Note that even if we replace one of the esters with a ketone, the reaction is still referred to as Claisen condensation. The important thing to realize as you study these reactions is that they all take place by essentially the same mechanism—attack by an enolate anion on a carbonyl group.

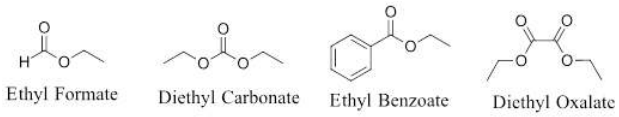
Crossed Claisen Condensation

Claisen condensations between different ester reactants are called **Crossed Claisen** reactions. Crossed Claisen reactions in which both reactants can serve as Claisen donors and Claisen acceptors generally give complex mixtures that are difficult to separate.



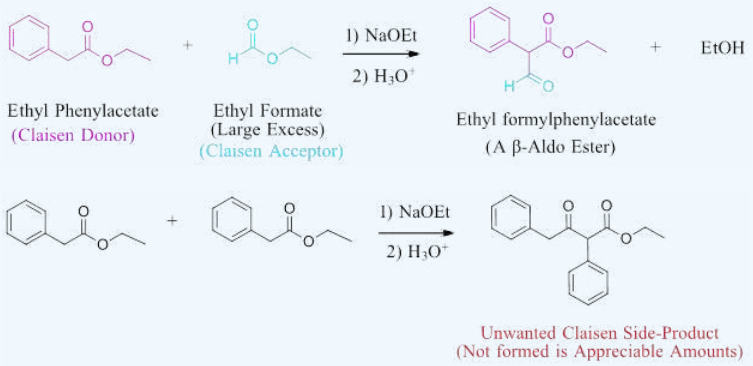
General Crossed Claisen Condensation Reaction

To avoid complex mixtures, most Crossed Claisen reactions are usually not successful unless one of the two esters has no alpha-hydrogens, as in the following examples.



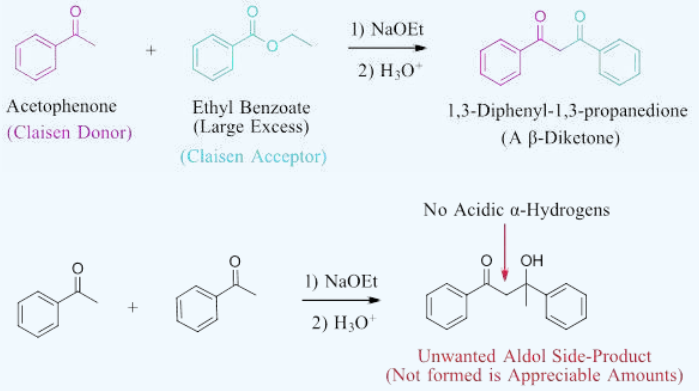
This forces the ester with alpha-hydrogens to be the Claisen donor (enolate) and the ester without alpha-hydrogens to be the Claisen acceptor (electrophile). Even with this differentiation, it is possible for the ester with alpha-hydrogens to undergo a Claisen Condensation with itself to produce an unwanted side-product. This is typically partially prevented by using the ester without alpha-hydrogens in a large excess.

Example: No Alpha Hydrogens



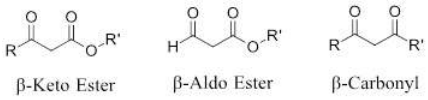
Another type of crossed Claisen condensation occurs when a ketone is reacted with an ester. The use of an ester without alpha-hydrogens is not necessary due to the greater reactivity of the ketone. The alpha-hydrogens of the ketone are much more acidic (pKa~20) than those of the ester (pKa~25). The alpha hydrogens of ketone will be preferably deprotonated to make it the enolate Claisen donor. The ester will therefore be the electrophilic Claisen acceptor and is likewise commonly used in a large excess. There is still a possibility of the ketone reacting with itself to form the product of an aldol reaction however the equilibrium is unfavorable. Also, the formation of the aldol product is reversible due to its lack of an acidic alpha hydrogen. The beta-diketone Claisen product can be irreversibly deprotonated due to its more acidic alpha-hydrogens, making it the reaction's main product.

Example: Ester with Ketone

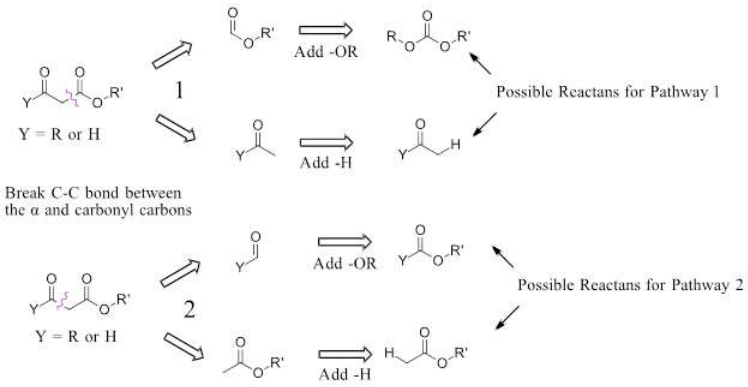


Planning a Synthesis using a Claisen or Crossed Claisen-like Reaction

A Claisen reaction should be considered for a synthesis pathway if the target molecule contains a beta-keto esters, a beta-aldo ester or a beta-dicarbonyl.



A beta-keto ester or a beta-aldo ester could possibly be made by a Claisen condensation of two esters. A beta-dicarbonyl could possibly be made by a Claisen-like condensation between a ketone and an ester. Here, the key bond cleavage is a C-C bond between one of the carbonyls and the alpha-carbon which lies between the carbonyl. In each of these situations, there are two such C-C bonds, so there will be two possible pathways to consider. After the C-C bond cleavage, the fragment with the alpha-carbon will gain hydrogen. The fragment with the bare carbonyl will gain an –OR group to become an ester. The –OR group added will be the same as any ester present in the target molecule. If none are present $–OCH_2CH_3$ is typically used.



Analysis for Beta-Keto and Aldo Esters

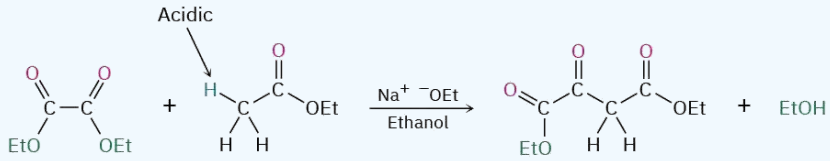
Worked Example 9.8.1: Predicting the Product of a Mixed Claisen Condensation Reaction

Diethyl oxalate, $(CO_2Et)_2$, often gives high yields in mixed Claisen reactions. What product would you expect to obtain from a mixed Claisen reaction of ethyl acetate with diethyl oxalate?

Strategy

A mixed Claisen reaction is effective when only one of the two partners has an acidic α hydrogen atom. In the present case, ethyl acetate can be converted into its enolate ion, but diethyl oxalate cannot. Thus, ethyl acetate acts as the donor and diethyl oxalate as the acceptor.

Solution

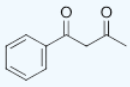


Diethyl oxalate **Ethyl acetate**

A similar analysis can be performed on a 1,3-diketone and will be presented in the worked example below.

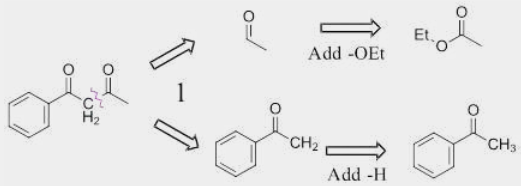
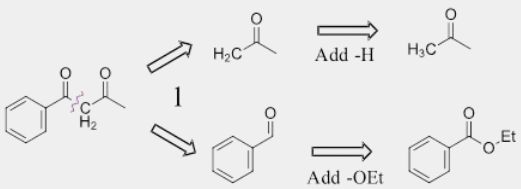
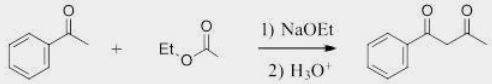
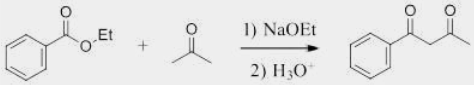
Worked Example 9.8.2

Show how the following molecule can be made using a Claisen-like condensation.


1-Phenyl-1,3-butanedione

Strategy

Focusing on the cleavage between the alfa-carbon and the second carbonyl, 2 Pathways can be analyzed:

Pathway 1	Pathway 2
	
Answer Pathway 1	**Answer Pathway 2**
	

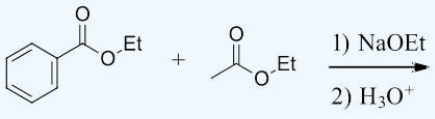
In the present case, Pathway 1 would produce two possible enolates ions: one from acetophenone and the other from ethyl acetate. This pathway won't be effective.

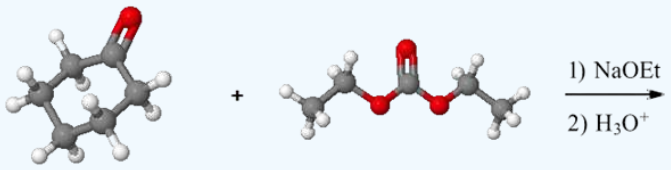
Solution

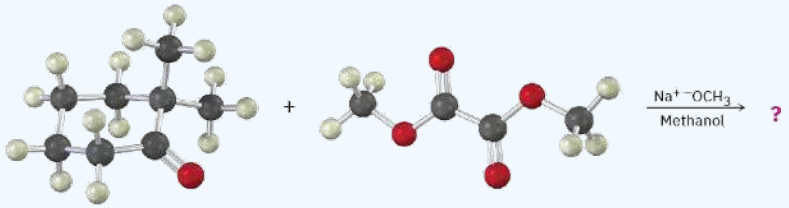
In Pathway 2, acetone can be converted into its enolate ion, but ethyl benzoate cannot. Thus, acetone is the donor, and ethyl benzoate is the acceptor. A mixed Claisen reaction is effective when only one of the two partners has an acidic α hydrogen atom.

Exercise 9.8.1

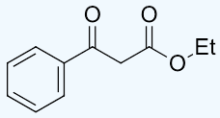
Draw the product of the following reactions:

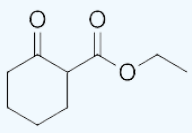
a. 

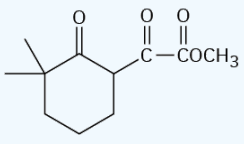
b. 

c. 

Answers

a. 

b. 

c. 

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9.9: Intramolecular Claisen Condensations - The Dieckmann Cyclization

Objectives

After completing this section, you should be able to

1. write an equation to illustrate an internal Claisen condensation, that is, a Dieckmann cyclization.
2. identify the product formed when a 1,6- or 1,7-diester undergoes an internal Claisen condensation.
3. identify the diester needed to prepare a given cyclic β-keto ester by an internal Claisen condensation.
4. identify the structural features present in a diester that lead to the formation of more than one product in an internal Claisen condensation.

Key Terms

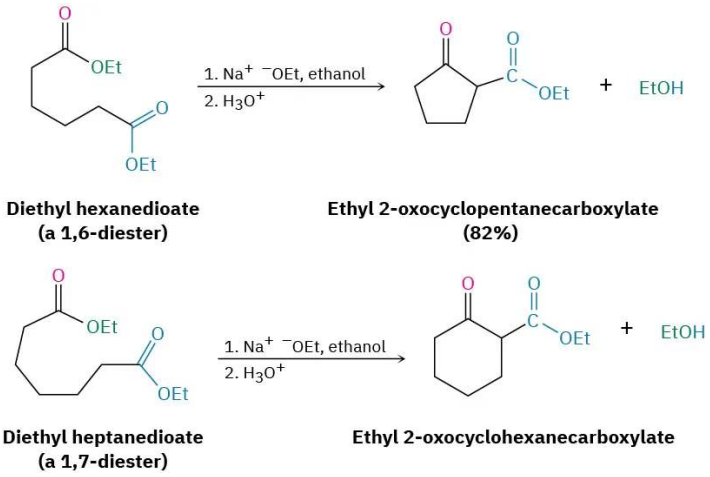
- Dieckmann cyclization

Study Notes

Essentially no new material is introduced in this section; Dieckmann cyclizations are intramolecular Claisen condensations. These reactions occur for 1,6- and 1,7-diesters, as these substances result in the formation of compounds containing five- and six-membered rings, respectively. You may recall that the formation of such ring systems is favoured because they are relatively free of strain.

The Dieckmann Cyclization

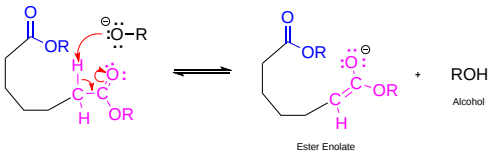
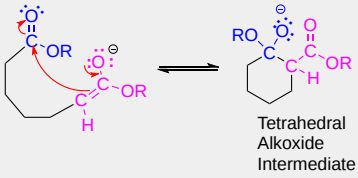
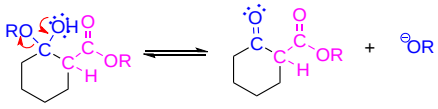
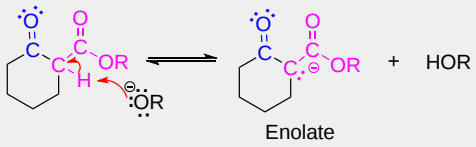
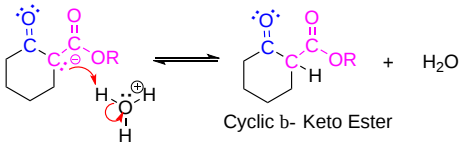
Diesters can undergo an intramolecular reaction, called the Dieckmann condensation, to produce cyclic beta-keto esters. This reaction works best with 1,6-diesters, which produce five-membered rings, and 1,7-diesters which produce six membered rings.



Examples of the Dieckmann Cyclization reaction.

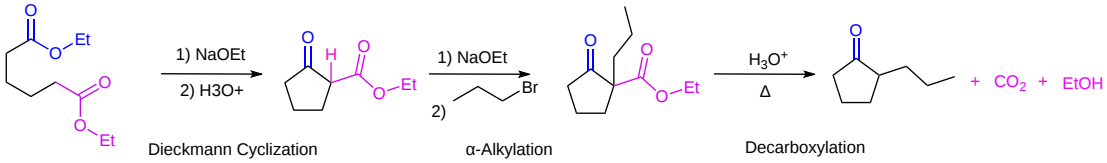
Mechanism

The mechanism of the Dieckmann condensation is the same as a Claisen condensation. A full equivalent of base is necessary during this reaction.

Step 1: Enolate formation An alkoxide base removes an alpha-hydrogen from one of the esters to form an ester enolate.	
Step 2: Nucleophilic attack The enolate then adds to the carbonyl carbon of the other ester to form a tetrahedral alkoxide intermediate.	
Step 3: Removal of leaving group The alkoxide reforms the carbonyl bond, which causes the elimination of the –OR leaving group and forms a cyclic beta-keto ester.	
Step 4: Deprotonation The high acidity of the beta-keto ester allows it to be deprotonated by the reactions base to form a second enolate. Like the Claisen condensation, this deprotonation step drives the equilibrium towards the products and is required for the reaction to occur.	
Step 5: Protonation Acidic Workup	

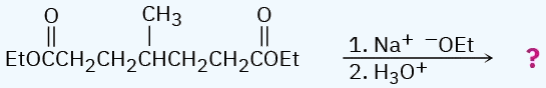
Further Reactions of the Dieckmann Cyclization Product

The cyclic beta-keto ester product of a Dieckmann cyclization can be modified by reaction similar to those used in the acetoacetic ester synthesis (**Section 22-7**). The acidic alpha-hydrogens of the beta-keto ester allow it to easily be deprotonated and alkylated in an alpha-substitution reaction. Having a carbonyl group in the beta position allows the ester to be removed through decarboxylation. The combination of these three reactions (1) Dieckmann cyclization, (2) alpha alkylation, and (3) decarboxylation provides an efficient method for preparing 2-substituted cyclopentanones and cyclohexanones.



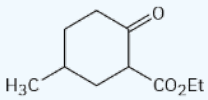
? Exercise 9.9.1

Draw the expected product for the following reaction:



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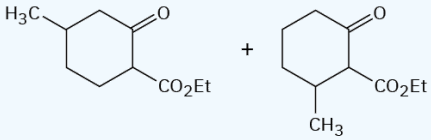
Answer



Exercise 9.9.2

Dieckmann cyclization of diethyl 3-methylheptanedioate gives a mixture of two β-keto ester products. What are their structures, and why is a mixture formed?

Answers



Each has the ability to act as a Claisen donor and a Claisen acceptor. The reaction should produce a roughly 50/50 mixture where each ester acts as a Claisen acceptor.

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9.10: Conjugate Carbonyl Additions - The Michael Reaction

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the Michael reaction.
2. write a detailed mechanism for a given typical Michael reaction.
3. identify the product formed in a given Michael reaction.
4. identify the reagents necessary to synthesize a given compound by a Michael reaction.

Key Terms

- Michael reaction

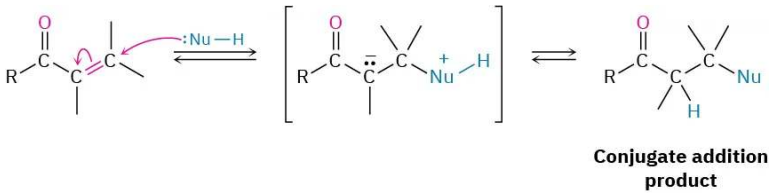
Study Notes

Before studying this section in detail, you should review conjugate addition to *α,β*-unsaturated carbonyl compounds (Section 5.14).

Notice the wide variety of compounds that can take part in a Michael reaction. As usual, you should not feel overwhelmed by the number of different compounds that can be used, just keep in mind that in all cases the mechanism is essentially the same.

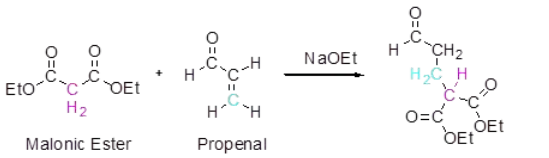
Michael Reaction

Certain nucleophiles undergo conjugate addition with the alkene of an α, β-unsaturated carbonyl compounds rather than undergo direct nucleophilic addition with the carbonyl. During conjugate addition, a nucleophile adds to the electrophilic β-alkene carbon to form a C-Nuc bond. If the starting materials contain an ester, the corresponding alkoxide is used as the base in the reaction. Otherwise, a hydroxide base, such as sodium or potassium hydroxide, is commonly used.



General Reaction of the Michael Reaction

When enolate nucleophiles undergo conjugate addition with an α, β-unsaturated carbonyl the process is called a Michael Reaction. The Michael reaction works best with particularly acidic enolate donors such as malonic esters, β-keto esters, etc. Enolates which are weaker acids tend to undergo nucleophilic addition to the carbonyl rather than conjugate addition. For example, malonic ester's acidic α-hydrogens can be easily deprotonated by sodium ethoxide to form an enolate. The enolate adds to propenal to form the conjugate addition product.



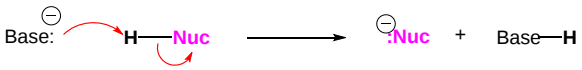
Mechanism of Michael Reaction

During a Michael reaction, the enolate acts as a nucleophilic donor, and the α, β-unsaturated carbonyl acts as the electrophilic acceptor. The mechanism is a mixture of an alpha-substitution for the enolate and a conjugate addition for the α, β-unsaturated carbonyl.

Notice that the Michael Reaction does not require the deprotonation of the product to push the reaction toward completion. The reaction is thermodynamically favorable because the C-C bond formed in the product is stronger than the C=C bond in the starting material. This means that, unlike the Claisen condensation, this reaction only requires a catalytic amount of reaction base.

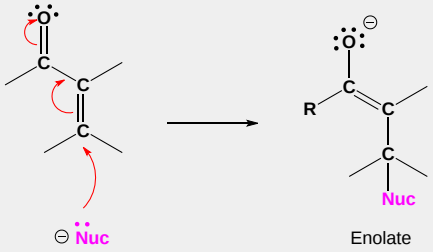
Step 1: Deprotonation

The alkoxide base removes an alpha-hydrogen to form an enolate nucleophile.



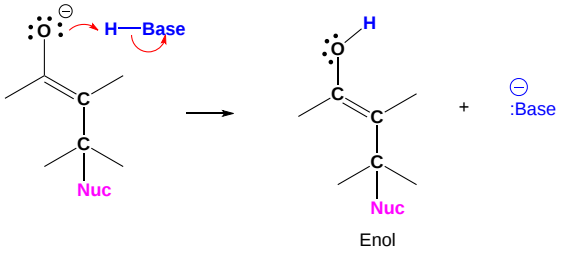
Step 2: Nucleophilic attack on the carbon β to the carbonyl

The enolate nucleophile then adds to the electrophilic β-carbon of the α, β-unsaturated carbonyl. Conjugation pushes the C=C pi bond electrons onto the carbonyl oxygen, forming a new enolate enolate.



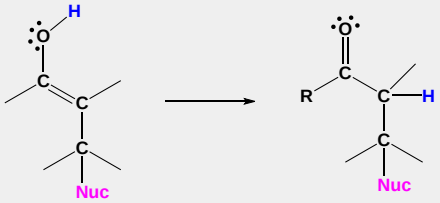
Step 3: Protonation

The alkoxide is protonated, forming an enol.



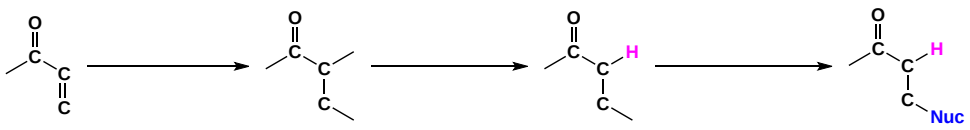
Step 4: Tautomerization

Tautomerization converts the enol back into a carbonyl, forming the neutral conjugate addition product.



Predicting the Product of a Michael Reaction

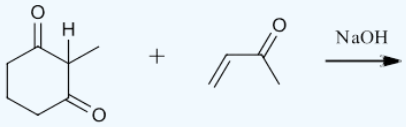
During the reaction the C=C pi bond of the α, β-unsaturated carbonyl is broken. An C-H bond is formed on the carbon in the α-position from the carbonyl. An acidic hydrogen is removed from the nucleophile and then it is used to form a C-C bond with the carbon in the beta position from the carbonyl.



a. In the first step, remove the double bond and add two single bonds
b. Add hydrogen to the bond adjacent to the carbonyl
c. Add the nucleophile to the other end of the double bond (remember to remove a hydrogen from the nucleophile)

Worked Example 9.10.1

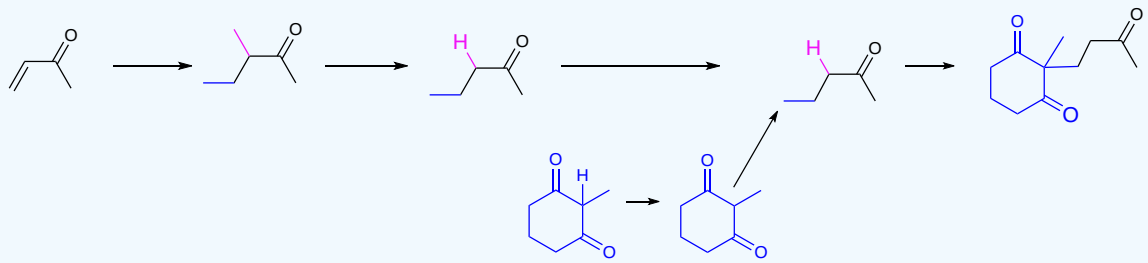
What would be the product of the following conjugate addition?



Strategy

1. Break the double bond and add two single bonds
2. Add a hydrogen to the bond adjacent to the carbonyl
3. Remove a hydrogen from the nucleophile.
4. Add the nucleophile to the other end of the double bond.

Solution



Michael Acceptors and Michael Donors

The Michael reaction can be performed with a wide variety of α, β-unsaturated carbonyl electrophilic acceptors and enolate donors. Michael acceptors such as α, β-unsaturated ketones, aldehydes, esters, amides, and nitro compounds can all participate in this reaction. Michael donors with particularly acidic α-hydrogens, such as β-diketones, β-keto esters, β-keto nitriles, α-nitro ketones, malonic esters, and nitro compounds can be used.

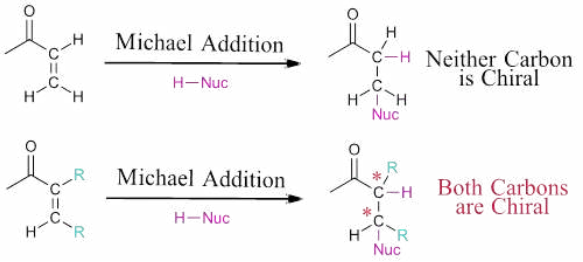
Table 9.10.1: Some Michael Acceptors and Michael Donors

Michael acceptors		Michael donors	
CH_2=CH-CH=O	Propenal α,*β*-unsaturated aldehyde	$RCCH_2CR'$ (O, O)	*β*-Diketone
$H_2C{=}CHCCH_3$ (O)	3-Buten-2-one α,*β*-unsaturated ketone	$RCCH_2COEt$ (O, O)	*β*-Keto ester
$H_2C{=}CHCOEt$ (O)	Ethyl propenoate α,*β*-unsaturated ester	$EtOCCH_2COEt$ (O, O)	Diethyl malonate
$H_2C{=}CHCNH_2$ (O)	Propenamide α,*β*-unsaturated amide	$RCCH_2C{\equiv}N$ (O)	*β*-Keto nitrile
$H_2C{=}CHC{\equiv}N$	Propenenitrile α,*β*-unsaturated nitrile	RCH_2NO_2	Nitro compound
$H_2C{=}CH(NO_2)$	Nitroethylene		

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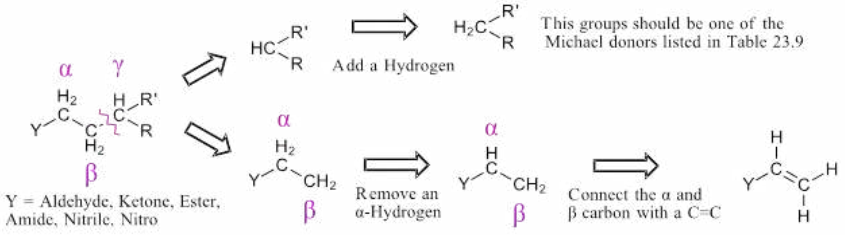
Stereochemical Consideration of Micheal Reactions

During a Michael reaction, two sp2 hybridized carbons are converted to sp^3 hybridization. Both of them have the possibility of creating a chiral carbon. Michael reactions are often performed using an α, β-unsaturated carbonyl with only hydrogen substituents on the alkene to prevent the formation of chiral carbons. If either carbon in the alkene has an alkyl substituent it will likely form a chiral carbon in the Michael reaction product. The α-carbon of the enolate donor also has the possibility of forming a chiral carbon as discussed in **Section 9-7.**



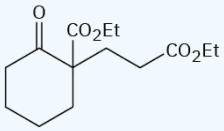
Planning a Synthesis Using a Michael Reaction

The true utility of the Michael reaction is seen when considering it use in a synthesis. The reaction can be used to prepare aldehydes, ketones, esters, amides, nitriles, and nitro compounds. A target molecule can possibly be made using a Michael reaction if it contains one of these functional groups and an alkyl chain at least three carbons long. The key bond cleavage is a C-C bond between β and gamma carbons from a carbonyl-like group. The fragment with the Y group loses an α-hydrogen and then forms a C=C bond between the α and beta carbon. The carbon of the other fragment gains a hydrogen. This fragment should possess an acidic α-hydrogen and should be made up of Michael donor fragments such as those listed in **Table** 9.10.1. In some cases, there may be more than one fragmentation variation. Each variation should be investigated and the possible starting materials compared for viability.



Worked Example 9.10.2: Using the Michael Reaction

How might you obtain the following compound using a Michael reaction?

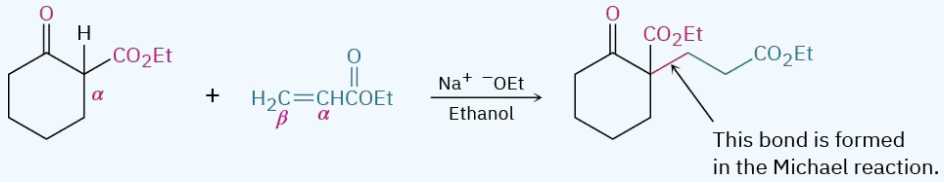


Strategy

A Michael reaction involves the conjugate addition of a stable enolate ion donor to an *α,β*-unsaturated carbonyl acceptor, yielding a 1,5-dicarbonyl product. Usually, the stable enolate ion is derived from a *β*-diketone, *β*-keto ester, malonic ester, or similar compound. The C–C bond formed in the conjugate addition step is the one between the *α* carbon of the acidic donor and the *β* carbon of the unsaturated acceptor.

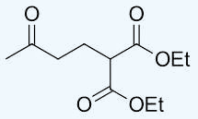
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Solution



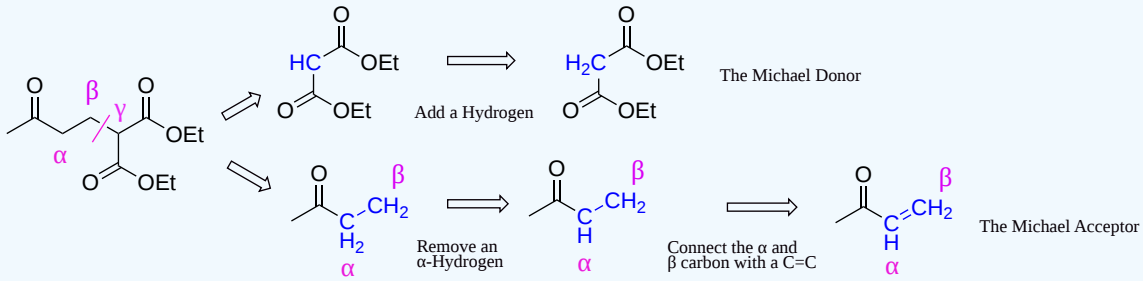
Worked Example 9.10.3: Using the Michael Reaction

How could the following molecule be synthesized using a Michael Reaction?

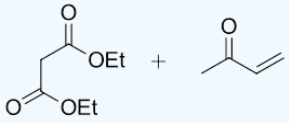


Strategy

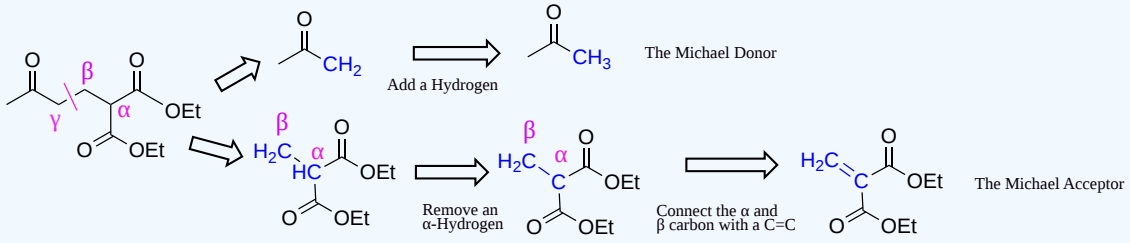
Pathway 1



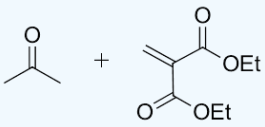
Starting Materials 1



Pathway 2



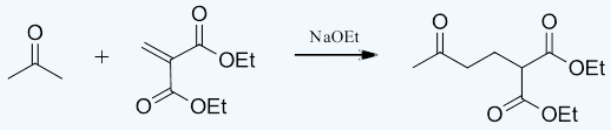
Starting Material 2



Solution

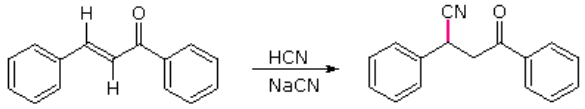
When comparing the two sets of possible starting materials pathway 1 is preferred. The Michael enolate donor is particularly acidic because its conjugate base is stabilized by two carbonyls. The Michael enolate donor for pathway 2 does not have the same acidity. Consequently, the enolate would preferably undergo nucleophilic addition rather than conjugate addition. This makes the starting materials of pathway 1 preferred for synthesizing the starting material.

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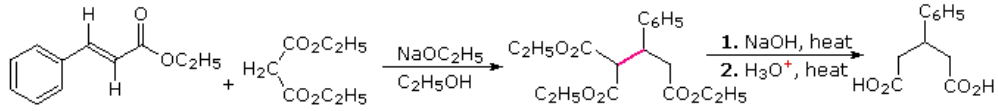


In combination with alkylations and condensations, the Michael reaction may be used to construct a wide variety of complex molecules from relatively simple starting materials. The carbon nucleophiles used in the following examples include cyanide ion, sodium diethylmalonate and the conjugate base of cyclohexane-1,3-dione. These anions are sufficiently stable that their addition reactions may be presumed reversible. If this is so, the thermodynamic argument used for hetero-nucleophile additions would apply here as well, and would indicate preferential formation of 1,4-addition products. Cyanide addition does not always follow this rule, and aldehydes often give 1,2-products (cyanohydrins). In each case the initial reaction is a Michael addition, and the new carbon-carbon bond is colored magenta. Any subsequent bonds that are formed by other reactions are colored orange.

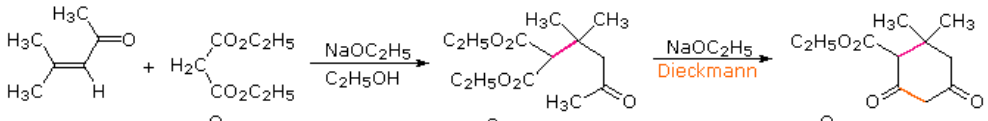
1.



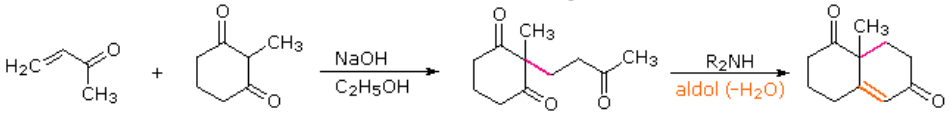
2.



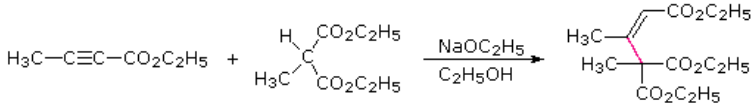
3.



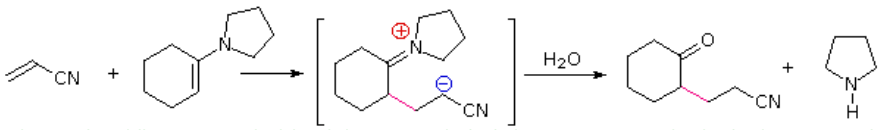
4.



5.

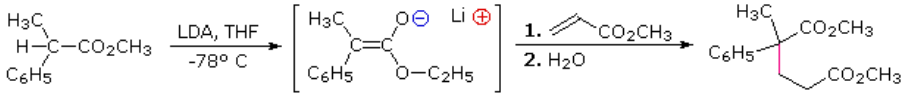


6.



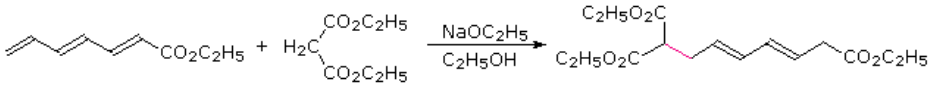
Enamine nucleophiles are good Michael donors. Hydrolysis is necessary to obtain the ketone product.

7.



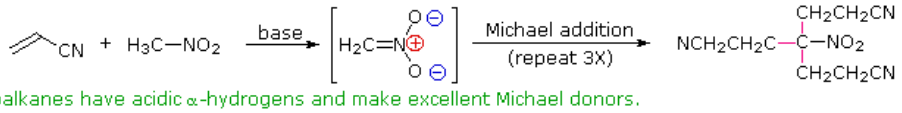
Weak carbon acids may be converted to their enolate anions prior to addition of the Michael acceptor.

8.



Extended vinylagous Michael acceptors have been used. This is a 1,6-addition (1,8 if the enol is counted).

9.



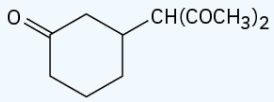
Nitroalkanes have acidic α-hydrogens and make excellent Michael donors.

Exercise 9.10.1

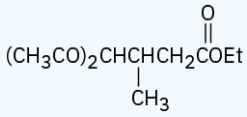
What product would you obtain from a base-catalyzed Michael reaction of 2,4-pentanedione with each of the following α,β-unsaturated acceptors?

a. 2-Cyclohexenone
b. Propenenitrile
c. Ethyl 2-butenoate

Answer

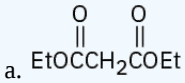
a. 

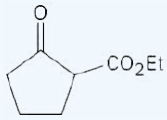
b. $(CH_3CO)_2CHCH_2CH_2CN$

c. 

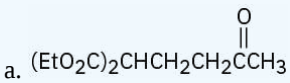
Exercise 9.10.2

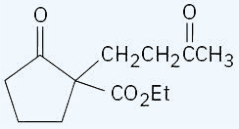
What product would you obtain from a base-catalyzed Michael reaction of 3-buten-2-one with each of the following nucleophilic donors?

a. 

b. 

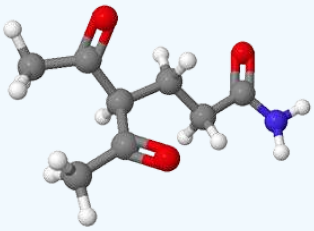
Answer

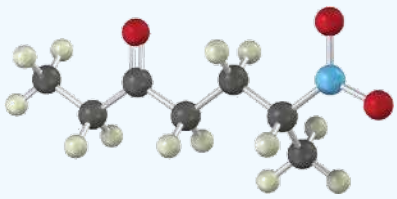
a. 

b. 

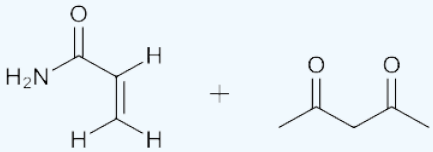
Exercise 9.10.3

What would be the starting materials required to make the following molecules using a Michael reaction? Red = Oxygen, Grey = Carbon, White = Hydrogen, Blue = Nitrogen.

a. 

b. 

Answers

a. 

b. $CH_3CH_2COCH{=}CH_2 + CH_3CH_2NO_2$

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9.11: Carbonyl Condensations with Enamines - The Stork Reaction

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the three-step Stork enamine reaction.
2. write a detailed mechanism for each of the three steps of the Stork enamine reaction.
3. identify the product formed, and the various intermediates (i.e., the enamine, the Michael-type adduct), in a given Stork enamine reaction.
4. identify the reagents needed to synthesize a given compound by a Stork enamine reaction.

Key Terms

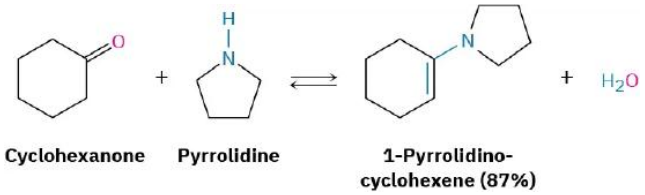
- Stork enamine reaction

Study Notes

If we try to use a monoketone as a donor molecule in a Michael reaction, we will obtain a poor yield. An alternative route to the product that would be expected from such a synthesis is via the Stork enamine reaction. You may wish to review the formation of enamines (from ketones and secondary amines) before you proceed with this section; if so, review Section 5.9.

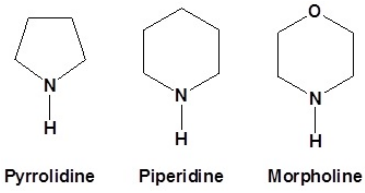
Synthesis of Enamines

In addition to enolate ions, other kinds of carbon nucleophiles also add to *α*,*β*-unsaturated acceptors in Michael-like reactions. Among the most important and useful of such nucleophiles, particularly in biological chemistry, are **enamines**, which are readily prepared by reaction between a ketone and a secondary amine (Section 19.8). For example:.

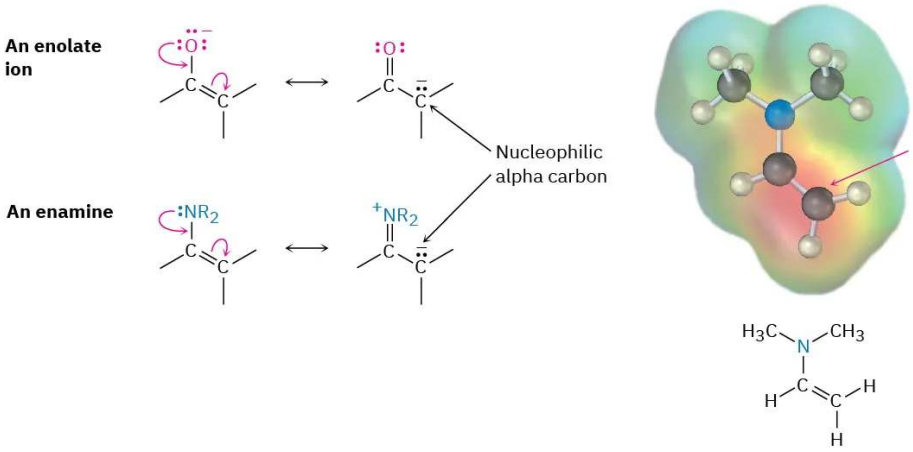


General Reaction

Typically, the following 2° amines are used for enamine reactions:



Enamines have resonance structures similar to enolates. The lone pair electrons on the nitrogen are conjugated with the double bond and can donate electron density to the α-carbon. This allows the α-carbon of enamines to be nucleophilic in much the same fashion as enolates. An electrostatic potential map of *N*,*N*-dimethylaminoethylene shows this shift of electron density (red) toward the *α* position. This is analogous to the increased electron density of the α-carbon of an enolate.



Enamines behave in much the same way as enolate ions and enter into many of the same kinds of reactions. In the Stork enamine reaction, named for its discoverer, Gilbert Stork of Columbia University, for example, an enamine adds to an *α*,*β*-unsaturated carbonyl acceptor in a Michael-like process. The initial product is then hydrolyzed by aqueous acid to yield a 1,5-dicarbonyl compound. The overall reaction is thus a three-step sequence of:

a. enamine formation from a ketone,
b. Michael addition to an *α*,*β*-unsaturated carbonyl compound, and
c. enamine hydrolysis back to a ketone.

The net effect of the Stork enamine reaction is the Michael addition of a ketone to an *α*,*β*-unsaturated carbonyl compound. For example, cyclohexanone reacts with the cyclic amine pyrrolidine to yield an enamine; further reaction with an enone such as 3-buten-2-one yields a Michael adduct; and aqueous hydrolysis completes the sequence to give a 1,5-diketone (Figure **9.11.1**).

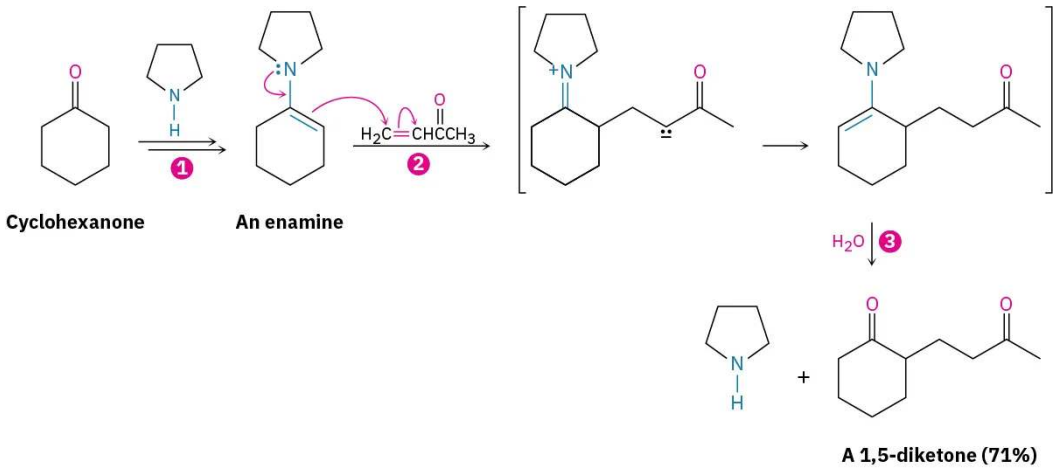
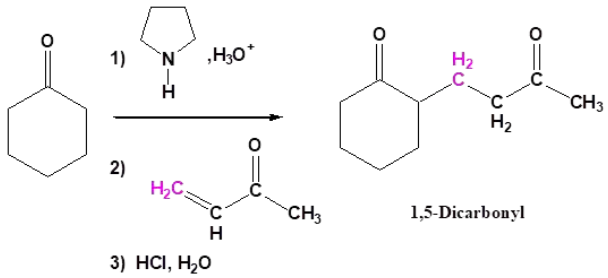


Figure **9.11.1**: The Stork enamine reaction between cyclohexanone and 3-buten-2-one. (**1**) Cyclohexanone is first converted into an enamine, (**2**) the enamine adds to the *α*,*β*-unsaturated ketone in a Michael reaction, and (**3**) the conjugate addition product is hydrolyzed to yield a 1,5-diketone.

Michael Reaction Using Enamines: The Stork Reaction

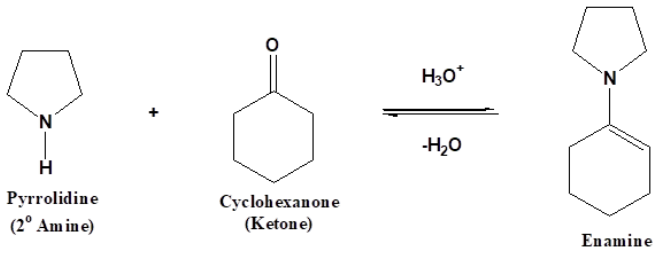
Enamines add to α, β-unsaturated carbonyls in a Michael-like reaction. The net reaction is the addition of a ketone to a α, β-unsaturated carbonyl to product a 1,5 dicarbonyl compound as the end product. This reaction is commonly known as the Stork enamine reaction after Gilbert Stork of Columbia University who originated the work.



Example of a The Stork Reaction

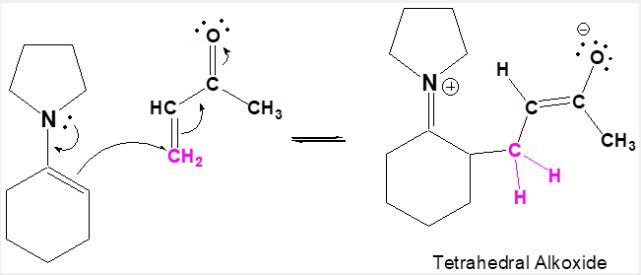
Mechanism of the Stork Reaction

Step 1: Formation of the enamine



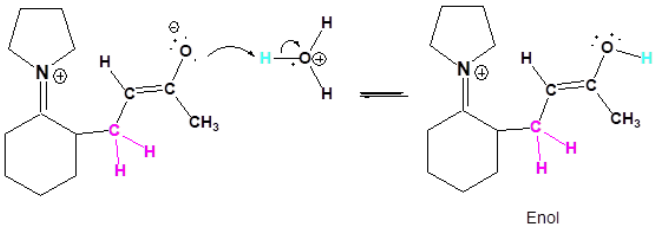
Step 2: Nucleophilic attack on the carbon β to the carbonyl

After formation, the enamine adds to the electrophilic alkene carbon of the a α, β-unsaturated carbonyl form an iminium bond. The pi electrons of the alkene are pushed onto the oxygen through conjugation to form an alkoxide as an intermediate.



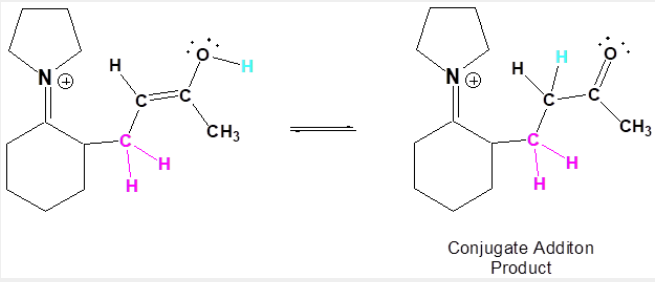
Step 3: Protonation

Protonation of the alkoxide forms an enol.



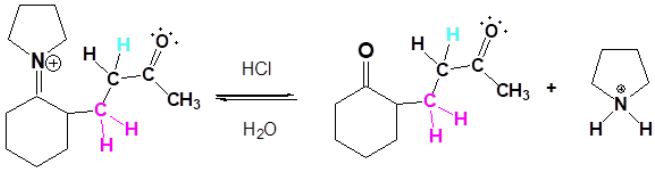
Step 4: Tautomerization

The enol undergoes tautomerization to reform the ketone.



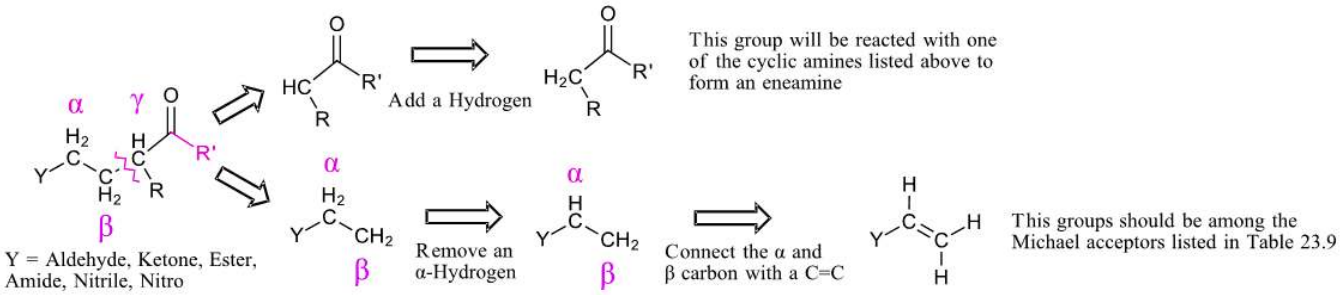
Step 5: Reform the carbonyl by hydrolysis

In the last step of the mechanism, the iminium bond is hydrolyzed to reform the carbonyl to create a 1,5-dicarbonyl compound as the product of a Michael-like reaction.



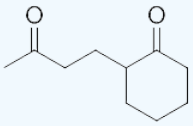
Planning a Synthesis Using the Stork Enamine Synthesis

Planning a synthesis using a Stork enamine reaction is very similar to that of a Michael reaction (**Section 9-11**). A target molecule can possibly be made using a Stork enamine reaction if it contains a 1,5-dicarbonyl. Like the Michael reaction, the key bond cleavage is a C-C bond between beta and gamma carbons from a carbonyl-like group. The fragment with the Y group loses an alpha-hydrogen and then forms a C=C bond between the alpha and beta carbon. The carbon of the other fragment gains a hydrogen. This fragment should possess an acidic alpha-hydrogen and should be made up of Michael donor fragments.



Worked Example

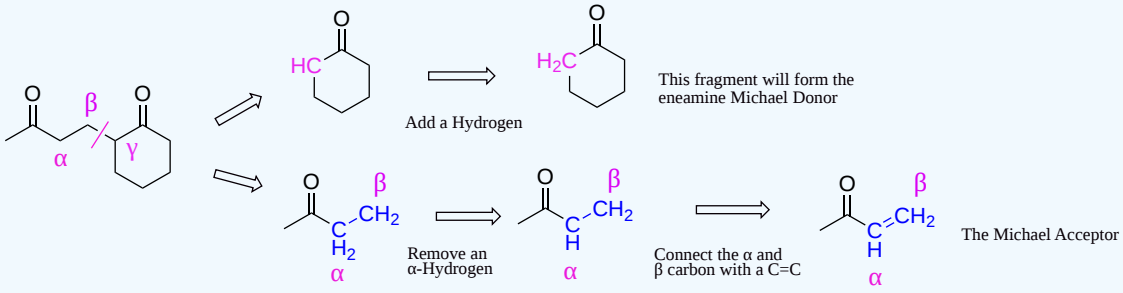
How could the following molecule be made using a Michael Reaction?



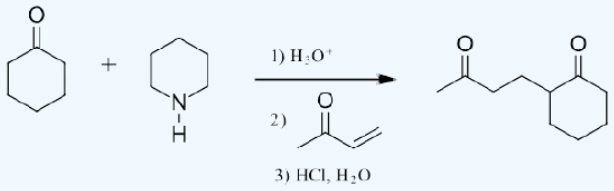
Strategy

The 1,5-dicarbonyl product is the overall result of an enamine (donor) addition to an *α,β*-unsaturated carbonyl compound (acceptor). The C–C bond formed in the Michael addition step is the one between the *α* carbon of the enamine donor and the *β*-carbon of the *α,β*-unsaturated acceptor.

Pathway 1



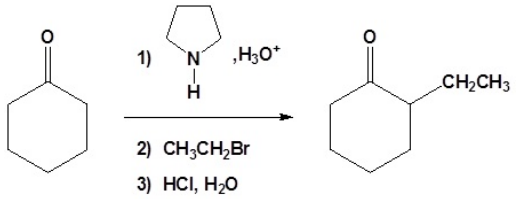
Solution



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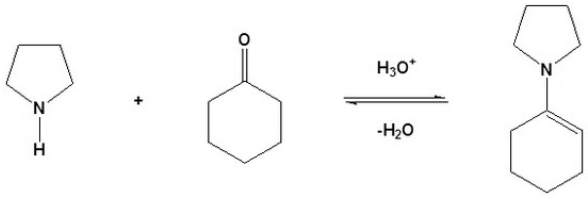
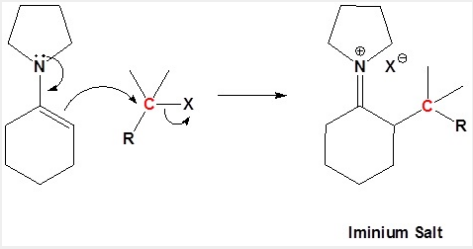
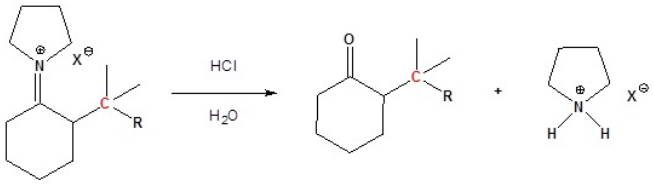
Alkylation of an Enamine

Enamines undergo an S_N2 reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl. The individual steps are below.



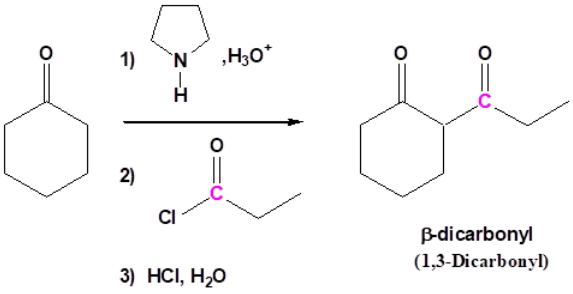
Example of an acylation of an enamine.

Mechanism on Enamine Alkylation

Step 1: Formation of the enamine	
Step 2: Alkylation Nucleophilic attack (S_N2) on the carbon with the Living Group	
Step 3: Acidic Workup Reform the carbonyl by hydrolysis.	

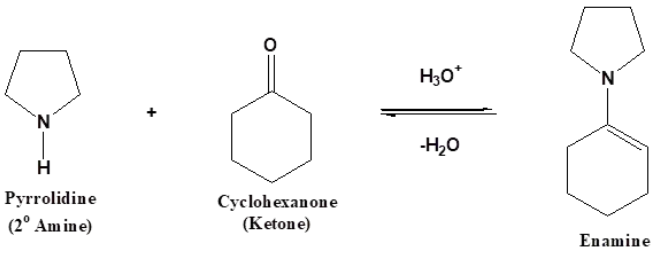
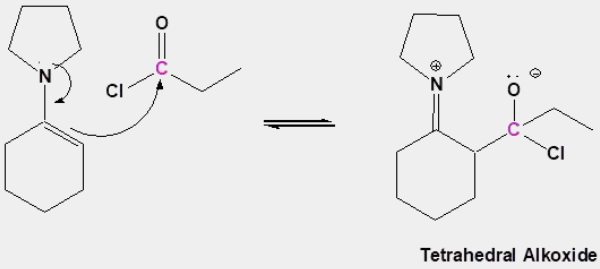
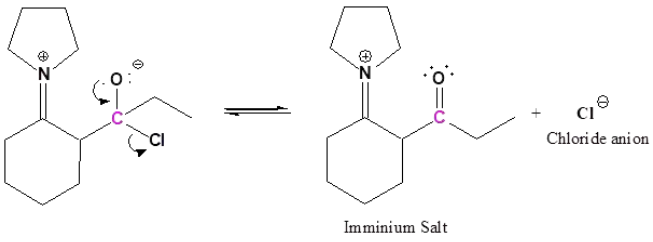
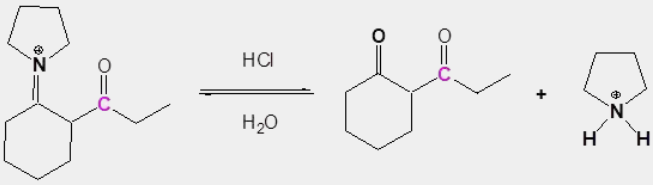
Acylation of Enamines

Acylation of Enamines involves the addition of an acyl group (RCO^-) to an enamines. Enamines can add to acid halides to form 1,3-diketones and α, β-unsaturated Michael acceptors to form 1,5-dicarbonyls. Resulting in the formation of an α-acylated product.



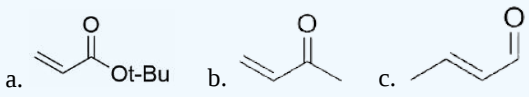
Example of an acylation of an enamine.

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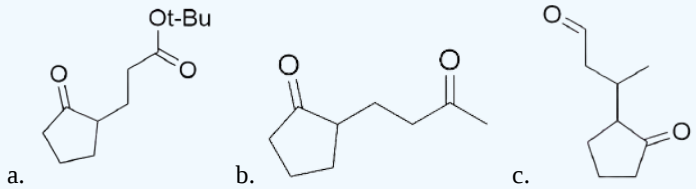
Step 1 Formation of the enamine The mechanism starts with the formation of an enamine.	
Step 2: Nucleophilic attack The enamine adds to the electrophilic carbonyl carbon of the acid halide to form an iminium bond with tetrahedral alkoxide as an intermediate.	
Step 3: Leaving group removal The alkoxide reforms the carbonyl bond and eliminates a halide anion as a leaving group.	
Step 4: Reform the carbonyl by hydrolysis The iminium bond is then hydrolyzed to reform the carbonyl to create a 1,3-dicarbonyl compound as a nucleophilic acyl substitution product.	

Exercise 9.11.1

What products would result after hydrolysis from reaction of the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

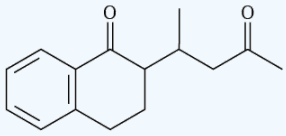


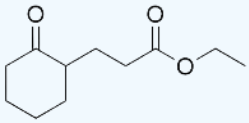
Answer

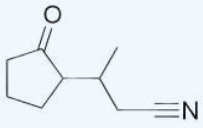


Exercise 9.11.2

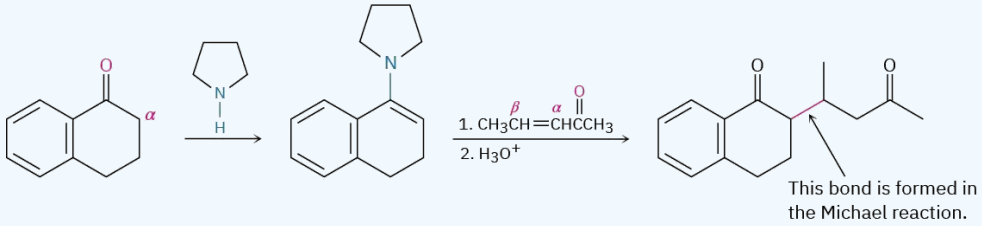
What starting materials are necessary to make the following molecules during a Stork enamine reaction? (in addition to pyrrolidine)

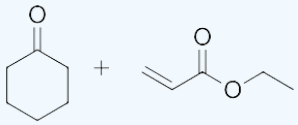
a. 

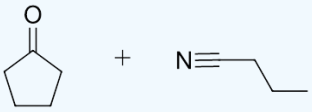
b. 

c. 

Answers

a. 

b. 

c. 

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9.12: The Robinson Annulation Reaction

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the Robinson annulation reaction.
2. identify the cyclic product formed when a 1,5-diketone is treated with base.
3. identify the carbonyl compounds and any other reagents needed to synthesize a given cyclic compound by a series of reactions, one of which is a Robinson annulation.

Key Terms

- Robinson annulation reaction

Study Notes

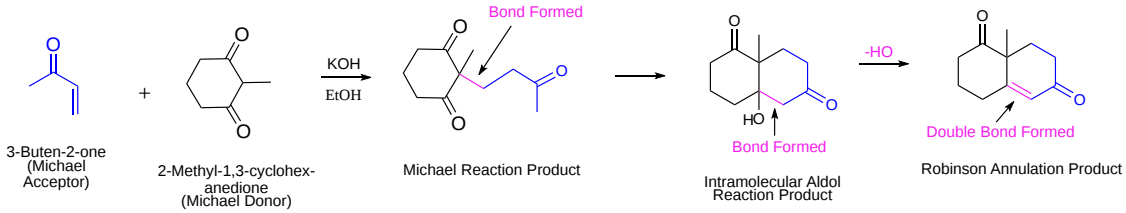
The building of an alicyclic compound from acyclic starting materials can present an interesting challenge to the synthetic organic chemist. One route by which such a synthesis can be achieved is through the use of the Robinson annulation reaction. This reaction, which may at first look very complex, can be readily understood once you realize that it simply involves a Michael reaction followed by an intramolecular aldol condensation. Both of these steps involve attack by enolate anions.

As in some of the other syntheses that you have studied, when you are simply given the structure of a compound and asked how it could have been prepared, it can be difficult to recognize which reactions might have been used. In this instance, keep in mind that you have studied relatively few reactions which have resulted in the formation of an alicyclic compound. Thus, when asked how such a compound might be prepared, you should keep the possibility of using a Robinson annulation reaction in mind.

The Robinson Annulation

Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction creates two new carbon-carbon bonds and also creates a ring. Ring-forming reactions are called annulations after the Latin work for ring annulus. The reaction is named after English chemist Sir Robert Robinson (1886-1975) who developed it. He received the Nobel prize in chemistry in 1947. Remember that during annulations five and six membered rings are preferred.

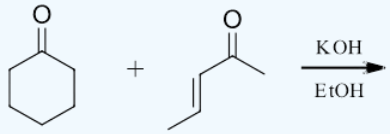
The nucleophilic enolate donor is typically an enolate ion or enamine of a cyclic ketone, β-keto ester or β-diketone. The electrophilic acceptor is usually an α, β-unsaturated ketone. In the example below, 2-methyl-1,3-cyclohexanedione is deprotonated to form an enolate which affects a Michael reaction addition on 3-buten-2-one forming a C-C bond. The product contains a 1,5-diketone fragment which can undergo an intramolecular aldol condensation. This occurs through creation of a new enolate at the methyl ketone which undergoes an intramolecular aldol reaction. A new C-C bond is formed to one of the ring carbonyls, creating a new six-membered ring. In the last step, the resulting alcohol is eliminated to form a α, β-unsaturated ketone as the final Robinson annulation product. Because the Robinson Annulation involves an aldol reaction, a full equivalent of base is required.



Example

? Example

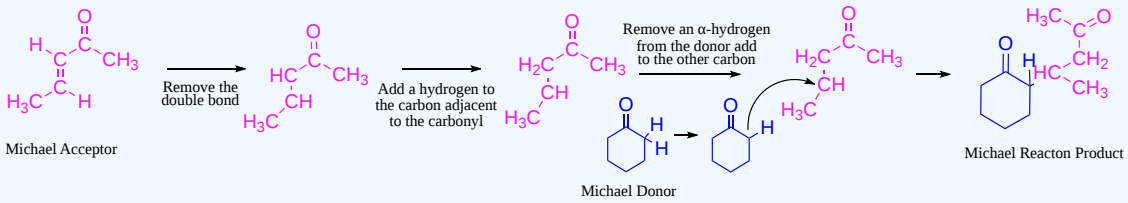
Draw the product of the following Robinson Annulation.



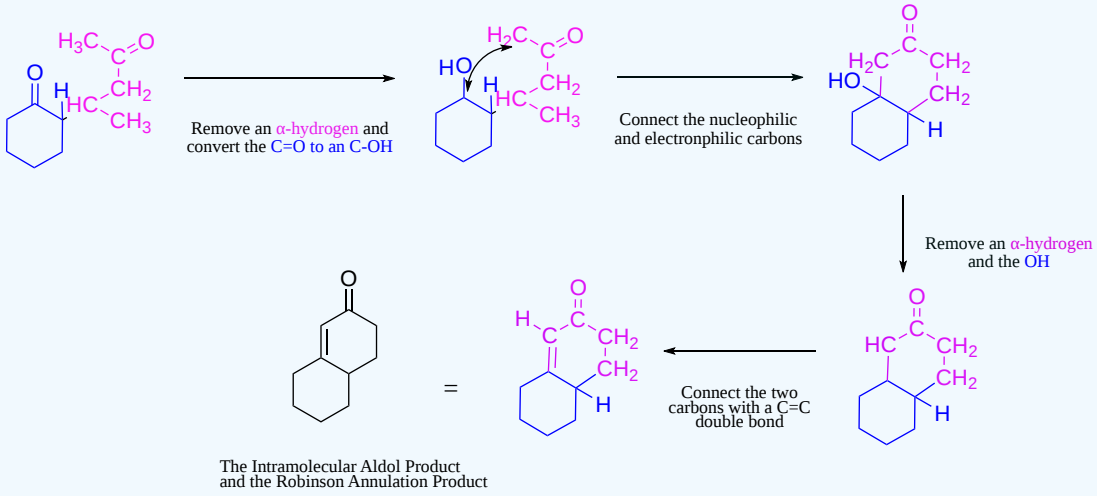
Analysis

When considering the product of a Robinson annulation it is usually best to consider each reaction individually. Use the steps discussed in Section 23.10 to convert the starting materials into the product of a Michael reaction, then into the product of an intramolecular aldol condensation. If the starting materials are drawn in a skeletal structure it may be helpful to convert to a condensed formula to better keep track of carbons and hydrogens.

Formation of the Michael reaction product

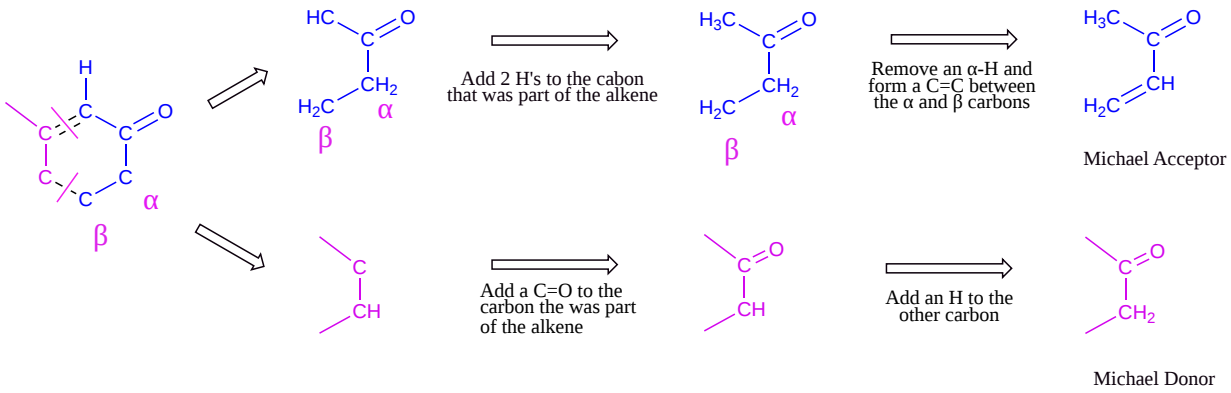


Formation of the intramolecular Aldol condensation product



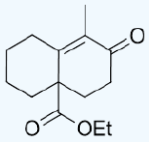
Planning a Synthesis Using a Robinson Annulation

The presence of a cyclic, six-membered α, β-unsaturated ketone in a target molecule suggest that a Robinson Annulation may be utilized in its synthesis. The key bond cleavages are the C=C bond of the α, β-unsaturated ketone and the C-C bond between carbons in the a and g on the opposite alkyl chain of the ketone.

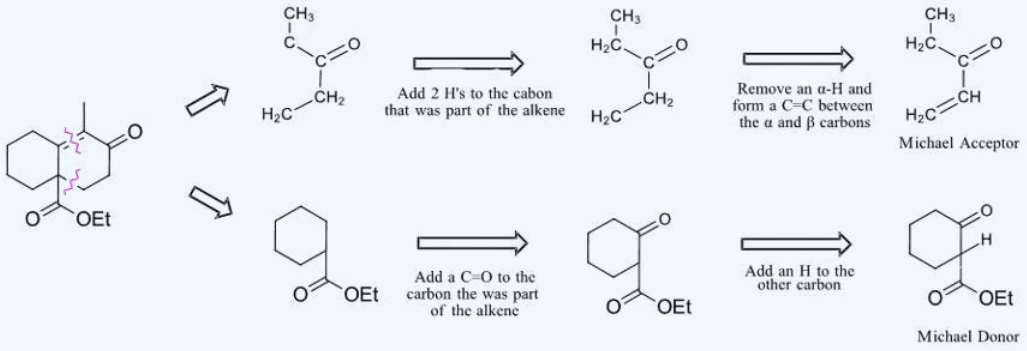


? Example

What would be the starting materials used if the following molecule was made using a Robinson annulation?

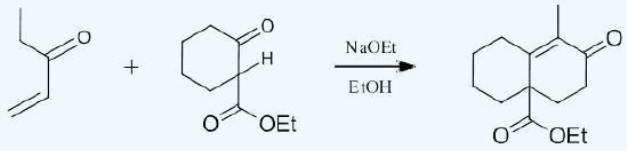


Analysis



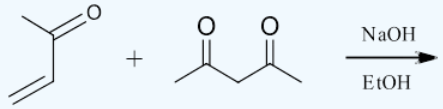
Solution

It is necessary to use sodium ethoxide as the reaction base due to the presence of an ester.

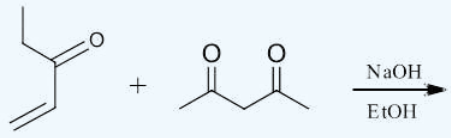


? Exercise 9.12.1

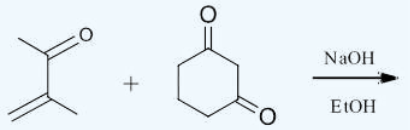
Provide products of the following Robinson annulations.

a. 

b.

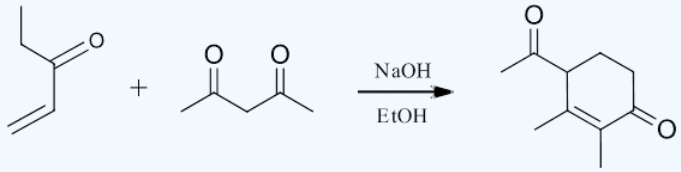


c.

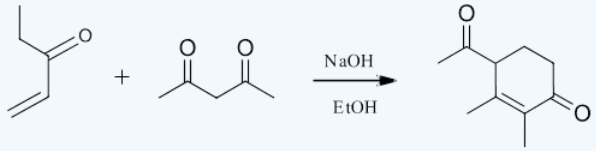


Answer

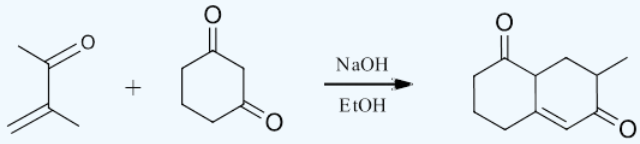
a.



b.

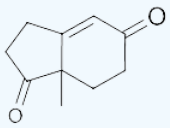


c.

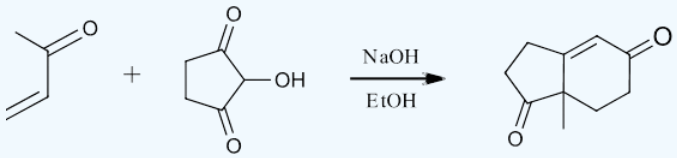


Exercise 9.12.2

What would be the starting materials required to make the following molecule using a Robinson annulation?



Answer



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9.13: Some Biological Carbonyl Condensation Reactions

Objectives

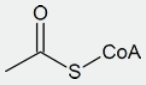
After completing this section, you should be able to

1. identify acetyl coenzyme A as an important biomolecule which undergoes carbonyl condensation reactions.
2. identify aldoases as enzymes that catalyze aldol reactions in biological systems.
3. identify the steps in which a carbonyl condensation reaction has occurred, given a general outline of a specific biosynthesis.

Study Notes

Carbonyl condensation reactions occur in biological systems; for example, in the biosynthesis of citric acid.

You first met acetyl coenzyme A in Section 21.8. Again, we stress that it is not essential that you know the detailed structure of this compound (or other large biochemical stuctures discussed), but you should know that it may be represented as



and that it has the ability to behave just as any other acetyl-containing compound.

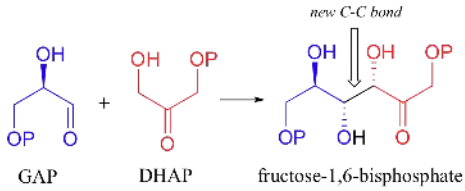
Aldol Reactions in Nature

So far, we have examined the non-enzymatic reaction of an aldehyde or ketone with itself (a so-called 'self-condensation' reaction, where 'condensation' means the formation of one larger molecule from two smaller ones). However, aldol reactions occur in several biological pathways, most commonly in the metabolism of carbohydrates (sugars). The enzymes that catalyze aldol reactions are called, not surprisingly, '**aldolases**'. They occur in all organisms, but note that **Class I aldoases** are usually found in animals and higher plants, while **Class II aldoases** normally appear in bacteria and fungi.

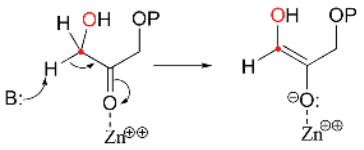
Typical aldolase reactions - three variations on a theme

The first step in an aldolase reaction is the deprotonation of an alpha-carbon to generate a nucleophilic carbanion. Nature has evolved several distinct strategies to stabilize the intermediate that results. Some aldolases use a metal ion to stabilize the negative charge on an enolate intermediate, while others catalyze reactions that proceed through neutral Schiff base or enol intermediates.

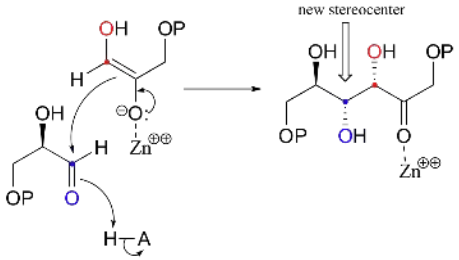
Let's examine first a reaction catalyzed by a so-called **'Class II' aldolase**, in which a metal cation - generally Zn^{2+} - bound in the active site serves to stabilize the negative charge on an enolate intermediate. Fructose 1,6-bisphosphate aldolase is an enzyme that participates in both the glycolytic (sugar burning) and gluconeogenesis (sugar building) biochemical pathways. For now, we will concentrate on its role in the gluconeogenesis pathway, but we will see it again later in its glycolytic role. The reaction catalyzed by fructose 1,6-bisphosphate aldolase is a condensation between two 3-carbon sugars, glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP), forming a six-carbon product (which leads, after three more enzymatic steps, to glucose).



In the first step of the condensation, an alpha-carbon on DHAP is deprotonated, leading to an enolate intermediate. The strategy used to stabilize this key intermediate is to coordinate the negatively-charged enolate oxygen to an enzyme-bound zinc cation.

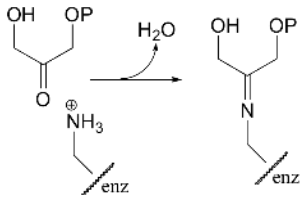


Next, the deprotonated a-carbon attacks the carbonyl carbon of GAP in a nucleophilic addition reaction, and protonation of the resulting alcohol leads directly to the fructose 1,6-bisphosphate product.

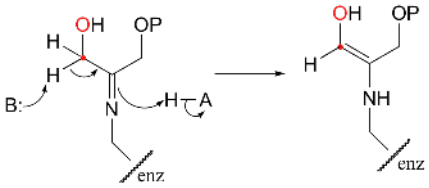


As with many other nucleophilic carbonyl addition reactions, a new stereocenter is created in this reaction, as a planar, achiral carbonyl group is converted to a tetrahedral, chiral alcohol. The enzyme-catalyzed reaction, not surprisingly, is completely stereospecific: the DHAP substrate is positioned in the active site so as to attack the *re* (front)face of the GAP carbonyl group, leading to the *R* configuration at the new stereocenter.

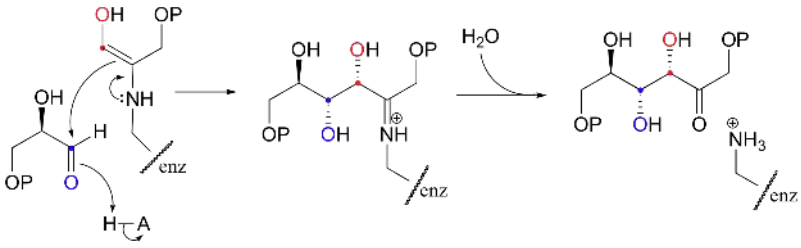
Interestingly, it appears that in bacteria, the fructose bisphosphate aldolase enzyme evolved separately from the corresponding enzyme in plants and animals. In plants and animals, the same aldol condensation reaction is carried out by a significantly different mechanism, in which the key intermediate is not a zinc-stabilized enolate but an enamine. The nucleophilic substrate (DHAP) is first linked to the enzyme through the formation of an imine (also known as a Schiff base) with a lysine residue in the active site.



The alpha-proton is then abstracted by an active site base to form an enamine.

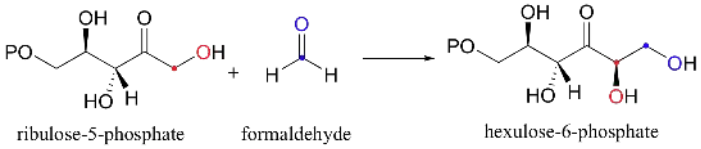


In the next step, the alpha-carbon attacks the carbonyl carbon of GAP, and the new carbon-carbon bond is formed. In order to release the product from the enzyme active site and free the enzyme to catalyze another reaction, the imine is hydrolyzed back to a ketone group.



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There are many more examples of **'Class I' aldolase** reactions in which the key intermediate is a lysine-linked imine. Many bacteria are able to incorporate formaldehyde, a toxic compound, into carbohydrate metabolism by condensing it with ribulose monophosphate. The reaction proceeds through imine and enamine intermediates.

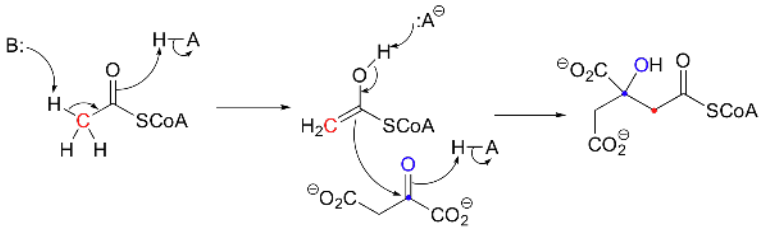


Example 23.13.1

a. Propose a complete mechanism for the condensation reaction shown above.
b. Propose a complete mechanism for the conversion of hexulose-6-phosphate (formed from the condensation of ribulose-5-phosphate and formaldehyde) into fructose-6-phosphate.

Solution

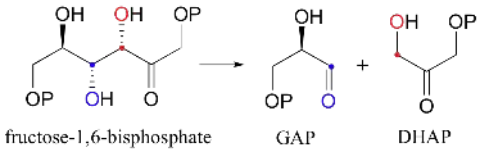
Along with aldehydes and ketones, esters and thioesters can act as the nucleophilic partner in aldol condensations. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA.



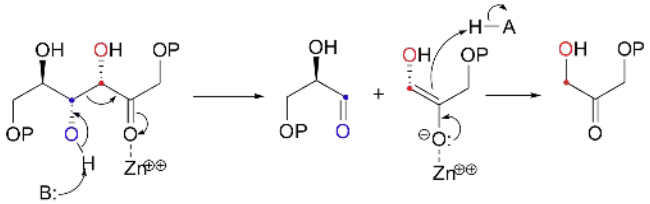
Notice that in this aldol reaction, the nucleophilic intermediate is stabilized by protonation, rather than by formation of an imine (as in the Class I aldolases) or by a metal ion (as in the Class II aldolases).

Going backwards: the retroaldol reaction

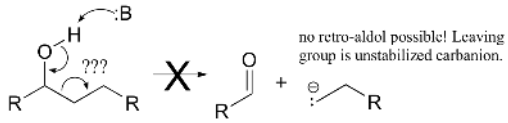
Although aldol reactions play a very important role in the formation of new carbon-carbon bonds in metabolic pathways, it is important to emphasize that they are also highly reversible: in most cases, the energy level of starting compounds and products are very close. This means that, depending on metabolic conditions, aldolases can also catalyze **retro-aldol** reactions (the reverse of aldol condensations, in which carbon-carbon bonds are *broken*). Recall that fructose 1,6-bisphosphate aldolase (section 13.3B) is active in the direction of sugar breakdown (glycolysis) as well as sugar synthesis (gluconeogenesis). In the glycolytic direction, the enzyme catalyzes - either by zinc cation or by imine/enamine mechanisms, depending on the organism - the retro-aldol cleavage of fructose bisphosphate into DHAP and GAP.



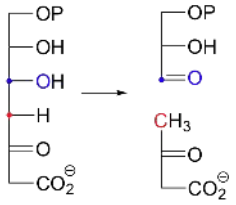
The mechanism is the exact reverse of the condensation reaction. Shown below is the mechanism for a Zn^{2+} - dependent (Type II) retroaldol cleavage. Notice that in the retroaldol reaction, the enolate intermediate is the *leaving group*, rather than the nucleophile.



The key thing to keep in mind when looking for a possible retro-aldol mechanism is that, when the carbon-carbon bond breaks, the electrons must have some place to go, where they will be stabilized by resonance. Generally, this means that there *must* be a carbonyl or imine group on the next carbon. If there is no adjacent carbonyl or imine group, the carbon-carbon bond is not free to break.



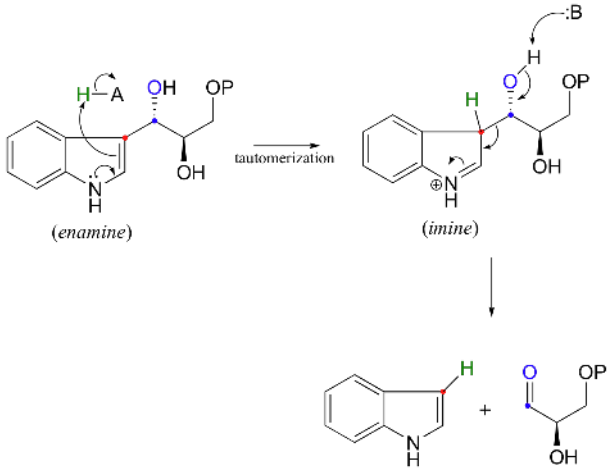
Here are two more examples of retro-aldol reactions. Bacterial carbohydrate metabolism involves this reversible, class I retro-aldol cleavage: (*Proc. Natl. Acad. Sci* **2001**, *98*, 3679).



Example 23.13.2

Draw the structure of the enamine intermediate in the retroaldol reaction shown above.

Another interesting example is the retro-aldol cleavage of indole-3-glycerol phosphate, a step in the biosynthesis of tryptophan.



Look carefully at this reaction - how is the leaving group stabilized? There is an imine group involved, but no participation by an enzymatic lysine. The imine is 'built into' the starting compound, available from the initial tautomerization of the cyclic enamine group in indole-3-glycerol phosphate.

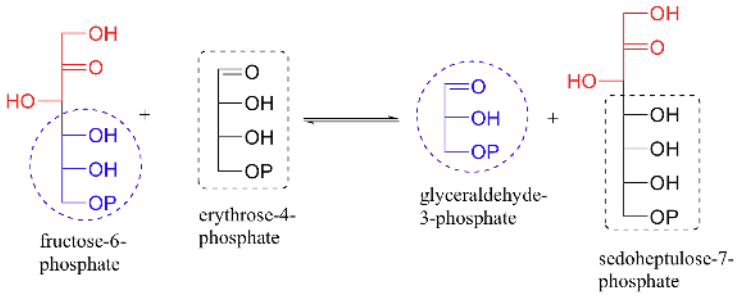
Example 23.13.3

Draw the reverse (aldol condensation) direction of the reaction above.

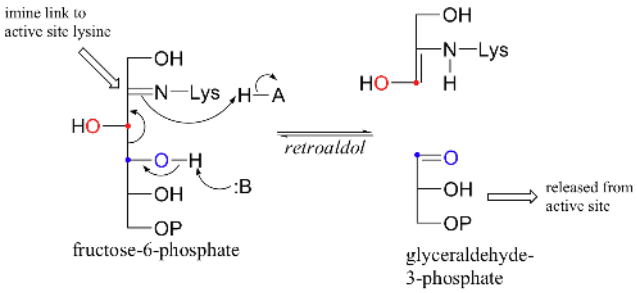
Solution

Going both ways: transaldolase

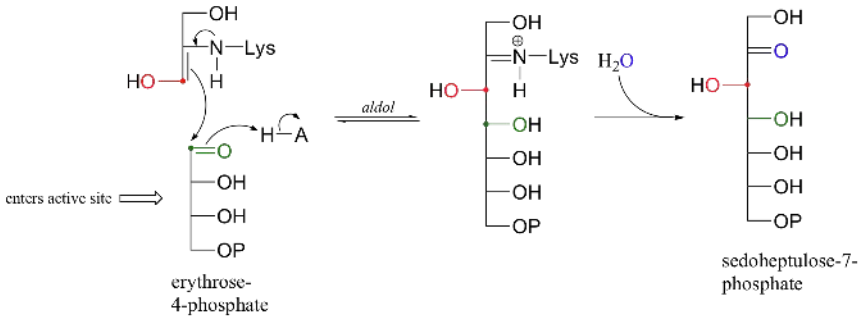
An enzyme called transaldolase, which is part of the 'pentose phosphate pathway' of carbohydrate metabolism, catalyzes an interesting combination of class I aldol and retro-aldol reactions. The overall reaction, which can proceed in either direction depending on metabolic requirements, converts 3- and 7-carbon sugars into 6- and 4-carbon sugars. Essentially, a 3-carbon unit breaks off from a ketone sugar (ketose) and then is condensed directly with an aldehyde sugar (aldose).



Let's follow the progress of the reaction in the left-to-right direction as depicted above. Because this is a class I aldolase, the first step is the formation of an imine linkage between the ketone carbon of fructose-6-phosphate (F6P) and a lysine group from the enzyme. The enzyme-substrate adduct then undergoes a retro-aldol step to free glyceralde-3-phosphate (GAP), which leaves the active site.



The second substrate, erythrose 4-phosphate (E4P), enters the active site, and an aldol condensation occurs between E4P and the 3-carbon fragment remaining from the cleavage of fructose-6-phosphate.



The final step is hydrolysis of the imine and subsequent dissociation of sedoheptulose 7-phosphate from the active site.

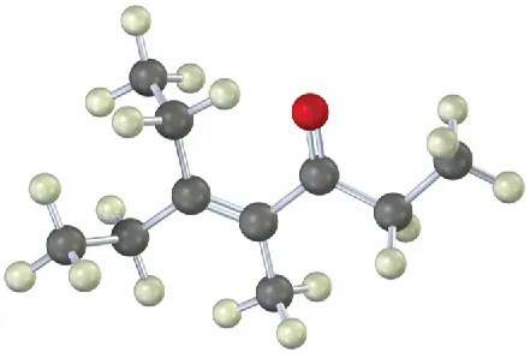
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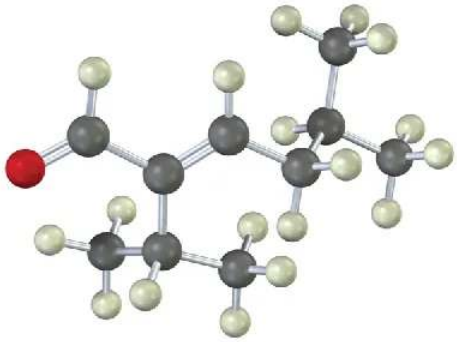
9.14: Additional Problems

Visualizing Chemistry

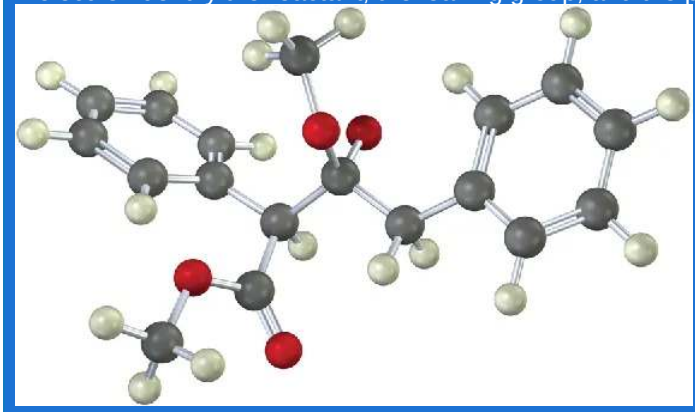
What ketones or aldehydes might the following enones have been prepared from by aldol reaction? (a)



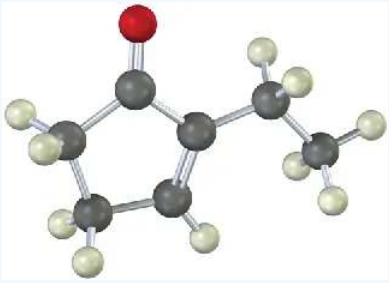
(b)



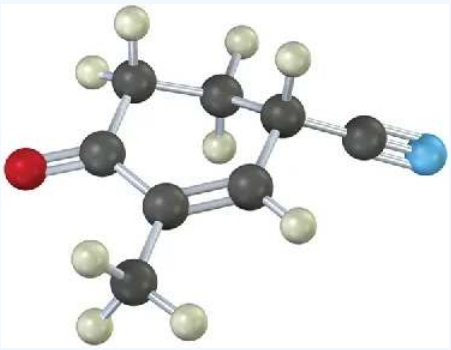
The following structure represents an intermediate formed by addition of an ester enolate ion to a second ester molecule. Identify the reactant, the leaving group, and the product.



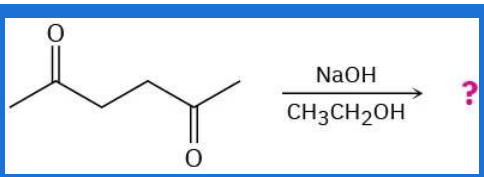
The following molecule was formed by an intramolecular aldol reaction. What dicarbonyl precursor was used for its preparation?

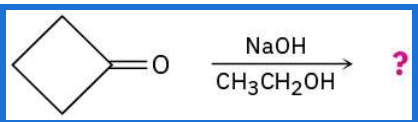


The following molecule was formed by a Robinson annulation reaction. What reactants were used?



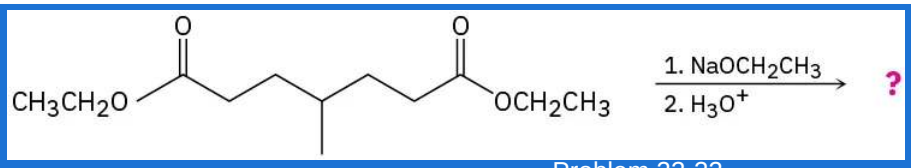
Mechanism Problems



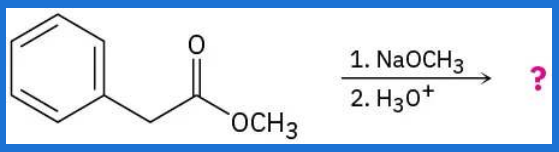


Problem 23-28 (b)

Based on your answers to Problem 23-27, predict the dehydration product for both reactions and write the mechanism.

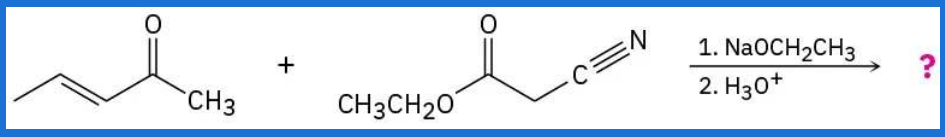


(b)

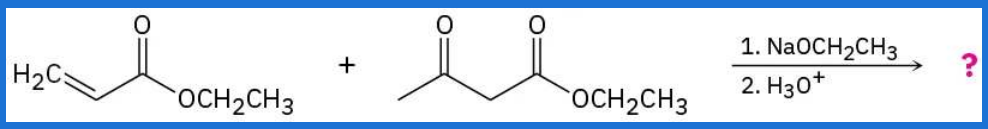


Problem 23-32

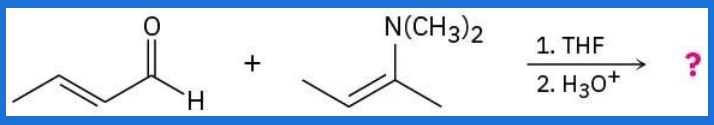
Problem 23-30 Predict the product(s) and provide the mechanisms for the following reactions. (a)



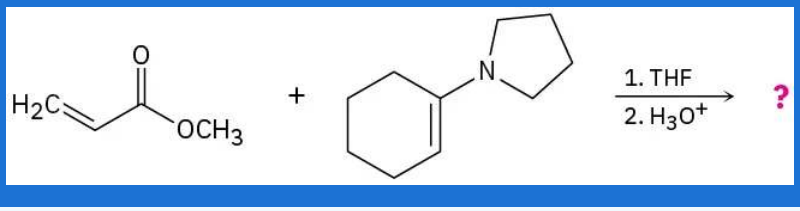
(b)



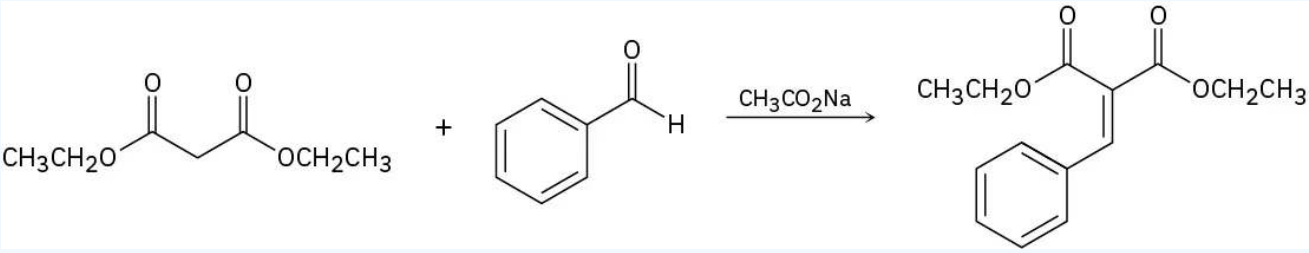
Problem 23-31 Predict the product(s) and provide the mechanisms for the following reactions. (a)



(b)

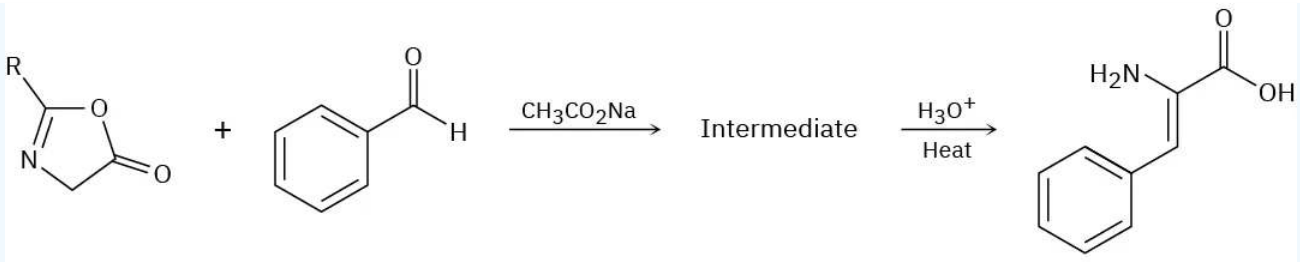


Knoevenagel condensation is a reaction involving an active methylene compound (a CH_2 flanked by two electron-withdrawing groups) and an aldehyde and ketone. Propose a mechanism for the reaction below.



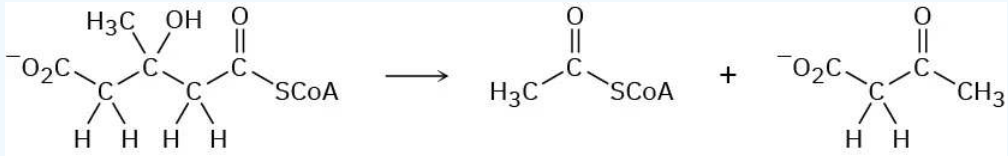
Azlactones are important starting materials used in the synthesis of dehydro α-aminoacids. They react with aldehydes to form an intermediate that is hydrolyzed under acidic conditions to give the final amino acid product. Provide the structure of the intermediate and propose a mechanism for its formation.

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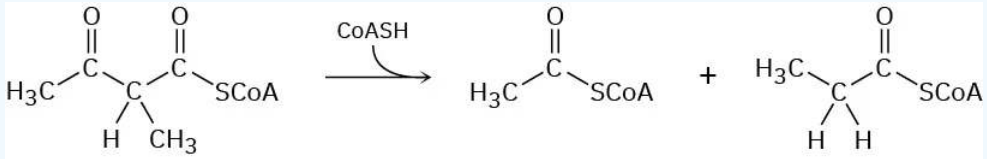
Azlactone **Deydro-α-amino acid**

Leucine, one of the twenty amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



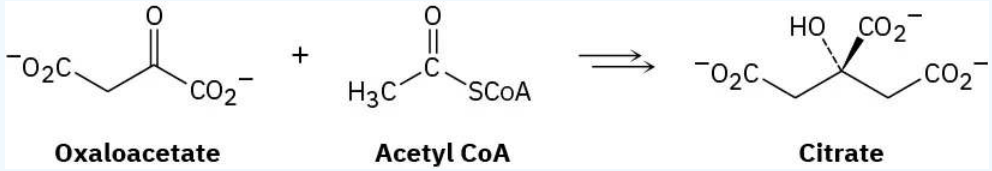
3-Hydroxy-3-methyl-glutaryl CoA **Acetyl CoA** **Acetoacetate**

Isoleucine, another of the twenty amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



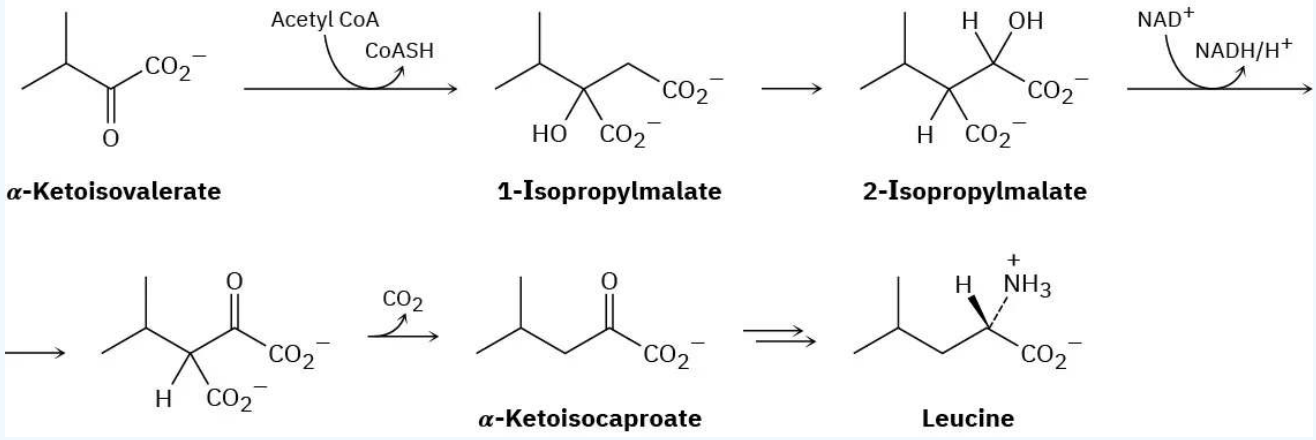
2-Methyl-3-keto-butyryl CoA **Acetyl CoA** **Propionyl CoA (propanoyl CoA)**

The first step in the citric acid cycle of food metabolism is reaction of oxaloacetate with acetyl CoA to give citrate. Propose a mechanism, using acid or base catalysis as needed.

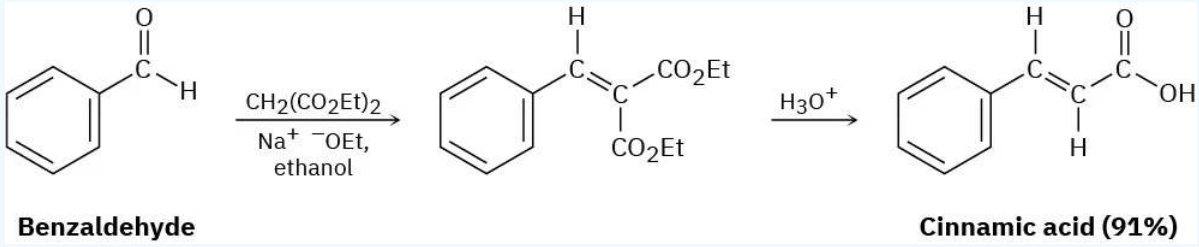


Oxaloacetate **Acetyl CoA** **Citrate**

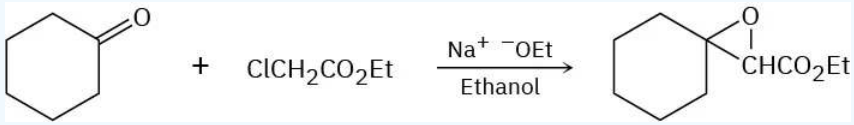
The amino acid leucine is biosynthesized from α-ketoisovalerate by the following sequence of steps. Show the mechanism of each.



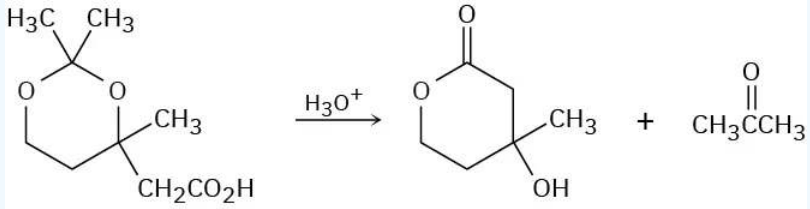
The Knoevenagel reaction was introduced in Problem 23-2. Show the mechanism for the Knoevenagel reaction of diethyl malonate with benzaldehyde.



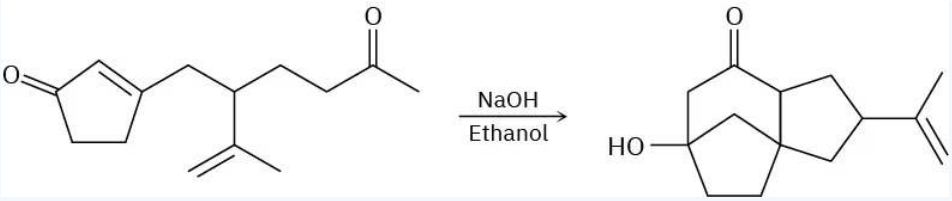
The Darzens reaction involves a two-step, base-catalyzed condensation of ethyl chloroacetate with a ketone to yield an epoxy ester. The first step is a carbonyl condensation reaction, and the second step is an S_N2 reaction. Write both steps, and show their mechanisms.



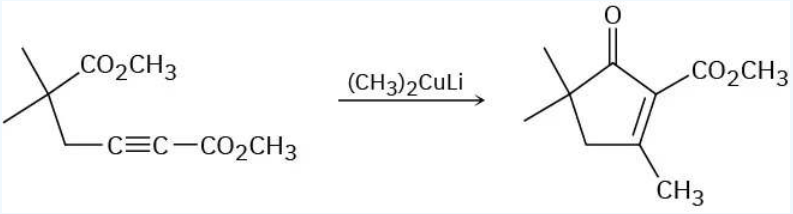
The following reaction involves a hydrolysis followed by an intramolecular nucleophilic acyl substitution reaction. Write both steps, and show their mechanisms.



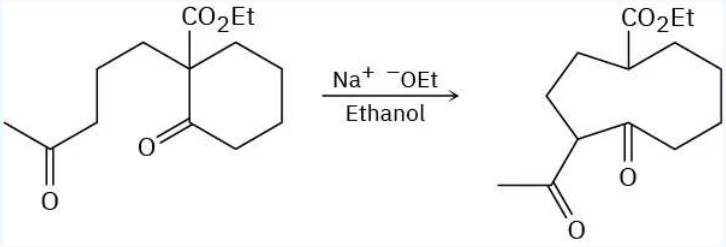
The following reaction involves an intramolecular Michael reaction followed by an intramolecular aldol reaction. Write both steps, and show their mechanisms.



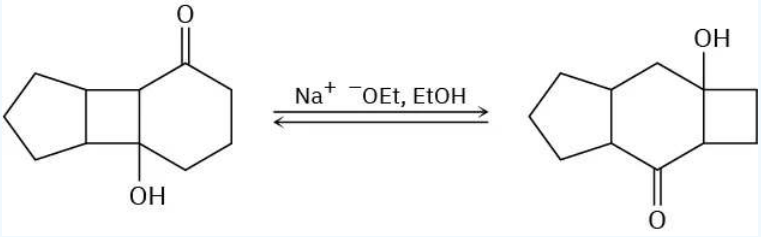
The following reaction involves a conjugate addition reaction followed by an intramolecular Claisen condensation. Write both steps, and show their mechanisms.



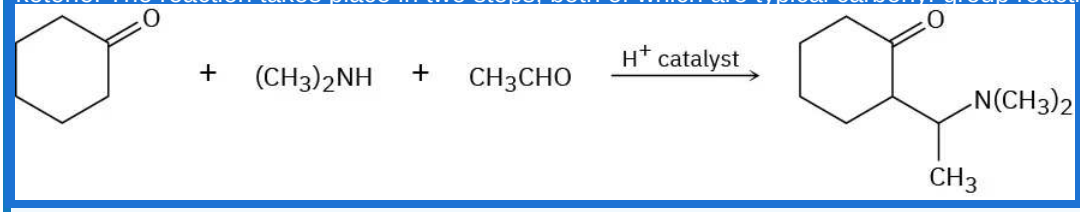
The following reaction involves an intramolecular aldol reaction followed by a *retro* aldol-like reaction. Write both steps, and show their mechanisms.



Propose a mechanism for the following base-catalyzed isomerization:



The Mannich reaction of a ketone, an amine, and an aldehyde is one of the few three-component reactions in organic chemistry. Cyclohexanone, for example, reacts with dimethylamine and acetaldehyde to yield an amino ketone. The reaction takes place in two steps, both of which are typical carbonyl-group reactions.

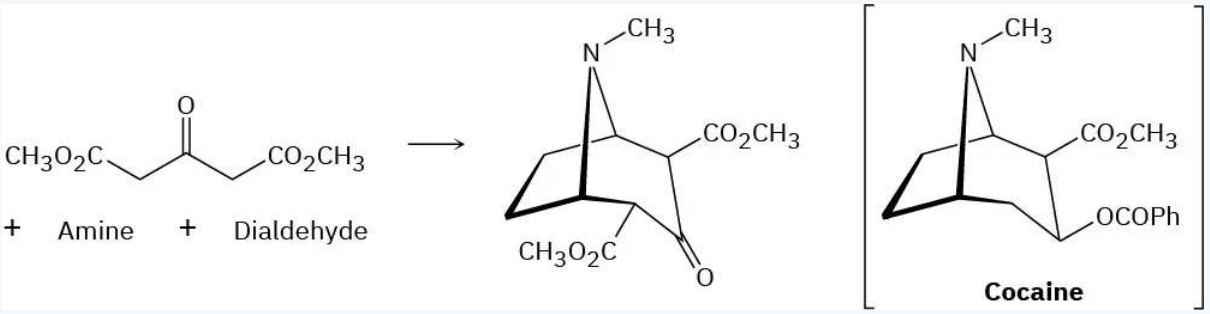


(a) The first step is reaction between the aldehyde and the amine to yield an intermediate iminium ion ($R_2C{=}NR_2^+$) plus water. Propose a mechanism, and show the structure of the intermediate iminium ion.

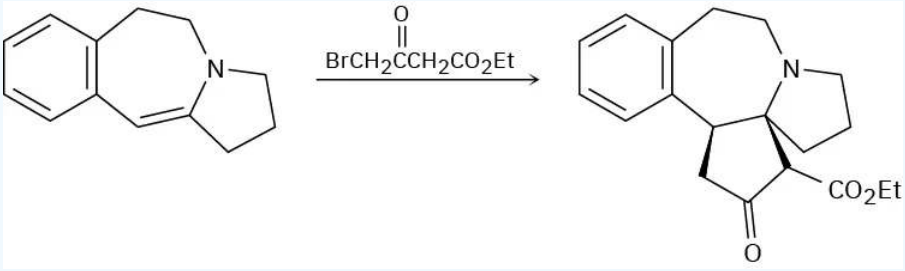
(b) The second step is reaction between the iminium ion intermediate and the ketone to yield the final product. Propose a mechanism.

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Cocaine has been prepared by a sequence beginning with a Mannich reaction (Problem 23-45) between dimethyl acetonedicarboxylate, an amine, and a dialdehyde. Show the structures of the amine and dialdehyde.



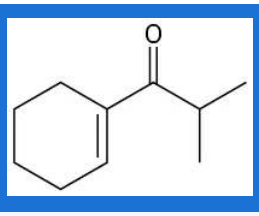
Propose a mechanism to account for the following reaction of an enamine with an alkyl halide:



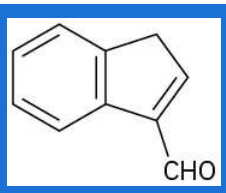
Aldol Reactions

Which of the following compounds would you expect to undergo aldol self-condensation? Show the product of each successful reaction.

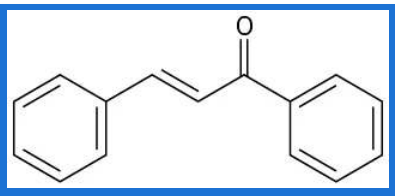
(a) Trimethylacetaldehyde **(b)** Cyclobutanone **(c)** Benzophenone (diphenyl ketone)
(d) 3-Pentanone **(e)** Decanal **(f)** 3-Phenyl-2-propenal



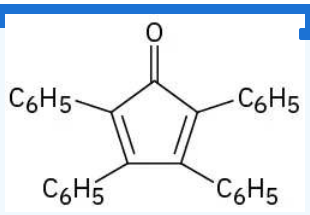
(c)



(d)



(b)



What product would you expect to obtain from aldol cyclization of hexanedial, OHCCH$_2$CH$_2$CH$_2$CH$_2$CHO ?

Intramolecular aldol cyclization of 2,5-heptanedione with aqueous NaOH yields a mixture of two enone products in the approximate ratio 9 : 1. Write their structures, and show how each is formed.

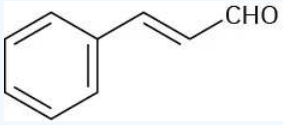
The major product formed by intramolecular aldol cyclization of 2,5-heptanedione (Problem 23-51) has two singlet absorptions in the ^{1}H NMR spectrum, at 1.65 δ and 1.90 δ, and has no absorptions in the range 3 to 10 δ. What is its structure?

Treatment of the minor product formed in the intramolecular aldol cyclization of 2,5-heptanedione (Problems 23-51 and 23-52) with aqueous NaOH converts it into the major product. Propose a mechanism to account for this base-catalyzed isomerization.

How can you account for the fact that 2,2,6-trimethylcyclohexanone yields no detectable aldol product even though it has an acidic α hydrogen?

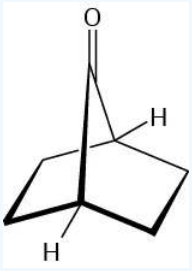
The aldol reaction is catalyzed by acid as well as base. What is the reactive nucleophile in the acid-catalyzed aldol reaction? Propose a mechanism.

Cinnamaldehyde, the aromatic constituent of cinnamon oil, can be synthesized by a mixed aldol condensation. Show the starting materials you would use, and write the reaction.



Cinnamaldehyde

The following bicyclic ketone does not undergo aldol self-condensation even though it has two α hydrogen atoms. Explain.



Claisen Condensations

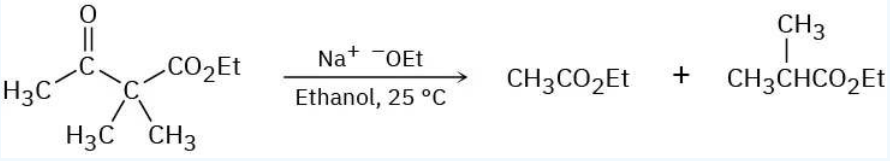
$CH_3CO_2Et + CH_3CH_2CO_2Et$

(b) $C_6H_5CO_2Et + C_6H_5CH_2CO_2Et$ (c) $EtOCO_2Et$ + cyclohexanone (d) $C_6H_5CHO + CH_3CO_2Et$

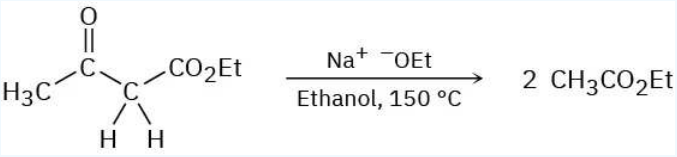
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In the mixed Claisen reaction of cyclopentanone with ethyl formate, a much higher yield of the desired product is obtained by first mixing the two carbonyl components and then adding base, rather than by first mixing base with cyclopentanone and then adding ethyl formate. Explain.

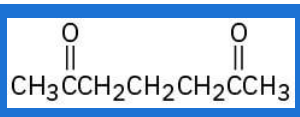
Ethyl dimethylacetoacetate reacts instantly at room temperature when treated with ethoxide ion to yield two products, ethyl acetate and ethyl 2-methylpropanoate. Propose a mechanism for this cleavage reaction.



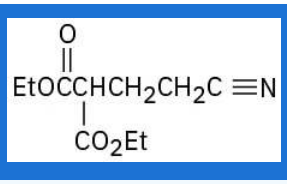
In contrast to the rapid reaction shown in Problem 23-60, ethyl acetoacetate requires a temperature over 150 °C to undergo the same kind of cleavage reaction. How can you explain the difference in reactivity?



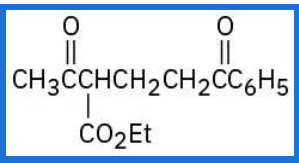
Michael and Enamine Reactions



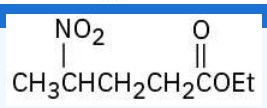
(c)



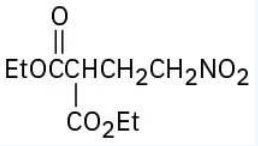
(d)



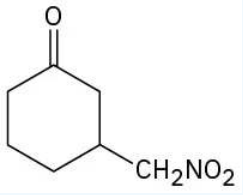
(b)

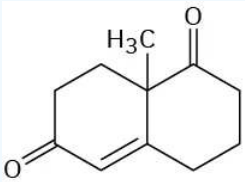


(e)



(f)

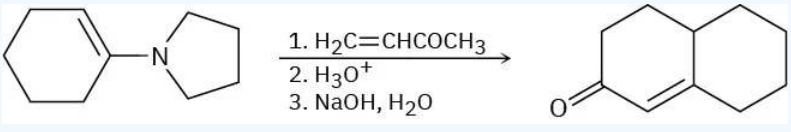




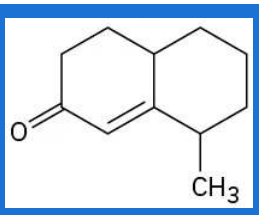
Wieland–Miescher ketone

The so-called Wieland–Miescher ketone is a valuable starting material used in the synthesis of steroid hormones. How might you prepare it from 1,3-cyclohexanedione?

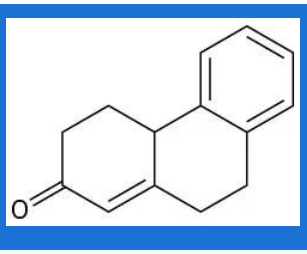
The Stork enamine reaction and the intramolecular aldol reaction can be carried out in sequence to allow the synthesis of cyclohexenones. For example, reaction of the pyrrolidine enamine of cyclohexanone with 3-buten-2-one, followed by enamine hydrolysis and base treatment, yields the product indicated. Write each step, and show the mechanism of each.



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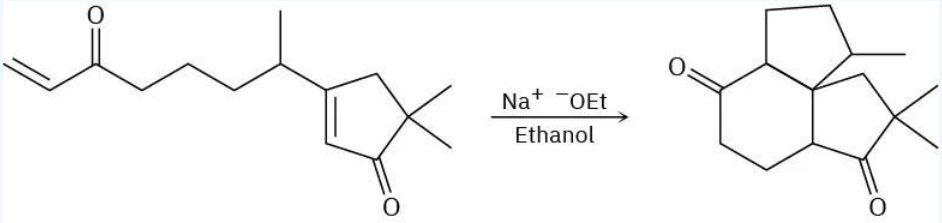
(c)



(b)

Problem 23-66

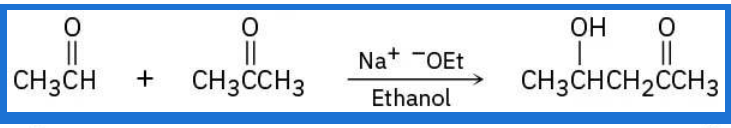
The following reaction involves two successive intramolecular Michael reactions. Write both steps, and show their mechanisms.



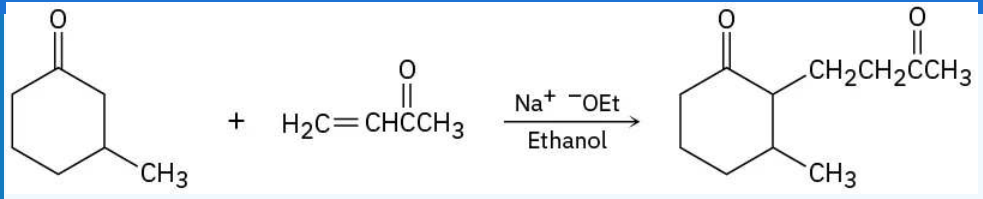
General Problems

Ethyl butanoate

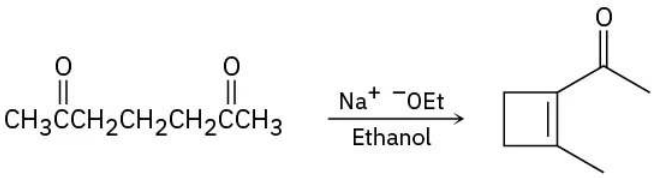
(b) Cycloheptanone (c) 3,7-Nonanedione (d) 3-Phenylpropanal



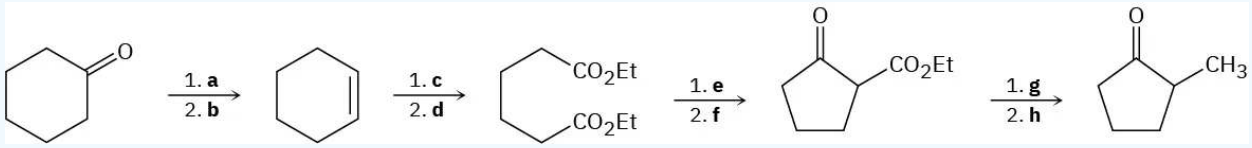
(b)



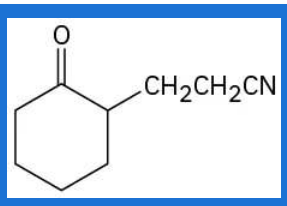
(c)



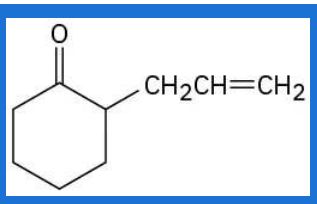
Fill in the missing reagents **a–h** in the following scheme:



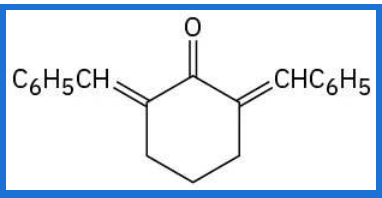
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(c)

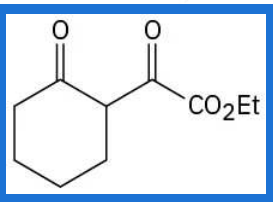


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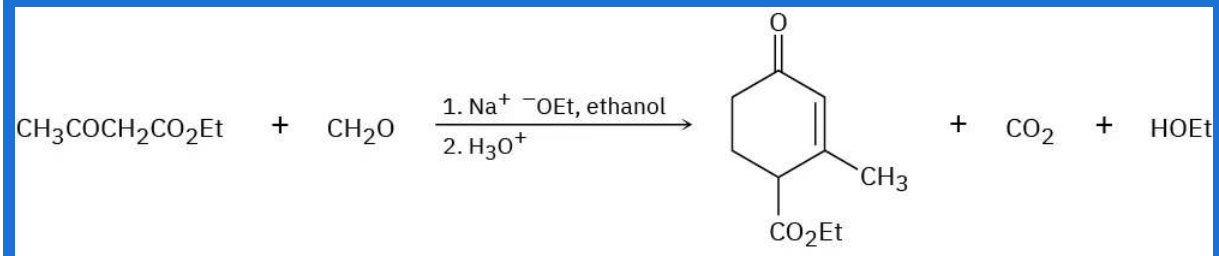


(b)

Problem 23-71



The compound known as Hagemann's ester is prepared by treatment of a mixture of formaldehyde and ethyl acetoacetate with base, followed by acid-catalyzed decarboxylation.



Hagemann's ester

(a)

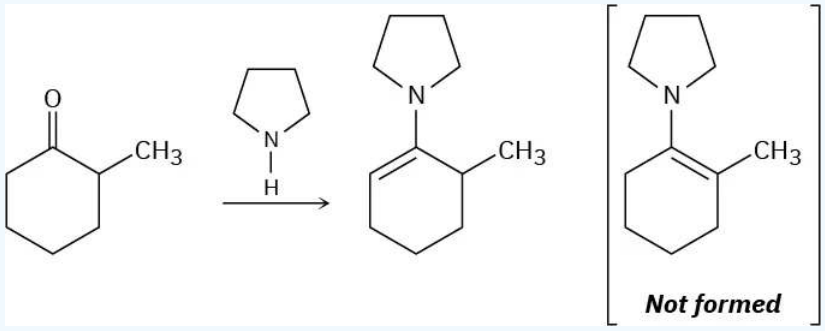
The first step is an aldol-like condensation between ethyl acetoacetate and formaldehyde to yield an α,β-unsaturated product. Write the reaction, and show the structure of the product.

(b)

The second step is a Michael reaction between ethyl acetoacetate and the unsaturated product of the first step. Show the structure of the product.

The third and fourth steps in the synthesis of Hagemann's ester from ethyl acetoacetate and formaldehyde (Problem 23-71) are an intramolecular aldol cyclization to yield a substituted cyclohexenone, and a decarboxylation reaction. Write both reactions, and show the products of each step.

When 2-methylcyclohexanone is converted into an enamine, only one product is formed despite the fact that the starting ketone is unsymmetrical. Build molecular models of the two possible products and explain the fact that the sole product is the one with the double bond opposite the methyl-substituted carbon.



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9.S: Carbonyl Condensation Reactions (Summary)

Concepts & Vocabulary

- Design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- Solve road-map problems that require a knowledge of carbonyl condensation reactions.
- Define, and use in context, any of the key terms introduced.

23.1 Carbonyl Condensations - The Aldol Reaction

- A carbon-carbon bond forming reaction at the alpha carbon through an enolate nucleophile.
- The Aldol Reaction proceeds by first making an enolate nucelophile on an aldehyde (or ketone).
- The enolate nucleophile then dimerizes by attacking the carbonyl of the same aldehyde (or ketone).
- The final product is a beta-hydroxy aldehyde (or ketone).

23.2 Carbonyl Condensations versus Alpha Substitutions

- Carbonyl condensation reactions are a type of alpha substitution reaction.
- Both involve an enolate nucleophile and end with an alpha substitution product.
- In carbonyl condensations, the electrophile is another carbonyl compound.
- Carbonyl condensations are reversible and use a catalytic amount of base.
- The electrophile is already present in the reaction as the enolate is formed in carbonyl condensations.
- Alpha substitution reactions are more directional by design, since a full equivalent of base is used to generate the enolate.
- The electrophile is introduced after the enolate is generated.

23.3 Dehydration of Aldol Products - Synthesis of Enones

- The aldol reaction can undergo a dehydration (loss of water) to yield an α,β-unsaturated aldehyde or ketone.
- The additional stability provided by the conjugated carbonyl system makes some of the products thermodynamically driven.
- The of small products, such as water in this case, are termed condensations, so this reaction is aldol condesation.
- Heat promotes the condensation reactions.
- Under basic conditions, the β-elimination occurs through an E1cb mechanism.
- Under acidic conditions, the β-elimination occurs through an E1 or E2 mechanism.

23.4 Using Aldol Reactions in Synthesis

- If the target contains a β-hydroxy carbonyl compound or an α,β-unsaturated carbonyl compound, then synthetically think aldol reaction or condensation.
- To reverse the aldol condensation, break the enone at the double bond.
- To reverse the aldol reaction, break the C-C bond between the alpha carbon and the carbon attached to the hydroxy group.

23.5 Mixed Aldol Reactions

- Aldol condensations between different reactants are called mixed or crossed Claisen reactions.
- Multiple products are possible, so the success of the mixed aldol reactions depends on two things:
  - The electrophile (or acceptor) is an aldehyde.
  - The aldehyde acceptor has no alpha protons.
- Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols.
- The aldol condensation of ketones with aryl aldehydes to form α,β-unsaturated derivatives is called the Claisen-Schmidt reaction.

23.6 Intramolecular Aldol Reactions

- Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction.

- In these intramolecular reactions, two sets of α-hydrogens need to be considered and most ring forming reaction five and six membered rings are preferred.

23.7 The Claisen Condensation Reaction

- Esters can contain α hydrogens, so can undergo a condensation reaction similar to the aldol reaction called a Claisen Condensation.
- One ester reacts as a nucleophile while the other reacts as an electrophile.
- A new C-C bond is formed in the reaction to form a β-keto ester product.
- An alkoxide that matches the ester group is used to help prevent side reactions in the Claisen Condensation.
- There is a thermodynamic driving step forming an enolate, which is followed by a protonation to obtain the neutral product.

23.8 Mixed Claisen Condensation Reactions

- Claisen condensations between different ester reactants are called Crossed Claisen reactions.
- Crossed Claisen reactions in which both reactants can serve as donors and acceptors generally give complex mixtures.
- Because of this most Crossed Claisen reactions are usually not performed unless one reactant has no alpha hydrogens.

23.9 Intramolecular Claisen Condensation Reactions - The Dieckmann Cyclization

- A diester can undergo an intramolecular reaction called a Dieckmann condensation.

23.10 Conjugate Carbonyl Additions - The Michael Reaction

- In 1,4 additions the nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.
- Enolates undergo 1,4 addition to α, β-unsaturated carbonyl compounds (product of the Aldol condensation) is a process called a Michael addition.
- A new C-C bond is formed between an enolate and the 4-C of the α, β-unsaturated carbonyl compound.
- The product is a 1,5-dicarbonyl species.

23.11 Carbonyl Condensations with Enamines - The Stork Reaction

- Aldehydes and ketones react with 2° amines to reversibly form enamines.
- Enamines act as nucleophiles similar to enolates.
- This process requires a three steps:
  - Formation of the enamine
  - Reaction with an eletrophile to form an iminium salt
  - Hydrolysis of the iminium salt to reform the aldehyde or ketone
- Advantages of using an enamine over an enolate
  - Neutral
  - Easier to prepare
  - Prevent overreaction issue that occurs when using enolates.
- Enamines undergo an S_N2 reaction with alkyl halides to yield the iminium salt.
- Enamines can react with acid halides to form β-dicarbonyls.
- Enamines can also be used as a nucleophile in a Michael reaction.

23.12 The Robinson Annulation Reaction

- Forms a cyclic product from acyclic starting materials by first creating a new C-C bond followed by ring formation.
- The Robinson Annulation reaction starts with a Michael reaction followed by an intramolecular Aldol condensation.
- The formation of 5 or 6 membered rings is preferred.

23.13 Some Biological Carbonyl Condensation Reactions

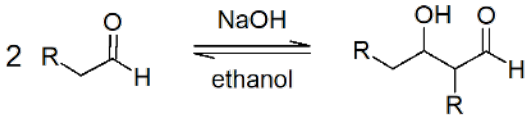
- Aldol reactions occur in several biological pathways.
- Enzymes that catalyze aldol reactions are called, not surprisingly, 'aldolases'.
- The first step in an aldolase reaction is the deprotonation of an alpha-carbon to generate a nucleophilic carbanion.

- Nature has evolved several distinct strategies to stabilize the intermediate that results.
  - Some aldolases use a metal ion to stabilize the negative charge on an enolate intermediate.
  - Others catalyze reactions that proceed through neutral Schiff base or enol intermediates.

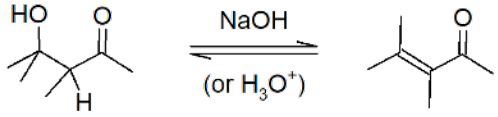
Skills to Master

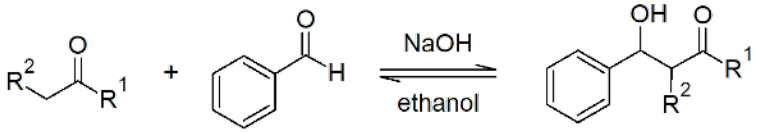
- Skill 23.1 Identify the product of an aldol reaction.
- Skill 23.2 Write the detailed mechanism for the aldol reaction.
- Skill 23.3 Describe the difference between a carbonyl condensation reaction and an alpha-substitution reaction.
- Skill 23.4 Know what an enone is.
- Skill 23.5 Write a detailed mechanism for the aldol condensation under basic conditions.
- Skill 23.6 Write a detailed mechanism for the aldol condensation under acidic conditions.
- Skill 23.7 Determine the products of an aldol condensation reaction.
- Skill 23.8 Provide the reactants for a target aldol condensation product.
- Skill 23.9 Write an equation to illustrate a mixed aldol reaction.
- Skill 23.10 Identify the structural features necessary to ensure that two carbonyl compounds will react together in a mixed aldol reaction to give a single product rather than a mixture of products.
- Skill 23.11 Determine whether a given mixed aldol reaction is likely to produce a single product or a mixture of products.
- Skill 23.12 Identify the carbonyl compounds needed to produce a given enone or β-hydroxy aldehyde or ketone by a mixed aldol reaction.
- Skill 23.13 Write a detailed mechanism for the intramolecular aldol condensation.
- Skill 23.14 Write an equation to illustrate a Claisen condensation reaction.
- Skill 23.15 Write a detailed mechanism for a Claisen condensation reaction or its reverse.
- Skill 23.16 Identify the ester and other reagents needed to form a given β-keto ester by a Claisen condensation reaction.
- Skill 23.17 Write an equation to illustrate a mixed Claisen condensation.
- Skill 23.18 Identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
- Skill 23.19 Identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
- Skill 23.20 Identify the esters that should be used to produce a given β-keto ester by a mixed Claisen condensation.
- Skill 23.21 Write detailed mechanisms for mixed Claisen condensation.
- Skill 23.22 Write a detailed mechanism for an intramolecular Claisen condensation.
- Skill 23.23 Write a detailed mechanism for a given typical Michael reaction.
- Skill 23.24 Identify the product formed in a given Michael reaction.
- Skill 23.25 Identify the reagents necessary to synthesize a given compound by a Michael reaction.
- Skill 23.26 Write a detailed mechanism for each of the three steps of the Stork enamine reaction.
- Skill 23.27 Identify the reagents needed to synthesize a given compound by a Stork enamine reaction.
- Skill 23.28 Write a detailed mechanism for the Robinson Annulation reaction.
- Skill 23.29 Identify the product from an enone and an dicarbonyl under basic conditions.
- Skill 23.30 Identify the steps in which a carbonyl condensation reaction has occurred, given a general outline of a specific biosynthesis.

Summary of Reactions

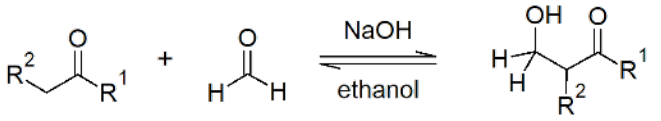


(Aldol)

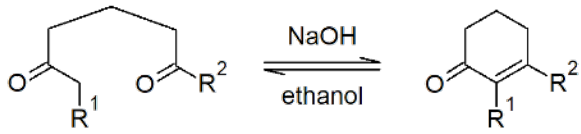




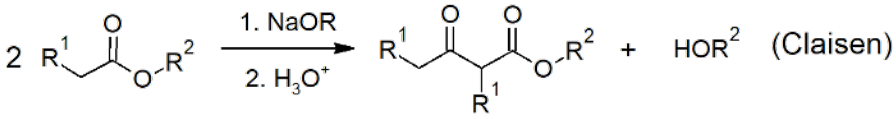
(mixedAldol)



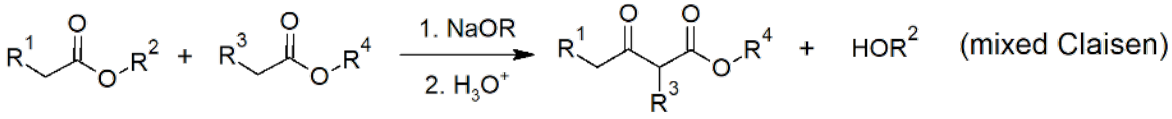
(mixedAldol)



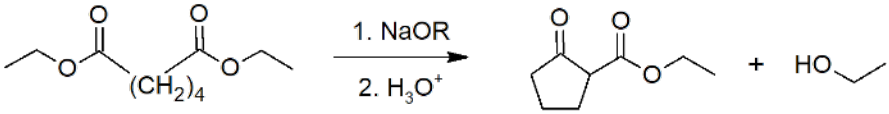
(intramolecular Aldol)



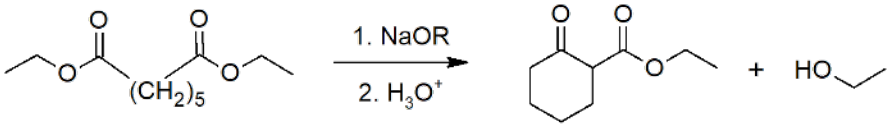
(Claisen)



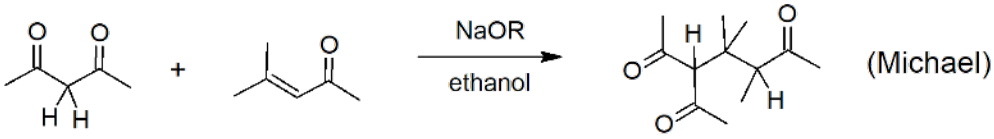
(mixed Claisen)



(Dieckmann)

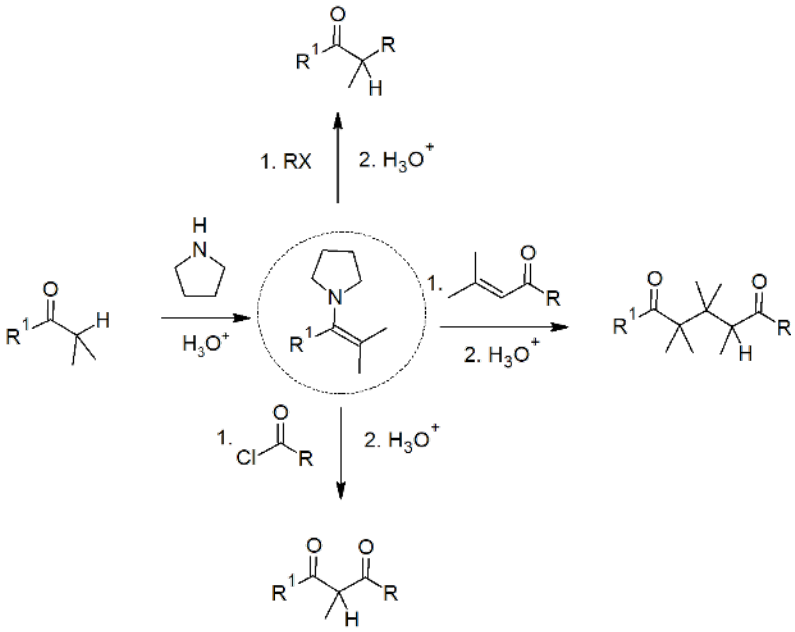


(Dieckmann)



(Michael)

Stork Enamine Reactions



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CHAPTER OVERVIEW

10: Amines and Heterocycles

Learning Objectives

When you have completed Chapter 10, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis that involves the use of any of the reactions described in this unit, and any of the reactions described in any previous unit.
3. solve road-map problems that require a knowledge of amine chemistry in addition to any of the chemistry discussed in previous units.
4. define, and use in context, the key terms introduced.

Amines are the first nitrogen-containing compounds that we study in detail in this course. We begin the chapter with an explanation of the differences in structure among primary, secondary and tertiary amines. We explain the nomenclature of aliphatic and arylamines, and examine the structure and bonding of these compounds, relating these features to their physical properties and basicity. We describe the use of amines to resolve racemic mixtures of chiral carboxylic acids.

Amines may be prepared by a number of different synthetic methods. We describe each of these methods and assess the relative merits of each. After a description of the reactions of aliphatic amines, we devote sections to a discussion of the use of tetraalkylammonium salts as phase-transfer agents. The chapter concludes with a summary of the spectroscopic properties of amines.

10.0: Introduction
10.1: Naming Amines
10.2: Structure and Properties of Amines
10.3: Basicity of Amines
10.4: Biological Amines and the Henderson-Hasselbalch Equation
10.5: Synthesis of Amines
10.6: Reactions of Amines
10.7: Heterocyclic Amines
10.8: Spectroscopy of Amines
10.9: Drugs and the Mind
10.10: Additional Problems
10.S: Amines and Heterocycles (Summary)

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10.0: Introduction

By the end of this chapter, we will have seen all the common functional groups. Of those groups, carbonyl compounds and amines are the most abundant and have the richest chemistry. In addition to proteins and nucleic acids, the majority of pharmaceutical agents contain amine functional groups, and many of the common coenzymes necessary for biological catalysis are amines.

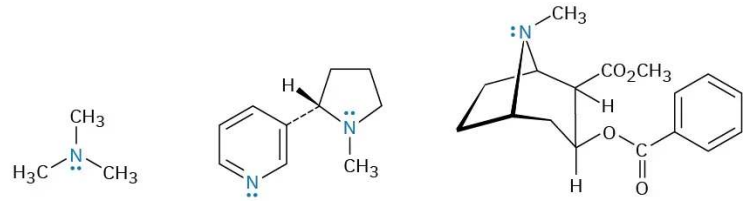


Figure 10.0.1: The characteristic and unmistakable odor of fish is due to a mixture of simple alkylamines. (credit: modification of work “Pike Place” by Sharat Ganapati/Flickr, CC BY 2.0)

Amines are organic derivatives of ammonia in the same way that alcohols and ethers are organic derivatives of water. Like ammonia, amines contain a nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic. We’ll soon see, in fact, that most of the chemistry of amines depends on the presence of this lone pair of electrons.

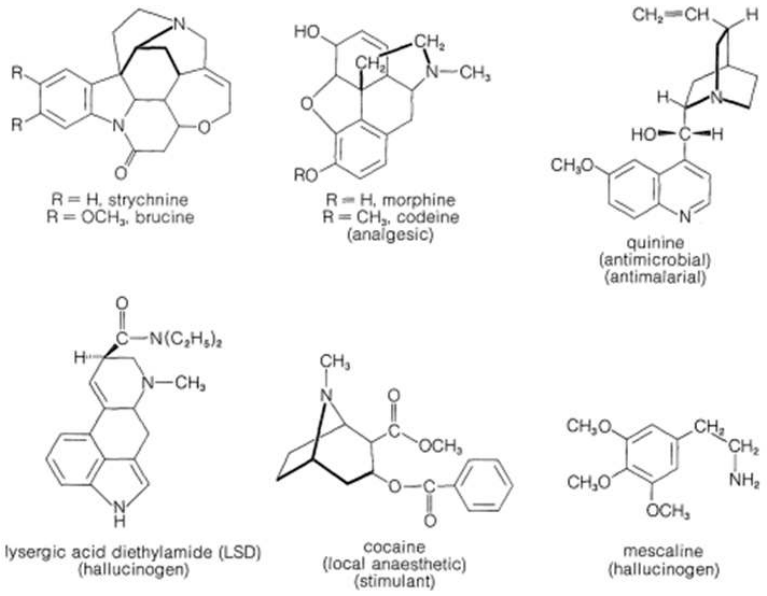
Naturally Occurring Amines

Amines occur widely in all living organisms. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish. A large and widespread class of naturally occurring amines is known as alkaloids. The structures of the plant alkaloids are extraordinarily complex, yet they are related to the simple amines in being weak nitrogen bases. Nicotine is found in tobacco; and cocaine is a stimulant found in the leaves of the South American coca bush. In addition, amino acids are the building blocks from which all proteins are made, and cyclic amine bases are constituents of nucleic acids.

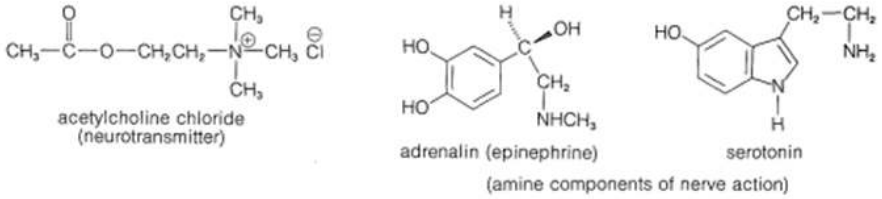


Trimethylamine **Nicotine** **Cocaine**

In fact, the first investigator to isolate an alkaloid in pure form was F. W. A. Sertürner who, in 1816, described morphine as basic, salt-forming, and ammonia-like. He used the term "organic alkali" from which is derived the name alkaloid. Alkaloids include compounds that may be classified as antimicrobial (quinine), as analgesics (morphine, codeine), as hallucinogens (mescaline, LSD), and as topical anesthetics (cocaine).



Certain amines and ammonium compounds play key roles in the function of the central nervous system as neurotransmitters and the balance of amines in the brain is critical for normal brain functioning. The amines acetylcholine chloride, adrenalin, and serotonin play important roles in nerve function in the human body.



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- **24.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.
- **24.2: Structure and Properties of Amines** by Dietmar Kennepohl, Layne Morsch, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

10.1: Naming Amines

Objectives

After completing this section, you should be able to

1. classify a given amine as being primary, secondary or tertiary.
2. explain, briefly, the difference in meaning of the terms primary, secondary and tertiary when they are applied to the structures of amines and alcohols.
3. determine whether a given structure represents a quaternary ammonium cation.
4. provide an acceptable IUPAC name for an amine, given its Kekulé, condensed or shorthand structure.
5. draw the structure of an amine, given its IUPAC name.
6. give the name and structure of one typical heterocyclic amine (e.g., pyridine).

Key Terms

Make certain that you can define, and use in context, the key terms below.

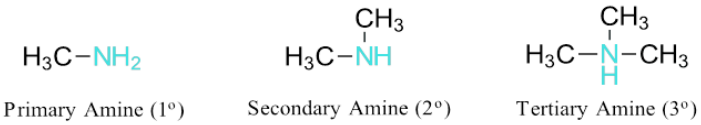
- amine
- primary amine
- secondary amine
- quaternary ammonium cation
- tertiary amine

Study Notes

You should recognize that heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are very common in organic chemistry. Be prepared to meet such compounds throughout this, and subsequent chapters, but do not try to memorize all of the names and structures givenin the reading. You should, however, commit the structures of pyridine and pyrrole to memory.

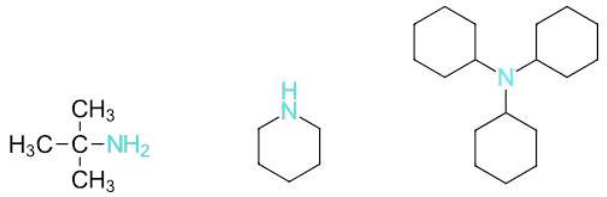
Classification of Amines

Amines can be either alkyl-substituted (alkylamines) or aryl-substituted (arylamines). Although much of the chemistry of the two classes is similar, there are also substantial differences. Amines are classified as primary (RNH_2), secondary (R_2NH), or tertiary (R_3N), depending on the number of organic substituents attached to nitrogen. Thus, methylamine (CH_3NH_2) is a primary amine, dimethylamine [$(CH_3)_2NH$] is a secondary amine, and trimethylamine [$(CH_3)_3N$] is a tertiary amine.



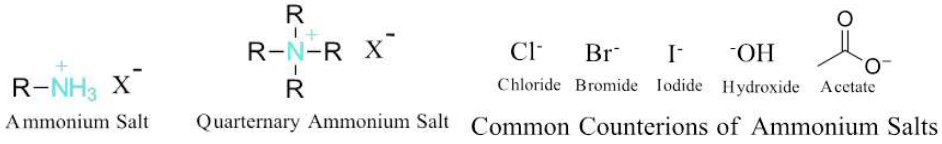
Primary Amine (1°) Secondary Amine (2°) Tertiary Amine (3°)

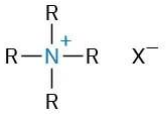
Example



Primary Amine (1°) Secondary Amine (2°) Tertiary Amine (3°)

Amines attached to 4 substituents and at least one substituent is a hydrogen are called ammonium salts. Amines attached to 4 alkyl substituents are called quaternary ammonium salts. The nitrogen in ammonium salts lacks lone pair electrons and carries a formal positive charge. Ammonium salts are also require a negatively charged counter-ion which can vary in composition.

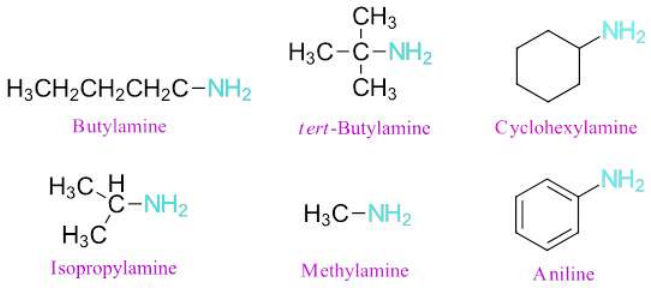



A quaternary ammonium salt

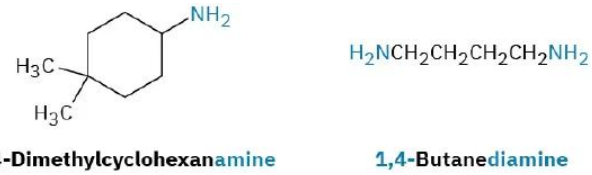
Nomenclature of Amines

Nomenclature of Primary Amines

Primary amines are named in two main ways using the IUPAC system. They can either be named as alkylamines or as alkanamines. Most 1º amines which are attached to linear alkanes, cycloalkanes, and alkyl groups with common names (Section 3.3), tend to be named as alkylamines. The alkyl groups is named as a substituent (**prefix + yl**) then the suffix -amine is added. Many amines have common names that are used by IUPAC, for example the primary arylamine ($C_6H_5NH_2$) is called aniline.



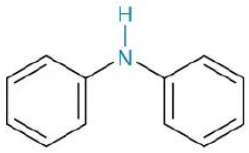
Other primary amines tend to be named as alkanamines. The alkyl group is named as an alkane (**prefix+ane**) and –e ending is replaced with the suffix **-amine**. The –e ending is not removed for diamines.


4,4-Dimethylcyclohexanamine **1,4-Butanediamine**

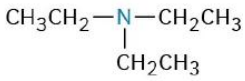


Nomenclature of Symmetrical Secondary and Tertiary Amines

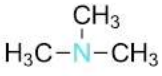
Symmetrical 2º and 3º amines (where all substituents are identical) are named as alkylamines and the prefix di- or tri -added to indicate the number of substituents.



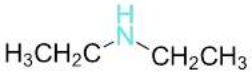
Diphenylamine



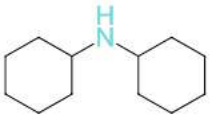
Triethylamine



Trimethylamine



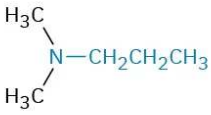
Diethylamine



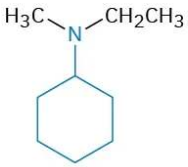
Dicyclohexylamine

Nomenclature of Unsymmetrical Secondary and Tertiary Amines

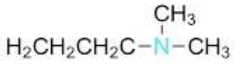
Unsymmetrical 2º and 3º amines are named with the largest chain being the base chain (**prefix+yl+amine**). The other alkyl groups are named as N-substituents. This notation is used to indicate that the substituent is attached to the amine nitrogen and not an alkyl carbon.



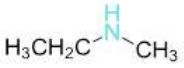
***N,N*-Dimethylpropylamine**



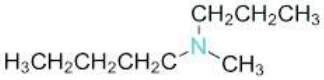
***N*-Ethyl-*N*-methylcyclohexylamine**



N,N-Dimethylpropylamine



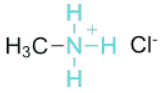
N-Methylethylamine



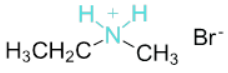
N-Methyl-N-propylbutylamine

Nomenclature of Ammonium Salts

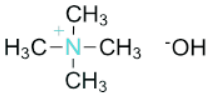
Ammonium salts and quaternary ammonium salts are named using the same rules as 2º and 3º amines except the –amine suffix is replaces with -ammonium + the name of the counter ion. The counter ion name is separated with a space.



Methylammonium Chloride



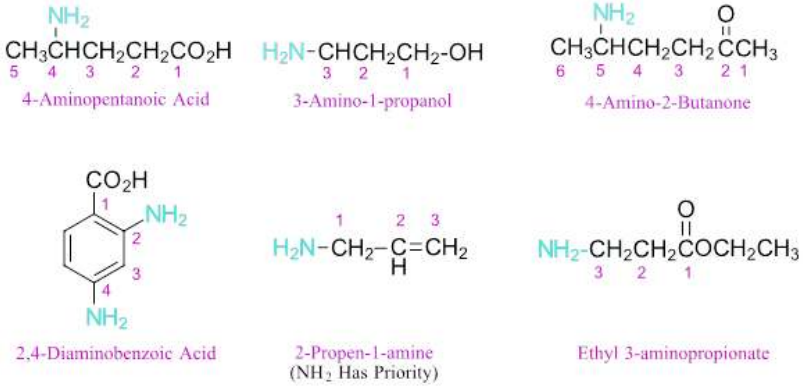
N-Methylethylammonium Bromide



Tetramethylammonium Hydroxide

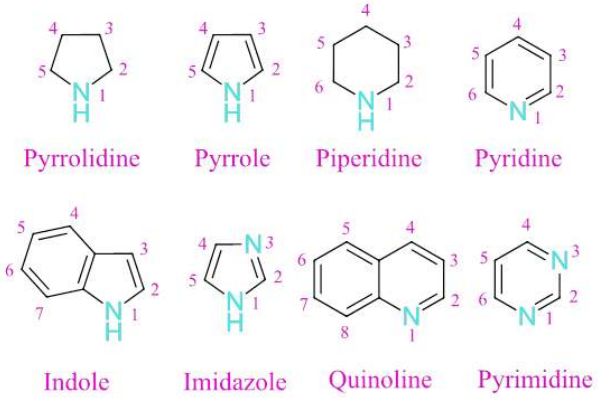
Amines as the lower functional group

Amines have one of the lower functional group priorities in the IUPAC nomenclature system. When present in a compound with a functional group of higher priority, the amine group is named as a substituent called **"amino."**

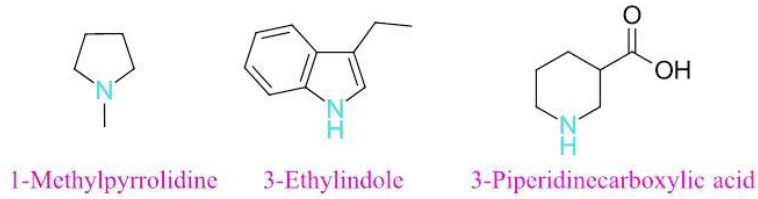


Nomenclature of Heterocyclic Amines

Heterocyclic amines have one or more nitrogens as part of the ring and can be aliphatic or aromatic. Most heterocyclic amine ring systems have a common name and are numbered such that the heterocyclic nitrogen always gets position 1. An amine attached to a heterocyclic ring is named as an amino substituent.

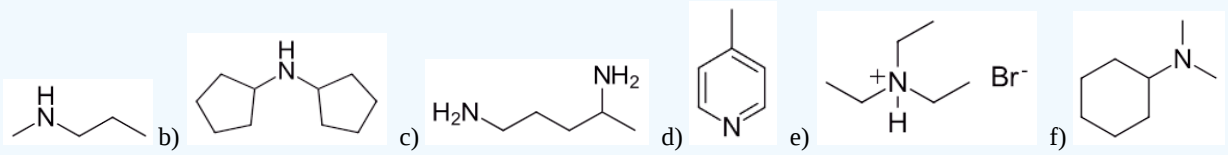


Examples:



? Exercises 10.1.1

Name the following compounds:



Answers

a. N-Methylpropylamine
b. Dicyclopentylamine
c. 1,4-Pentanediamine
d. 4-Methylpyridine

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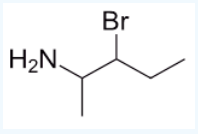
e. Triethylammonium Bromide
f. N,N-Dimethylcyclohexylamine

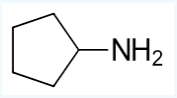
Exercise 10.1.2

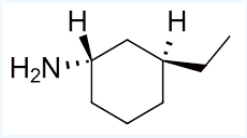
Draw the structures corresponding to the following names:

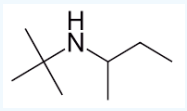
a. 3-Bromo-pentan-2-amine
b. Cyclopentanamine
c. *Trans*-3-ethylcyclohexanamine
d. *Sec*-butyl-*tert*-butyl amine
e. N,N-Dimethyl-3-pentanamine
f. 4-Methyl-2-hexanamine
g. 6-Bromo-4-amino-2-heptanol

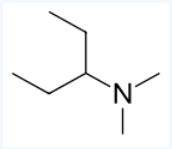
Answer

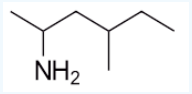
a) 

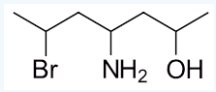
b) 

c) 

d) 

e) 

f) 

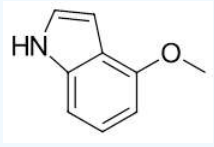
g) 

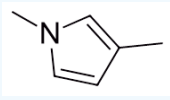
Exercise 10.1.3

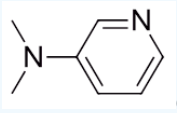
Draw the structures of the following heterocyclic compounds:

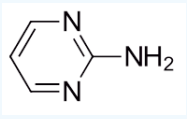
a. 4-Methoxyindole
b. 1,4-Dimethylpyrrole
c. 3-(N,N-Dimethylamino)pyridine
d. 2-Aminopyrimidine

Answer

a) 

b) 

c) 

d) 

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10.2: Structure and Properties of Amines

Objectives

After completing this section, you should be able to

1. describe the geometry and bonding of simple amines.
2. explain why most chiral amines cannot be resolved into their two enantiomers.

Key Terms

Make certain that you can define, and use in context, the key term below.

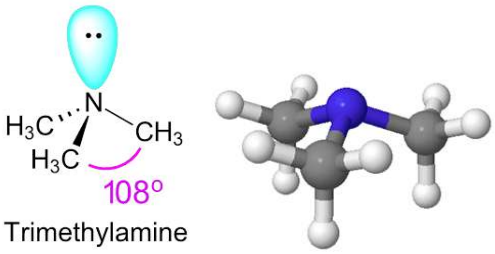
- pyramidal inversion

Study Notes

Molecular models may help you to understand pyramidal inversion.

Bonding, Shape, and Hybridization of Amines

The nitrogen atom in most amines is sp^3 hybridized. Three of the sp^3 hybrid orbitals form sigma bonds with the fourth orbital carrying the lone pair electrons. Single-bonded nitrogen is trigonal pyramidal in shape, with the non-bonding lone electron pair pointing to the unoccupied corner of a tetrahedron. Due to crowding by the lone pair electrons, the C-N-C bond angle between alkyl substituents on an amine is roughly 108º which is slightly less than the 109.5º bond angle for a perfect tetrahedral geometry.

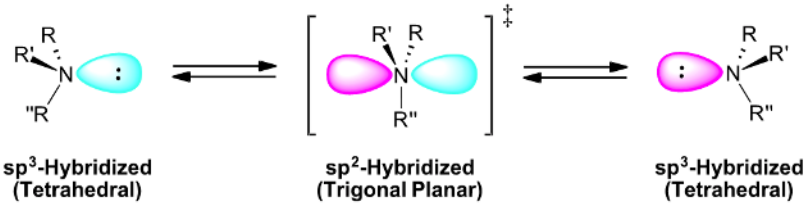


Trimethylamine

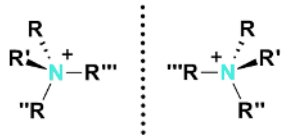
The C-N bonds (147 pm) of non-conjugated amines is shorter than C-C bond (154 pm) in alkanes, and longer than the C-O bond (143 pm) present in alcohols. This difference in bond length is expected given that the relative atom sizes are C > O > N.

Chirality of Amines

Due to their tetrahedral configuration, amines with three different substituents are chiral. The R and S enantiomeric forms of a chiral amine cannot be resolved due to their rapid interconversion by a process called pyramidal or nitrogen inversion. During the inversion, the sp^3 hybridized amine momentarily rehybridizes to a sp^2 hybridized, trigonal planar, transition state where the lone pair electrons occupy a p orbital. The nitrogen then returns to a tetrahedral sp^3 hybridization causing the lone pair electrons to return to a sp^3 orbital on the opposite side of the nitrogen. During this process substituents invert to form the enantiomer. The thermodynamic barrier for this inversion (~25 kJ/mol) is low enough to allow rapid inversion at room temperature, leading to a mixture of interconverting R and S configurations. At room temperature a nitrogen atom exists as a racemic mixture of R and S configurations at equilibrium.



Quarternary amines lack lone pair electrons and therefore do not undergo pyramidal inversions. Quarternary amines with four different substituents are chiral and are readily resolved into separate enantiomers.



Enantiomers of a Chiral Quarternary Amine

Boiling Point and Water Solubility

Methyl, dimethyl, trimethyl, and ethyl amines are gases under standard conditions. Most common alkyl amines are liquids, and high molecular weight amines are, quite naturally, solids at standard temperatures.

It is instructive to compare the boiling points and water solubility of amines with those of corresponding alcohols and ethers. The dominant factor here is hydrogen bonding, and the first table below documents the powerful intermolecular attraction that results from -O-H---O- hydrogen bonding in alcohols (light blue columns). Corresponding -N-H---N- hydrogen bonding is weaker, as the lower boiling points of similarly sized amines demonstrate. Alkanes provide reference compounds in which hydrogen bonding is not possible, and the increase in boiling point for equivalent 1º-amines is roughly half the increase observed for equivalent alcohols.

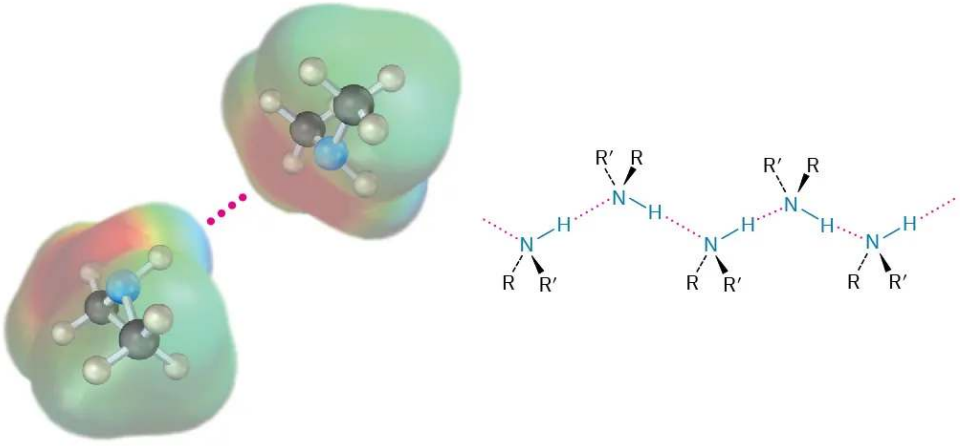


Figure 10.2.1: Hydrogen bonding in amines.

As a result, amines have higher boiling points than alkanes of similar molecular weight. Diethylamine (MW = 73 amu) boils at 56.3 °C, for instance, while pentane (MW = 72 amu) boils at 36.1 °C.

Compound	CH_3CH_3	CH_3OH	CH_3NH_2	$CH_3CH_2CH_3$	CH_3CH_2OH	$CH_3CH_2NH_2$
Mol.Wt.	30	32	31	44	46	45
Boiling Point ºC	-88.6º	65º	-6.0º	-42º	78.5º	16.6º

The second table illustrates differences associated with isomeric 1º, 2º & 3º-amines, as well as the influence of chain branching. Since 1º-amines have two hydrogens available for hydrogen bonding, we expect them to have higher boiling points than isomeric 2º-amines, which in turn should boil higher than isomeric 3º-amines (no hydrogen bonding). Indeed, 3º-amines have boiling points

similar to equivalent-sized ethers, and in all but the smallest compounds, corresponding ethers, 3º-amines, and alkanes have similar boiling points. In the examples shown here, it is further demonstrated that chain branching reduces boiling points by 10 to 15 ºC.

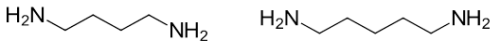
Compound	$CH_3(CH_2)_2CH_3$	$CH_3(CH_2)_2OH$	$CH_3(CH_2)_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3CH$	$(CH_3)_2CHOH$	$(CH_3)_2CHNH_2$	$(CH_3)_3N$
Mol.Wt.	58	60	59	59	58	60	59	59
Boiling Point ºC	-0.5º	97º	48º	37º	-12º	82º	34º	3º

Most aliphatic amines display some solubility in water, reflecting their ability to form hydrogen bonds. Solubility decreases proportionally with the increase in the number of carbon atoms in the molecule – especially when the carbon atom number is greater than six. Aliphatic amines also display significant solubility in organic solvents, especially in polar organic solvents.

The water solubility of 1º and 2º-amines is similar to that of comparable alcohols. As expected, the water solubility of 3º-amines and ethers is also similar. The basicity of amines allows them to be dissolved in dilute mineral acid solutions, and this property facilitates their separation from neutral compounds such as alcohols and hydrocarbons by partitioning between the phases of non-miscible solvents.

Smell

Most amines have “interesting” odors. The simple ones smell very much like ammonia. Higher aliphatic amines smell like decaying meat. The stench of rotting meat is due in part to two diamines: putrescine and cadaverine. They are made during the decarboxylation of the amino acids, ornithine and lysine, by bacteria.



Putrescine Cadaverine

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10.3: Basicity of Amines

Objectives

After completing this section, you should be able to

1. account for the basicity and nucleophilicity of amines.
2. explain why amines are more basic than amides, and better nucleophiles.
3. describe how an amine can be extracted from a mixture that also contains neutral compounds illustrating the reactions which take place with appropriate equations.
4. explain why primary and secondary (but not tertiary) amines may be regarded as very weak acids, and illustrate the synthetic usefulness of the strong bases that can be formed from these weak acids.

Key Terms

Make certain that you can define, and use in context, the key term below.

- amide

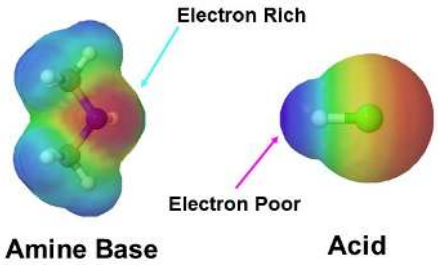
Study Notes

The lone pair of electrons on the nitrogen atom of amines makes these compounds not only basic, but also good nucleophiles. Indeed, we have seen in past chapters that amines react with electrophiles in several polar reactions (see for example the nucleophilic addition of amines in the formation of imines and enamines in Section 7.8).

The ammonium ions of most simple aliphatic amines have a pK_a of about 10 or 11. However, these simple amines are all more basic (i.e., have a higher pK_a) than ammonia. Why? Remember that, relative to hydrogen, alkyl groups are electron releasing, and that the presence of an electron-releasing group stabilizes ions carrying a positive charge. Thus, the free energy difference between an alkylamine and an alkylammonium ion is less than the free energy difference between ammonia and an ammonium ion; consequently, an alkylamine is more easily protonated than ammonia, and therefore the former has a higher pK_a than the latter.

Basicity of nitrogen groups

In this section, we consider the relative basicity of amines. When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic and nucleophilic) is the lone pair on the nitrogen? In other words, how much does that lone pair want to break away from the nitrogen nucleus and form a new bond with a hydrogen. The lone pair electrons makes the nitrogen in amines electron dense, which is represents by a red color in the electrostatic potential map present below left. Amine are basic and easily react with the hydrogen of acids which are electron poor as seen below.



Amines are one of the only neutral functional groups considered bases and nucleophiles, which is a consequence of the lone pair electrons on the nitrogen. During an acid/base reaction, the lone pair electrons attack an acidic hydrogen to form an N-H bond. This gives the nitrogen in the resulting ammonium salt four single bonds and a positive charge.

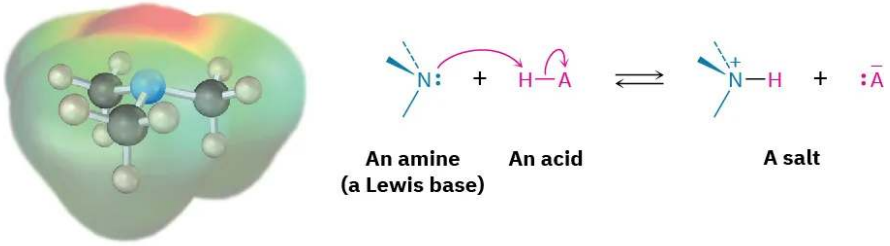


Figure 10.3.1: the lone pair electrons of an amine attack an acidic hydrogen to form an N-H bond, forming ammonium salt.

Amines react with water to establish an equilibrium where a proton is transferred to the amine to produce an ammonium salt and the hydroxide ion, as shown in the following general equation:

$$RNH2_{(aq)} + H_2O_{(l)} \rightleftharpoons RNH3^+_{(aq)} + OH^-_{(aq)} \tag{10.3.1}$$

The equilibrium constant for this reaction is the base ionization constant (K_b), also called the base dissociation constant:

$$K_b = \frac{[RNH3^+][OH^-]}{[NH2]} \tag{10.3.2}$$

$$pK_b = -\log K_b$$

Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a (Section 2-8), the base strength of an amine can be measured by defining an analogous basicity constant K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

However, Kb values are often not used to discuss relative basicity of amines. It is common to compare basicity's of amines by using the K_a's of their conjugate acids, which is the corresponding ammonium ion. Fortunately, the K_a and K_b values for amines are directly related.

Consider the reactions for a conjugate acid-base pair, $RNH_3^+ - RNH_2$:

$$\mathrm{RNH_3^+}(aq) + \mathrm{H_2O}(l) \rightleftharpoons \mathrm{RNH_2}(aq) + \mathrm{H_3O^+}(aq) \quad K_a = \frac{[RNH2][H3O]}{[RNH3+]}$$

$$\mathrm{RNH_2}(aq) + \mathrm{H_2O}(l) \rightleftharpoons \mathrm{RNH_3^+}(aq) + \mathrm{OH^-}(aq) \quad K_b = \frac{[RNH3+][OH-]}{[RNH2]}$$

Adding these two chemical equations together yields the equation for the autoionization for water:

$$\cancel{\mathrm{RNH_3^+}(aq)} + \mathrm{H_2O}(l) + \cancel{\mathrm{RNH_2}(aq)} + \mathrm{H_2O}(l) \rightleftharpoons \mathrm{H_3O^+}(aq) + \cancel{\mathrm{RNH_2}(aq)} + \mathrm{OH^-}(aq) + \cancel{\mathrm{RNH_3^+}(aq)}$$

$$2\,\mathrm{H_2O}(l) \rightleftharpoons \mathrm{H_3O^+}(aq) + \mathrm{OH^-}(aq)$$

Given that the *K* expression for a chemical equation formed from adding two or more other equations is the mathematical product of the input equations' *K* constants.

$$K_a \text{ X } K_b = \{2\ H_2O\} / (H_3O^+)\{OH^-\} = Kw$$

$$K_a = \frac{K_w}{K_b}$$

$$pK_a + pK_b = 14$$

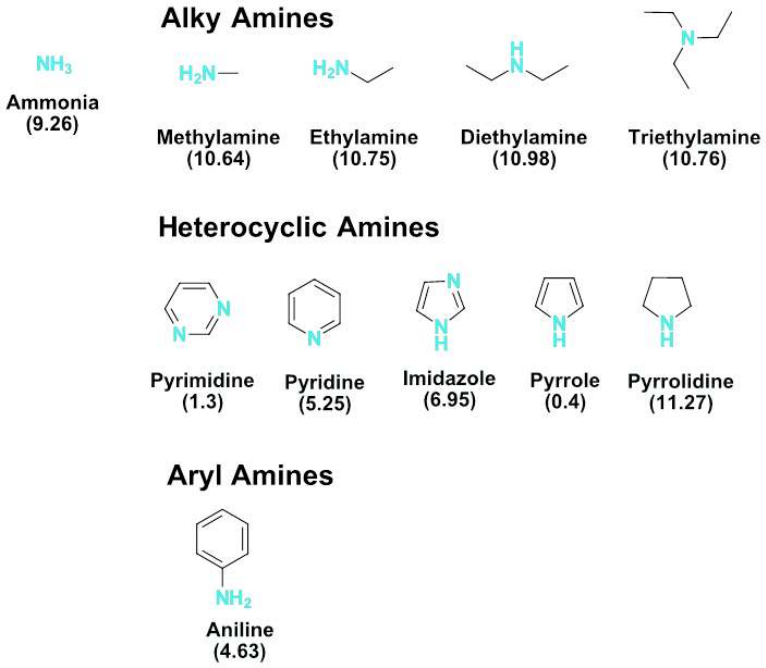
Thus if the K_a for an ammonium ion is know the K_b for the corresponding amine can be calculated using the equation $K_b = K_w / K_a$. This relationship shows that as an ammonium ion becomes more acidic (K_a increases / pK_a decreases) the correspond base becomes weaker (K_b decreases / pK_b increases)

Weaker Base = Larger K_a and Smaller pK_a of the Ammonium ion

Stronger Base = Smaller K_a and Larger pK_a of the Ammonium ion

Like ammonia, most amines are Brønsted-Lowry and Lewis bases, but their base strength can be changed enormously by substituents. Most simple alkyl amines have pK_a's in the range 9.5 to 11.0, and their aqueous solutions are basic (have a pH of 11 to 12, depending on concentration).

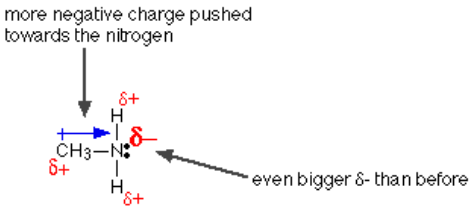
Aromatic heterocyclic amines (such as pyrimidine, pyridine, imidazole, and pyrrole) are significantly weaker bases as a consequence of three factors. The first of these is the hybridization of the nitrogen. In each case, the heterocyclic nitrogen is sp^2 hybridized. The increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton compared to sp^3 hybridized nitrogens. The very low basicity of pyrrole reflects the exceptional delocalization of the nitrogen electron pair associated with its incorporation in an aromatic ring. Imidazole (pK_a = 6.95) is over a million times more basic than pyrrole because the sp^2 nitrogen that is part of one double bond is structurally similar to pyridine, and has a comparable basicity.



Basicity of common amines (pK_a of the conjugate ammonium ions)

Inductive Effects on Nitrogen Basicity

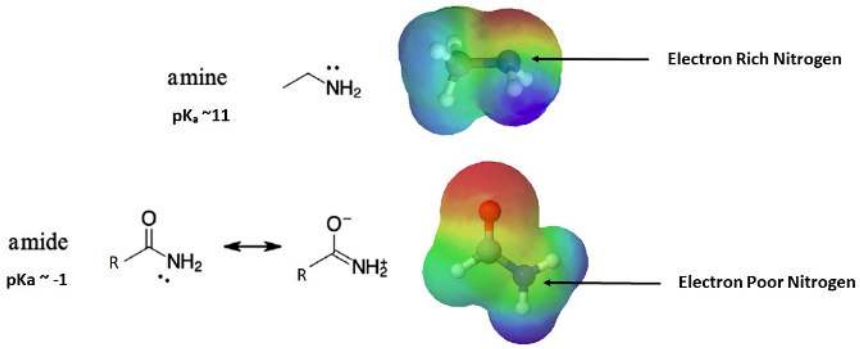
Alkyl groups donate electrons to the more electronegative nitrogen. The inductive effect makes the electron density on the alkylamine's nitrogen greater than the nitrogen of ammonia. The small amount of extra negative charge built up on the nitrogen atom makes the lone pair even more attractive towards hydrogen ions. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia.



Compound	pK_a of the conjugate ammonium ions
NH_3	9.3
CH_3NH_2	10.66
$(CH_3)_2NH$	10.74
$(CH_3)_3N$	9.81

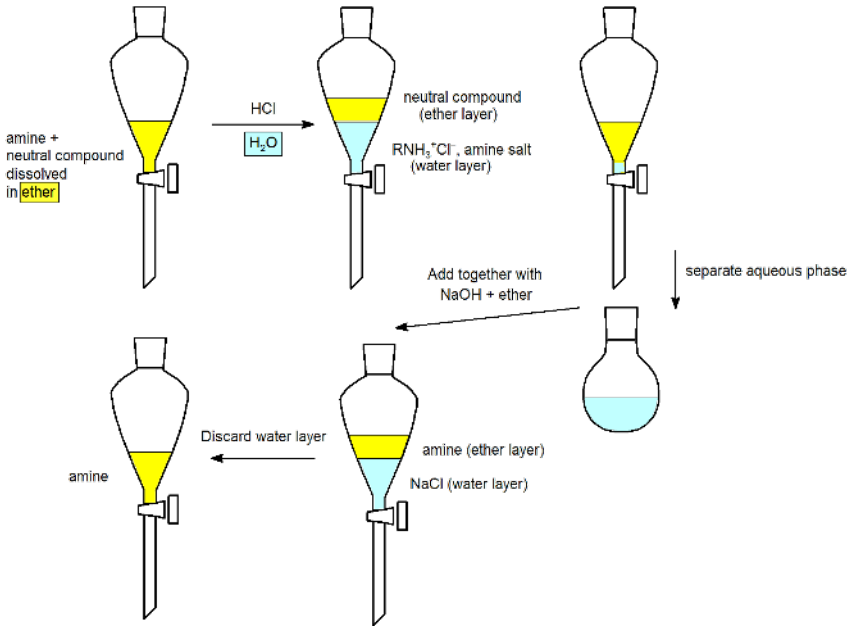
Comparing the Basicity of Alkylamines to Amides

The nitrogen atom is strongly basic when it is in an amine, but *not* significantly basic when it is part of an amide group. While the electron lone pair of an amine nitrogen is localized in one place, the lone pair on an amide nitrogen is delocalized by resonance. The electron density – in the form of a lone pair – is stabilized by resonance delocalization, even though there is not a negative charge involved. Here's another way to think about it: the lone pair on an amide nitrogen is not as available for bonding with a proton – these two electrons are too stable being part of the delocalized pi-bonding system. The electrostatic potential map shows the effect of resonance on the basicity of an amide. The map shows that the electron density, shown in red, is almost completely shifted towards the oxygen. This greatly reduces the basicity of the lone-pair electrons on the nitrogen atom in an amide.



Amine Extraction in the Laboratory

Extraction is often employed in organic chemistry to purify compounds. Liquid-liquid extractions take advantage of the difference in solubility of a substance in two immiscible liquids (e.g. ether and water). The two immiscible liquids used in an extraction process are (1) the solvent in which the solids are dissolved, and (2) the extracting solvent. The two immiscible liquids are then easily separated using a separatory funnel. For amines, one can take advantage of their basicity by forming the protonated salt ($RNH_2^+Cl^-$), which is soluble in water. The salt will be extracted into the aqueous phase, leaving neutral compounds in the non-aqueous phase. The aqueous layer is then treated with a base (NaOH) to regenerate the amine and NaCl. A second extraction-separation is then done to isolate the amine in the non-aqueous layer and leave behind NaCl in the aqueous layer.



Flow chart for separation to provide the pure amine (Figure 10.3.2).

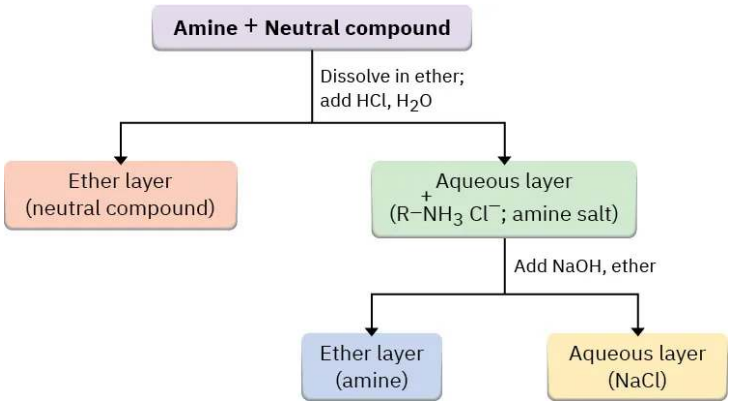
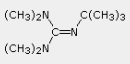


Figure 10.3.2: Separation and purification of an amine component from a mixture by extraction of its ammonium salt into water.

Important Reagent Bases

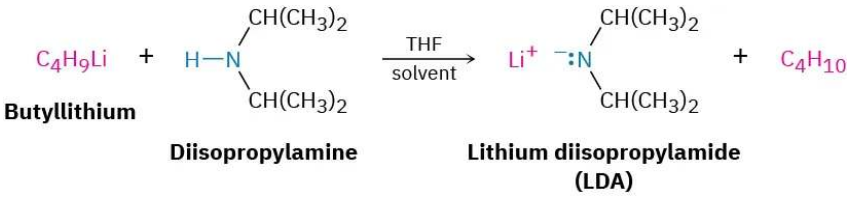
The significance of all these acid-base relationships to practical organic chemistry lies in the need for organic bases of varying strength, as reagents tailored to the requirements of specific reactions. The common base sodium hydroxide is not soluble in many organic solvents, and is therefore not widely used as a reagent in organic reactions. Most base reagents are alkoxide salts, amines or amide salts. Since alcohols are much stronger acids than amines, their conjugate bases are weaker than amine bases, and fill the gap in base strength between amines and amide salts.

Basicity of common amines (pK_a of the conjugate ammonium ions)

Base Name	Pyridine	Triethyl Amine	Hünig's Base	Barton's Base	Potassium t-Butoxide	Sodium HMDS	LDA
Formula		$(C_2H_5)_3N$			$(CH_3)_3CO^{(-)}\ K^{(+)}$	$[(CH_3)_3Si]_2N^{(-)}\ Na^{(+)}$	$[(CH_3)_2CH]_2N^{(-)}\ Li^{(+)}$
pK_a of conjugate acid	5.3	10.7	11.4	14	19	26	35.7

Pyridine is commonly used as an acid scavenger in reactions that produce mineral acid co-products. Its basicity and nucleophilicity may be modified by steric hindrance, as in the case of 2,6-dimethylpyridine (pK_a=6.7), or resonance stabilization, as in the case of 4-dimethylaminopyridine (pK_a=9.7). Hünig's base is relatively non-nucleophilic (due to steric hindrance), and is often used as the base in E2 elimination reactions conducted in non-polar solvents. Barton's base is a strong, poorly-nucleophilic, neutral base that serves in cases where electrophilic substitution of other amine bases is a problem. The alkoxides are stronger bases that are often used in the corresponding alcohol as solvent, or for greater reactivity in DMSO. Finally, the two amide bases see widespread use in generating enolate bases from carbonyl compounds and other weak carbon acids.

In addition to acting as a base, 1° and 2° amines can act as very weak acids. Their N-H proton can be removed if they are reacted with a strong enough base. An example is the formation of lithium diisopropylamide (LDA, $LiN[CH(CH_3)_2]_2$) by reacting *n*-butyllithium with diisopropylamine (pK_a 36) **(Section 8-4)**. LDA is a very strong base and is commonly used to create enolate ions by deprotonating an alpha-hydrogen from carbonyl compounds **(Section 8-6)**.



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Exercise 10.3.1

Select the more basic amine from each of the following pairs of compounds.

a. $CH_3CH_2NH_2$ or $CH_3CH_2CONH_2$
b. NaOH or CH_3NH_2
c. CH_3NHCH_3 or pyridine

Answer

(a) $CH_3CH_2NH_2$
(b) NaOH
(c) CH_3NHCH_3

Exercise 10.3.2

The 4-methylbenzylammonium ion has a pKa of 9.51, and the butylammonium ion has a pKa of 10.59. Which is more basic? What's the pKb for each compound?

Answer

The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49.

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10.4: Biological Amines and the Henderson-Hasselbalch Equation

Objectives

1. identify the form that amine bases take within living cells.
2. use the Henderson-Hasselbalch equation to calculate the percentage of a base that is protonated in a solution, given the pK_a value of the associated ion and the pH of the solution.
3. explain why organic chemists write cellular amines in their protonated form and amino acids in their ammonium carboxylate form.

In Section 6.7, we saw that the extent of dissociation of a carboxylic acid HA in an aqueous solution buffered to a given pH can be calculated with the Henderson–Hasselbalch equation. Furthermore, we concluded that at the physiological pH of 7.3 inside living cells, carboxylic acids are almost entirely dissociated into their carboxylate anions, RCO_2^-.

Henderson–Hasselbalch equation:

$$\mathrm{pH} = \mathrm{pK_a} + \log\left(\frac{\text{concentration of}}{\text{concentration of}}\right) \qquad \text{(Henderson-Hasselbalch equation)}$$

pH = pKa + log ([A–]/[HA]) so log([A–]/[HA]) = pH – pKa

What about amine bases?

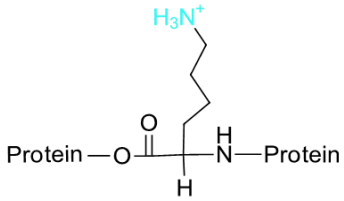
The Henderson-Hasselbalch equation is very useful relating the pKa of a buffered solution to the relative amounts of an acid and its conjugate base. In **Section 6-3**, we used the Henderson-Hasselbalch equation to show that under physiological pH, carboxylic acids are almost completely dissociated into their carboxylate ions.

So, what does the side chain of a lysine amino acid residue look like if it is on the surface of a protein in an aqueous solution buffered pH 7.0? Is it protonated or deprotonated? The values in the Henderson-Hasselbalch can be used for an amine with the ammonium salt written as, HA = RNH_3^+, and the amine as being, A^- = RNH_2. With an approximate pK_a of 10.8 for the protonated amine HA, it should be >99% protonated, in the positively-charged, ammonium form:

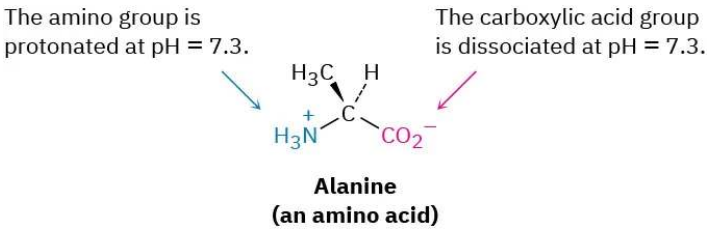
$$7.0 = 10.8 + \log\left(\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]}\right)$$

$$\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]} = 1.6 \times 10^{-4}$$

So, $[\mathrm{RNH_3^+}] \gg [\mathrm{RNH_2}]$ at this pH. Consequently, in an aqueous solution buffered at pH 7, carboxylic acid groups can be expected to be essentially 100% deprotonated and negatively charged (ie. in the carboxylate form), and amine groups essentially 100% protonated and positively charged (i.e., in the ammonium form).



Alcohols are fully protonated and neutral at pH 7, as are thiols. The imidazole group on the histidine side chain has a pK_a near 7, and thus exists in physiological solutions as mixture of both protonated and deprotonated forms.



Alanine
(an amino acid)

? Exercise 10.4.1

Would you expect an aromatic hetererocycle, pyrrole, to be protonated at pH = 7.3? Use the Henderson-Hasselbalch equation to determine your answer. pKa of protonated pyrrole is 0.4.

Answer

$$7.3 = 0.4 + \log\left(\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3{}^+}]}\right)$$

$$\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3{}^+}]} = 7.9 \times 10^6$$

So, $[\mathrm{RNH_2}] \gg [\mathrm{RNH_3{}^+}]$. Thus pyrrole would be almost completely unprotonated at pH = 7.

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10.5: Synthesis of Amines

Objectives

After completing this section, you should be able to

1. write equations to illustrate the synthesis of amines by
   a. reduction of nitriles or amides and nitro compounds.
   b. reactions involving alkyl groups:
      i. S_N2 reactions of alkyl halides, ammonia and other amines.
      ii. nucleophilic attack by an azide ion on an alkyl halide, followed by reduction of the azide so formed.
      iii. alkylation of potassium phthalimide, followed by hydrolysis of the *N*-alkyl phthalimide so formed (i.e., the Gabriel synthesis).
   c. reductive amination of aldehydes or ketones.
   d. Hofmann or Curtius rearrangements.
2. write detailed mechanisms for each of the steps involved in the synthetic routes outlined in Objective 1.
3. identify the product or products formed when
   a. a given nitrile or amide is reduced using lithium aluminum hydride.
   b. a given alkyl halide is reacted with ammonia or an alkylamine.
   c. a given alkyl halide is reacted with azide ion and the resulting product is reduced.
   d. a given alkyl halide is reacted with potassium phthalimide and the resulting product is hydrolyzed.
   e. a given aldehyde or ketone is reacted with ammonia or an amine in the presence of nickel catalyst.
   f. a given amide is treated with halogen and base.
   g. a given acyl azide is heated and then hydrolyzed.
4. identify the starting material, the other reagents, or both, needed to synthesize a given amine by any of the routes listed in Objective 1.
5. write a general equation to illustrate the preparation of an arylamine by the reduction of a nitro compound, and balance such an equation.
6. identify the product formed from the reduction of a given aromatic nitro compound.
7. identify the organic compound, the inorganic reagents, or both, needed to prepare a given arylamine.

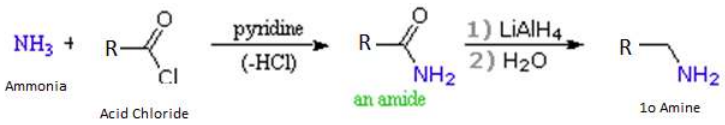
Key Terms

Make certain that you can define, and use in context, the key terms below.

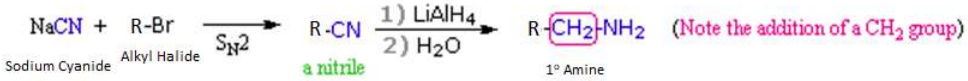
- azide synthesis
- Curtius rearrangement
- Hofmann rearrangement
- Gabriel synthesis
- imide
- reductive amination

Reduction of Nitriles, Amides, and Nitro Compounds

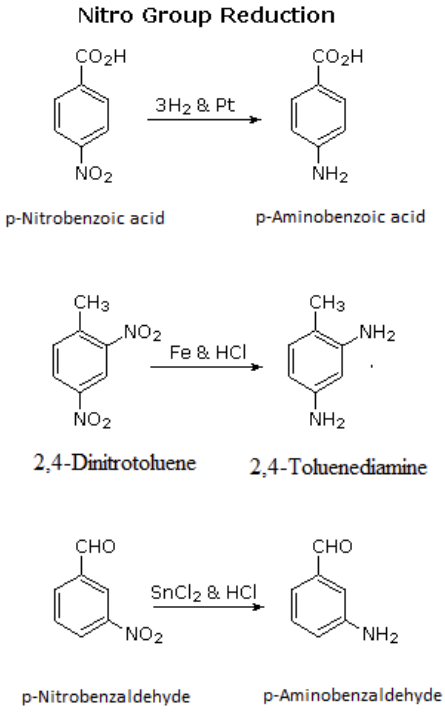
Acid chlorides react with ammonia to give amides, by an addition-elimination path, and these are reduced to amines by $LiAlH_4$ (Section 21-7).



Alkyl halides can be converted to primary amines through a two-step process. First an S_N2 reaction with a cyanide anion converts the alkyl halide into a nitrile. Then the nitrile is reduced to a primary amine by $LiAlH_4$ (Section 20-7). During this reaction sequence an additional carbon atom is added.

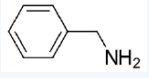


Arylamines are typically prepared by the reduction of a nitro group on an aromatic ring. Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + platinum catalyst), and zinc, iron, or tin(II) chloride in dilute mineral acid. The procedures described above are sufficient for most cases. Catalytic hydrogenation can be problematic because it is known to reduce other functional groups such as alkenes, alkynes, and some carbonyl groups.



? Exercise 10.5.1

Propose structures of the starting materials needed to make the following amines using the reduction of a nitrile or an amide:

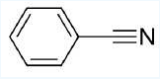
a. $CH_3CH_2CH_2CH_2NH_2$
b. $(CH_3CH_2)_2NH$
c. 

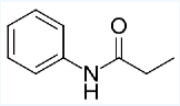
d. N-Propylaniline

Answer

a. $CH_3CH_2CH_2CONH_2$

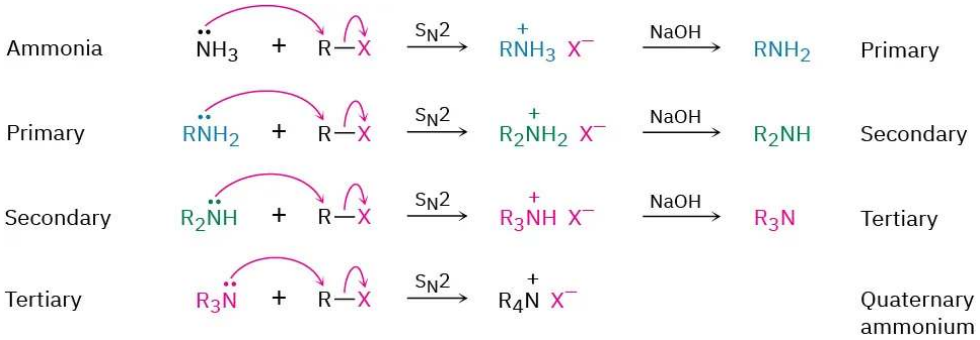
b. $CH_3CONHCH_2CH_3$

c. 

d. 

S_N2 Reactions of Alkyl Halides

Because they posses lone pair electrons, ammonia and amines are considered good nucleophiles. Ammonia and amines can by alkylated by an S_N2 reaction with alkyl halides. The product of the reaction is an ammonium salt where the negative counter-ion is the halogen of the alkyl halide. When the alkylated products are 1°, 2°, and 3° amines, they can be deprotonated with NaOH to produce the neutral amine. When a 3° amine is alkylated, a quaternary ammonium salt is produced.



Alkylation is an efficient method for the synthesis of 3° and 4° amines. However, when 1° and 2° amines are alkylated, a mixture of products is typically produced. When ammonia is reacted with an alkylhalide an monoalkylammonium salt is formed.

$$RX + NH_3 \rightarrow RNH_3^+ + X^-$$

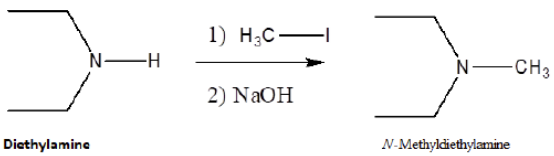
It is possible for any remaining ammonia present in the reaction to deprotonate the ammonium salt to produce the neutral monoalkyl amine.

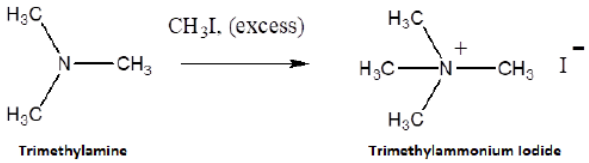
$$RNH_3^+ + NH_3 \rightarrow RNH_2 + NH_4^+$$

The monoalkyl amine is then free to react with a second alkyl halide creating a dialkylammonium salt. This process can be repeated to eventually create a tetralkylammonium salt. Typically, when an alkyl halide is reacted with ammonia, a mixture of mostly 1° and 2° amines, with trace amounts of 3° amines and 4° ammonium salts, is produced.

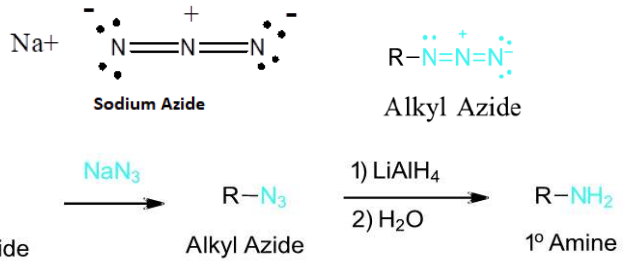
$$RNH_2 + RX \rightarrow R_2NH_2^+ + X^-$$

Example





To synthesize a 1° or 2° amine, specific reactions are usually employed. A more efficient method starts with an S_N2 reaction between a 1° or 2° alkyl halide and the nucleophilic azide anion (N_3^-) to produce an alkyl azide. The alkyl azide is not nucleophilic, so it cannot react with additional alkyl halides to produce overalkylation. Alkyl azide is then reduced with $LiAlH_4$ to produce a 1° amine.

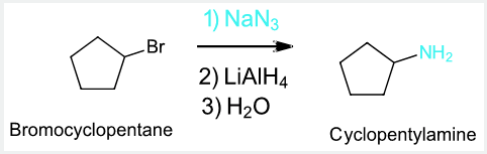


Examples:

a-

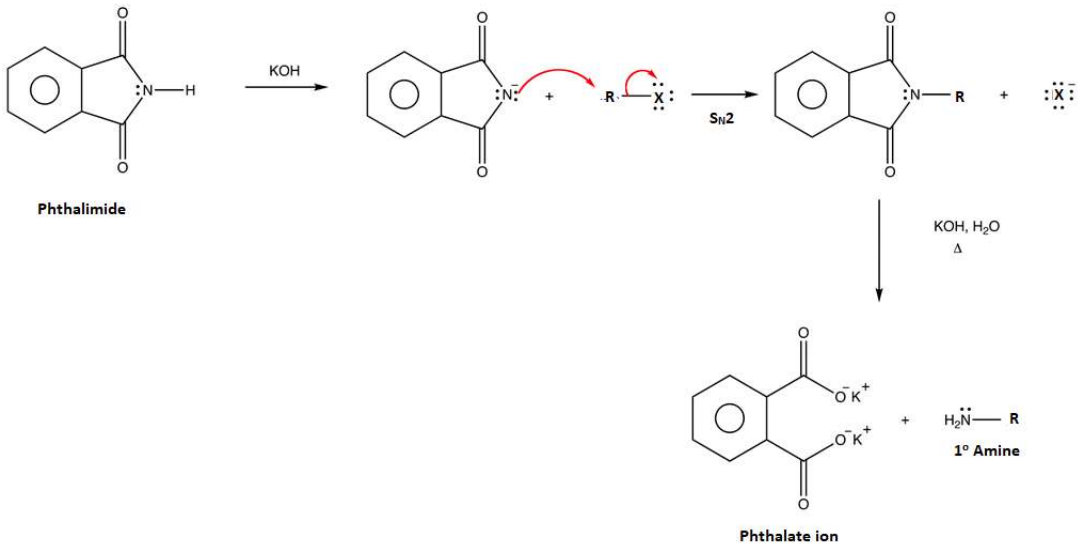


b-

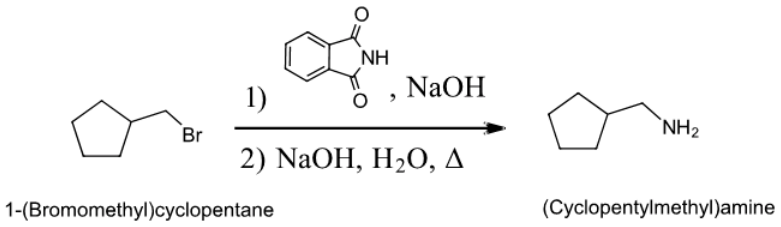


Gabriel Amine Synthesis

Another common method for the synthesis of 1° amines is called the **Gabriel amine synthesis**. This reaction starts with the deprotonation of phthalimide by a hydroxide base such as potassium hydroxide (KOH). The N-H hydrogen of an imide functional group is acidic because its conjugate base is resonance stabilized by two carbonyl groups. The phthalimide anion is nucleophilic and easily alkylated through an S_N2 reaction with an alkyl halide. The resulting N-alkylated phthalimide then undergoes base hydrolysis to produce a 1° amine product. The mechanism for the base-promoted hydrolysis of the N-alkylated phthalimide is analogous to the hydrolysis of an amide (Section 7-8).



Example

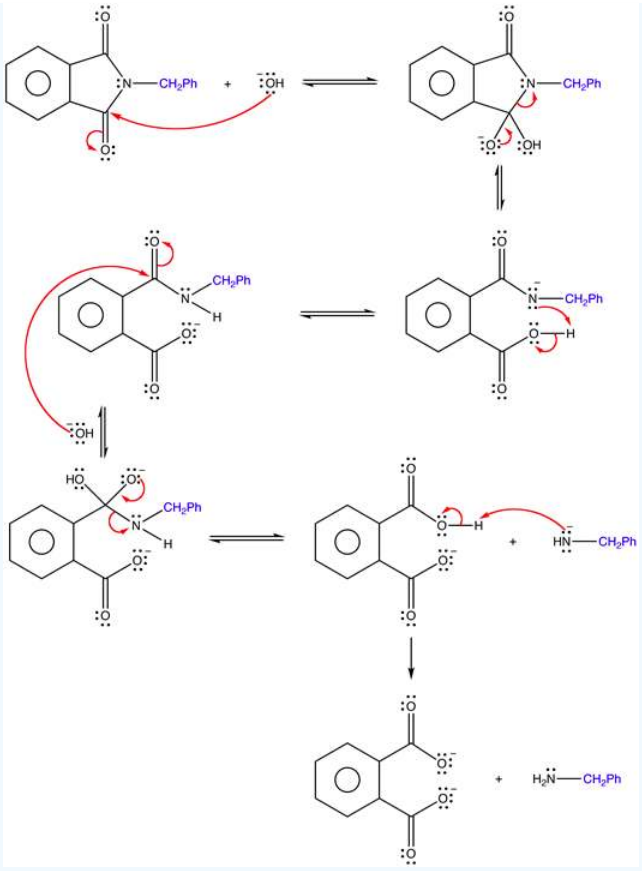


Exercises 10.5.2

Write the mechanism for the base-promoted hydrolysis of an N-alkyl phthalimide to create a 1° amine and the phthalate ion.2)

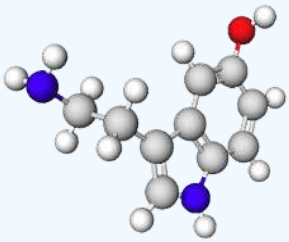
Answers

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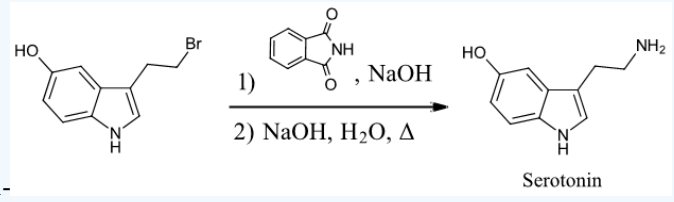
Exercise 10.5.3: Serotonin

Starting with any alkyl halide, show two methods to synthesize the neurotransmitter serotonin.

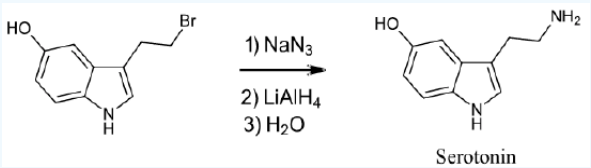


Answer

1-



2-

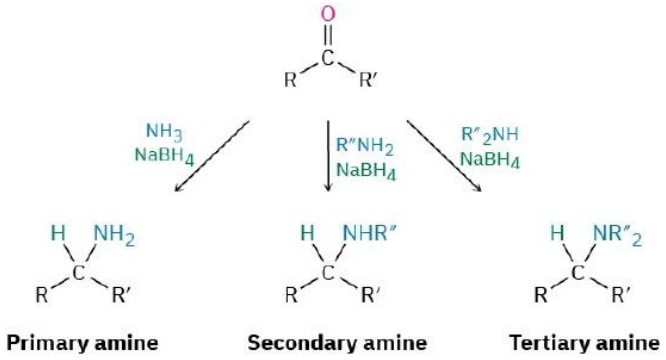


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Reductive Amination

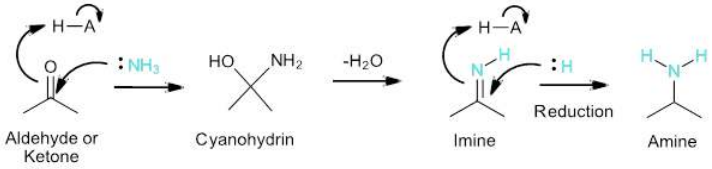
Aldehydes and ketones can be converted into 1°, 2° and 3° amines using **reductive amination**. The reaction takes place in two parts. The first step is the nucleophiic addition of ammonia, a 1° amine, or a 2° amine to a carbonyl group to form an imine **(Section 5-9)**. The second step is the reduction of the imine to an amine using a hydride reducing agent. Some common reducing agents used for this reaction are: sodium borohydride ($NaBH_4$), sodium cyanoborohydride ($NaBH_3CN$), $NaBH(OAc)_3$, or hydrogen gas (H_2) over a nickel catalyst.

General Reaction

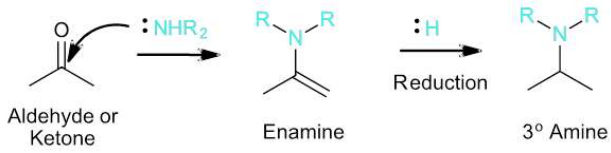


Mechanism

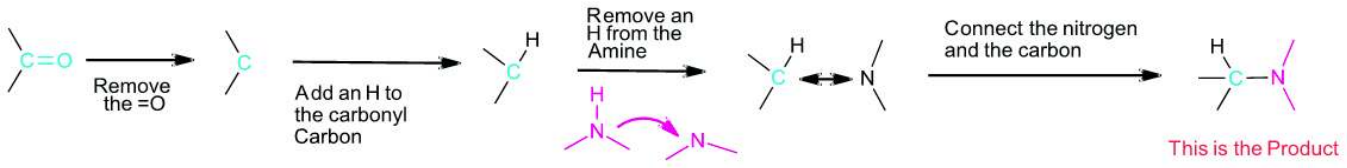
Reductive amination starts with the nucleophilic addition of ammonia or a 1° amine to an aldehyde or ketone, which forms a cyanohydrin intermediate. Subsequent dehydration forms an imine intermediate (Section 5-9). The imine undergoes hydride reduction in a similar fashion as C=O carbonyl bonds are reduced to an alcohol.



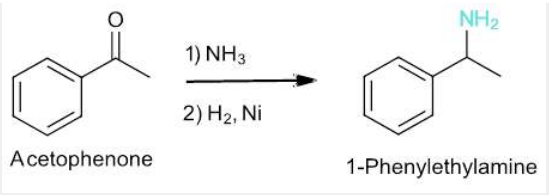
When a 2° amine is used for reductive amination, an enamine intermediate is formed which then undergoes hydride reduction to form a 3° amine.

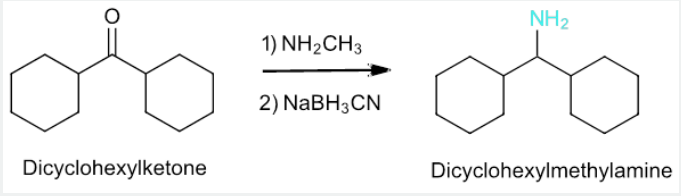


Predicting the Products of a Reductive Amination



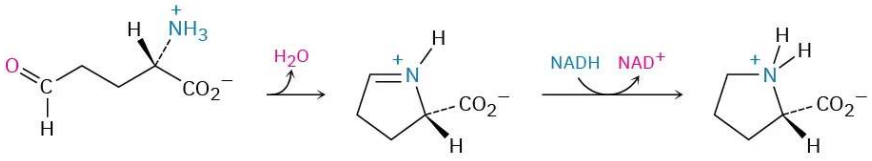
Examples





Biological Reductive Aminations

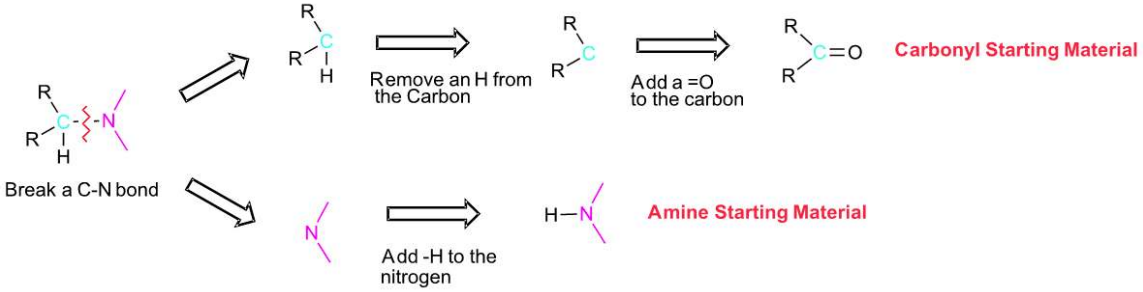
Reductive amination is used in the biosynthesis of the amino acid proline. The enzyme pyrroline-5-carboxylate synthase **(P5CS)** catalyzes glutamate undergoing an intramolecular imine formation to produce 1-pyrrolinium 5-carboxylate. Then the enzyme pyrroline-5-carboxylate reductase **(PYCR)** catalyzed the nucleophilic hydride reduction of the C=N bond to produce proline. The biological hydride reducing agent for this sequence is reduced nicotinamide adenine dinucleotide **(NADH).**



Glutamate 5-semialdehyde | **1-Pyrrolinium 5-carboxylate** | **Proline**

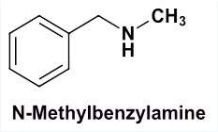
Planning a Synthesis using a Reductive Amination

If you are trying to develop a synthesis of an amine molecule, the key bond break is a C-N bond in the target molecule. There may be multiple C-N bonds present, so each should be broken separately to produce a possible set of starting materials. Because the amine is commonly used in excess during a reductive animation, the pathway which provides the simplest amine starting material is preferred. The carbon from the broken C-N bond goes on to become a carbonyl starting material. The nitrogen gains a hydrogen to become the amine starting material.



? Worked Exercise 10.5.1

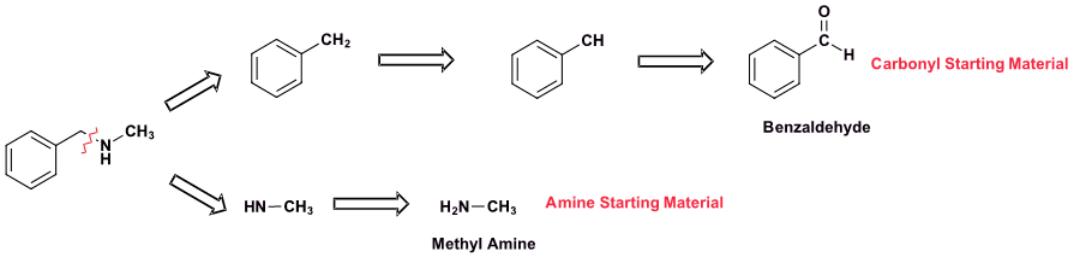
Show how N-methylbenzylamine can be synthesized using a reductive amination. If more than one pathway is possible, draw them both and determine which one would be preferred.



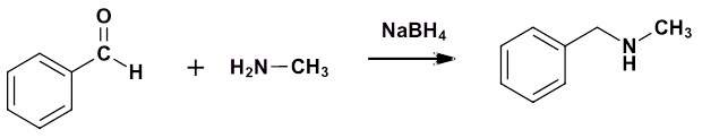
N-Methylbenzylamine

Answer

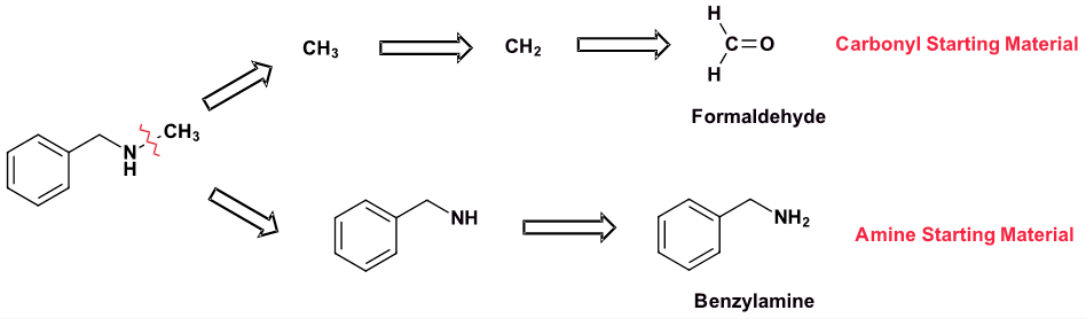
Pathway 1



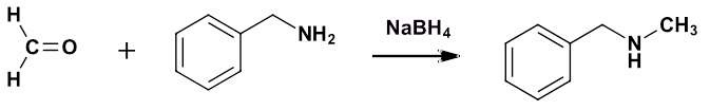
Solution 1



Pathway 2



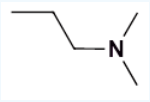
Solution 2

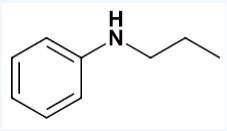


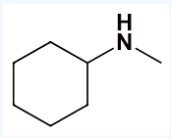
Because N-methylbenzylamine has two C-N bonds there are two possible synthesis pathways. Pathway 1 is most likely preferred because it uses the simplest amine starting material, methyl amine.

? Exercise 10.5.4

Provide starting materials that could be used to prepare the following compounds using a reductive amination. Show all possible pathways.

a. 

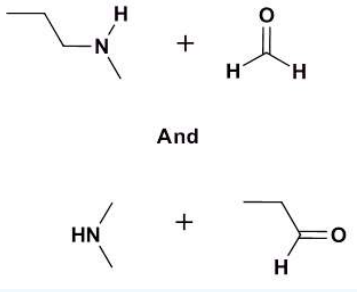
b. 

c. 

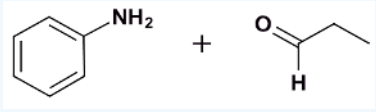
Answers

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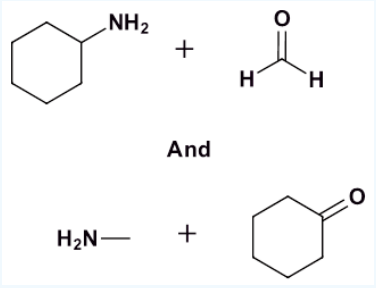
a.



b.

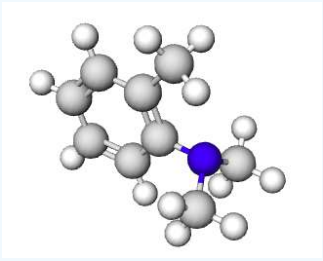


c.

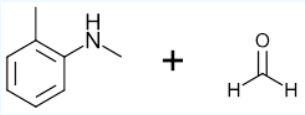


? Exercise 10.5.5

Identify the starting materials that could provide the following molecule using a reductive amination.



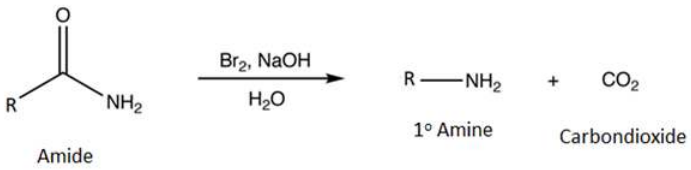
Answer



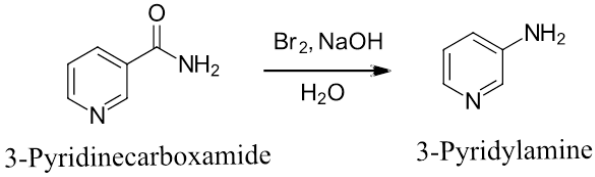
Hofmann Rearrangement

The Hofmann rearrangement occurs when a 1º amide is reacted with bromine (Br_2) and a base. The products are a 1º amine with one less carbon and carbon dioxide (CO_2).

General Reaction



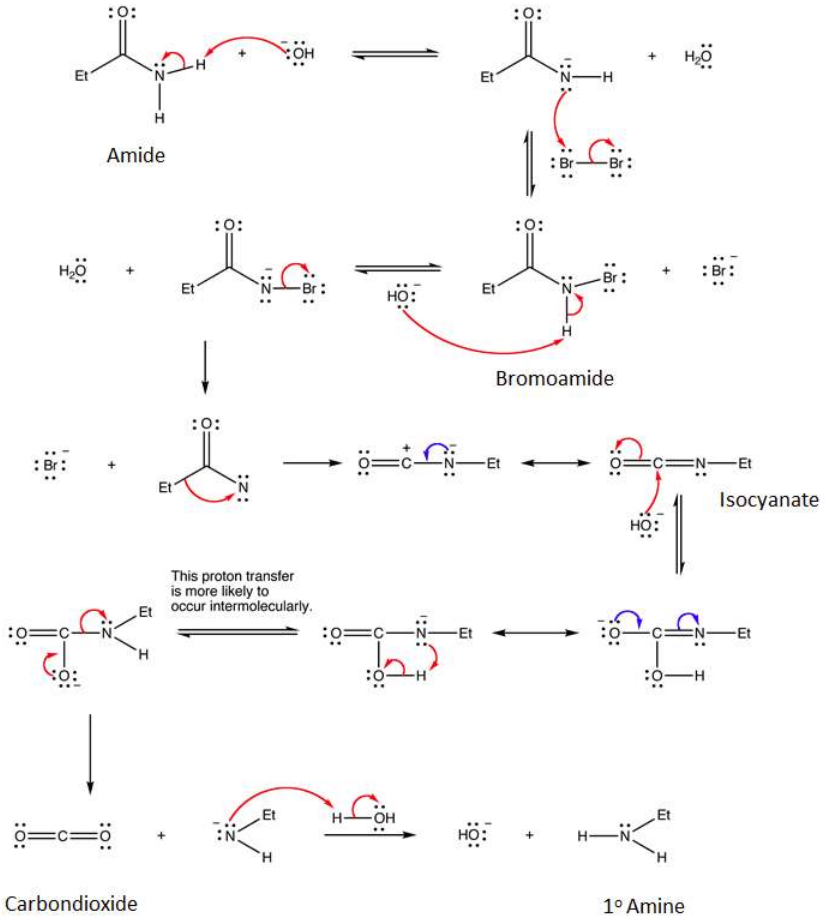
Example



Mechanism

The mechanism for the Hofmann rearrangement is quite complex. The mechanism starts with the deprontation of the primary amide by a base. The nitrogen is brominated during an S_N2 reaction with Br_2 to produce an N-bromoamide. Bromide is eliminated

as a leaving group to produce a electron deficient nitrene-like nitrogen. Electrons from the adjacent C-C bond migrate to the nitrogen as part of a rearrangment to finally produce an isocyanate. The carbon in the isocyante is electrophilic and reacts with a nucleophilic hydroxide to create a C-O bond. After movement of electrons through resonance and a proton transfer a carbamate intermediate is formed. The carbamate decomposes to create an amide anion and a stable CO_2 molecule. Finally, water protonates the amide anion to produce a 1° amine.

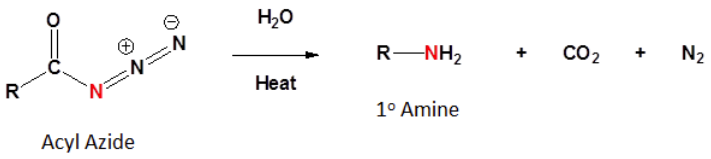


Curtius Rearrangement

The Curtius Rearrangement is another method used to synthesize a 1° amine.

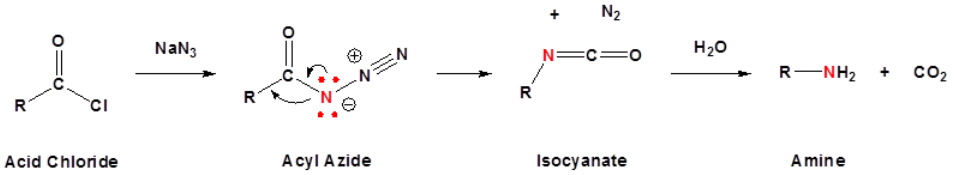
General Reaction

The Curtius rearrangement involves an acyl azide reacting with water and heat to produce a 1° amine along with CO_2 and N_2. The acyl azide is usually made by a nucleophilic substitution of an acid chloride with sodium azide (NaN_3)

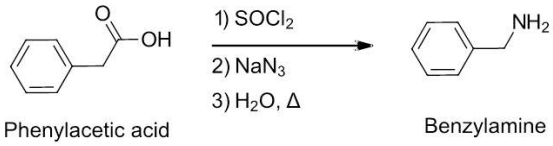


Mechanism

The mechanism of the Curtius rearrangement is quite similar to the Hoffman rearrangement. The loss of N_2 as a leaving group creates an electron deficient nitrogen. The adjacent -R group migrates to form an isocyanate. Reaction of the isocyanate forms a carbamate which decomposes to form a 1° amine and CO_2.

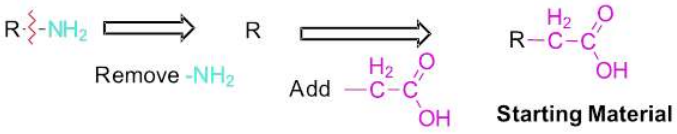


Example



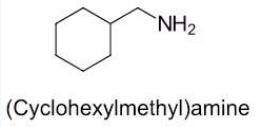
Planning a Synthesis using a Hoffman or Curtius Rearrangement

Because the amide and the acyl azide required for these rearrangements are both best made from an acid chloride, synthesis of amines using these reactions is best started from the corresponding carboxylic acid. For retrosynthetic analysis starting from the desired amine product, the key break is the C-NH_2 bond. The amine is removed and replaced with a -CH_2CO_2H fragment to provide the required carboxylic acid starting material.



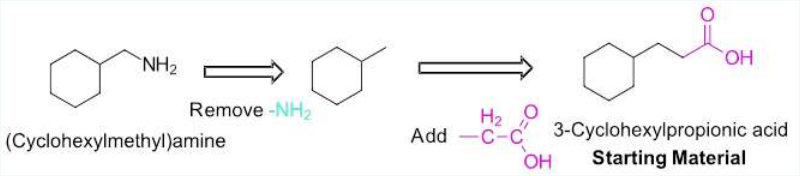
? Worked Example 10.5.2

Show how the following molecule could be prepared from a carboxylic acid starting material using both the Hoffman and Curtius rearrangements.



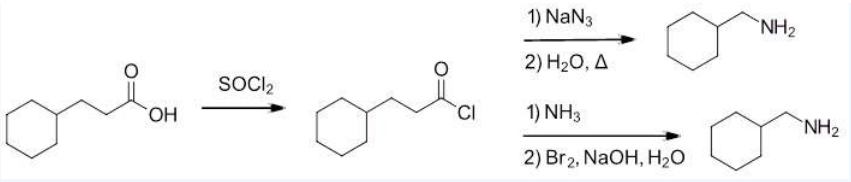
Answer

First determine the structure of the carboxylic acid starting material. This will be the starting material for both rearrangements. In the first step, convert the carboxylic acid into an acid halide using thionyl chloride ($SOCl_2$). Then use the required conditions for each rearrangement.



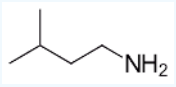
Solution

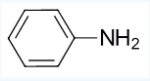
The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



Exercises 10.5.6

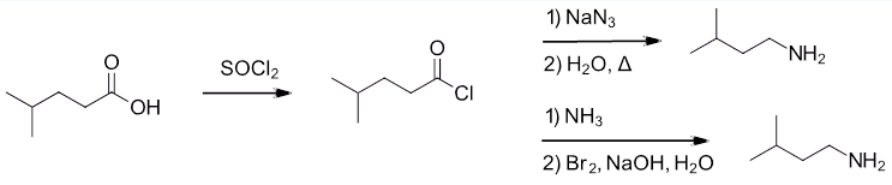
1) Using a carboxylic acid starting material explain how to prepare the following molecules using both the Hoffman and Curtius rearrangements.

a) 

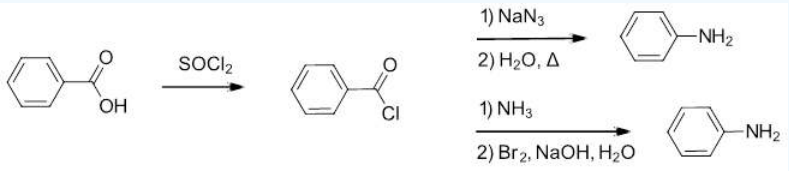
b) 

Answers

a) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



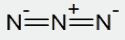
b) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



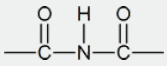
Study Notes

You may wish to review the mechanism of S_N2 reactions, which is discussed in some detail in CHEM 231 Sections 11.2 and 11.3.

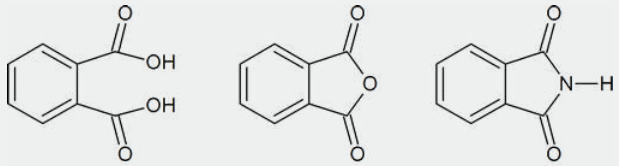
Azide synthesis is the first method on the table of synthesis of primary amines. The Lewis structure of the azide ion, N_3^-, is as shown below.



An “imide” is a compound in which an N$\ce{-}$H group is attached to two carbonyl groups; that is,



You should note the commonly used trivial names of the following compounds.



phthalic acid phthalic anhydride phthalimide

The phthalimide alkylation mentioned in the reading is also known as the Gabriel synthesis.

Before you read the section on reductive amination, you may wish to remind yourself of the structure of an imine.

The Hofmann rearrangement is usually called the Hofmann degradation. In a true rearrangement reaction, no atoms are lost or gained; however, in this particular reaction, one atom of carbon and one atom of oxygen are lost from the amide starting material, thus the term “rearrangement” is not really appropriate. There is a rearrangement step in the overall degradation process; however, this is the step in which the alkyl group of the acyl nitrene migrates from carbon to nitrogen to produce an isocyanate.

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10.6: Reactions of Amines

Objectives

After completing this section, you should be able to

1. write an equation to represent the reaction that takes place between ammonia, a primary or secondary amine, and an acid chloride.
2. identify the product formed when a given amine reacts with a given acid chloride.
3. identify the amine, the acid chloride, or both, needed to synthesize a given amide.
4. write a reaction sequence to illustrate the overall conversion of an amine to an alkene via a Hofmann elimination.
5. identify the alkene most likely to be formed when a given quaternary ammonium salt is heated with moist silver oxide (or silver hydroxide).
6. deduce the structure of an unknown quaternary ammonium salt, given the identity of the alkene or alkenes produced when the salt is heated with moist silver oxide.

Key Terms

Make certain that you can define, and use in context, the key term below.

- Hofmann elimination

Study Notes

The alkylation and acylation of amines have been dealt with in previous sections: alkylation in Section 10.7 and acylation in Sections 7.3 and 7.6. Review these sections if necessary.

Alkylation of Amines

It is instructive to examine these nitrogen substitution reactions using the common alkyl halide class of electrophiles. Thus, reaction of a primary alkyl bromide with a large excess of ammonia yields the corresponding 1°-amine, presumably by an S_N2 mechanism. The hydrogen bromide produced in the reaction combines with some of the excess ammonia, giving ammonium bromide as a by-product. Water does not normally react with 1°-alkyl halides to give alcohols, so the enhanced nucleophilicity of nitrogen relative to oxygen is clearly demonstrated.

$$2\,RCH_2Br + NH_3(\text{large excess}) \longrightarrow RCH_2NH_2 + {NH_4}^{(+)}Br^{(-)}$$

It follows that simple amines should also be more nucleophilic than their alcohol or ether equivalents. If, for example, we wish to carry out an S_N2 reaction of an alcohol with an alkyl halide to produce an ether (the Williamson synthesis), it is necessary to convert the weakly nucleophilic alcohol to its more nucleophilic conjugate base for the reaction to occur. In contrast, amines react with alkyl halides directly to give N-alkylated products. Since this reaction produces HBr as a byproduct, hydrobromide salts of the alkylated amine or unreacted starting amine (in equilibrium) will also be formed.

$$2\,RNH_2 + C_2H_5Br \longrightarrow RNHC_2H_5 + {RNH_3}^{(+)}Br^{(-)} \rightleftharpoons {RNH_2C_2H_5}^{(+)}Br^{(-)} + RNH_2$$

Unfortunately, the direct alkylation of 1° or 2°-amines to give a more substituted product does not proceed cleanly. If a 1:1 ratio of amine to alkyl halide is used, only 50% of the amine will react because the remaining amine will be tied up as an ammonium halide salt (remember that one equivalent of the strong acid HX is produced). If a 2:1 ratio of amine to alkylating agent is used, as in the above equation, the HX issue is solved, but another problem arises. Both the starting amine and the product amine are nucleophiles. Consequently, once the reaction has started, the product amine competes with the starting material in the later stages of alkylation, and some higher alkylated products are also formed. Even 3°-amines may be alkylated to form quaternary (4°) ammonium salts. When tetraalkyl ammonium salts are desired, as shown in the following example, Hünig's base (N,N-diisopropylethylamine) may be used to scavenge the HI produced in the three S_N2 reactions. Steric hindrance prevents this 3°-amine (Hünig's base) from being methylated.

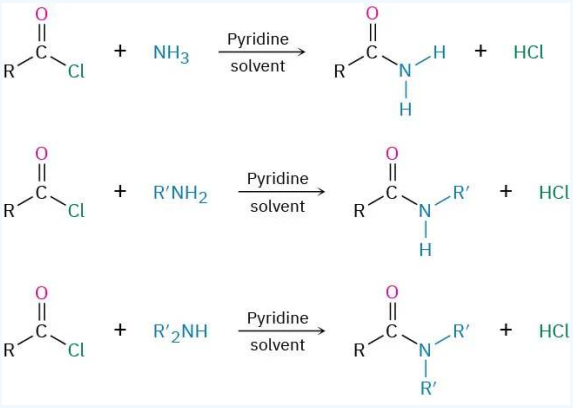
$$C_6H_5NH_2 + 3\,CH_3I + \text{Hünig's base} \longrightarrow {C_6H_5N(CH_3)_3}^{(+)}I^{(-)} + \text{HI salt of Hünig's base}$$

Acylation of Amines

Ammonia, 1° amines, and 2° amines react rapidly with acid chlorides or acid anhydrides to form 1°, 2°, and 3° amides, respectively **(Sections 7-5 and 7-6)**. These reactions typically take place rapidly at room temperature and provide high reaction yields.

The reaction is commonly run with a base, such as NaOH or pyridine, to neutralize the HCl produced. Over-acylation does not occur because the lone pair electrons on the amide nitrogen are conjugated with the carbonyl, making it less nucleophilic than an amine starting material.

Example 10.8.1

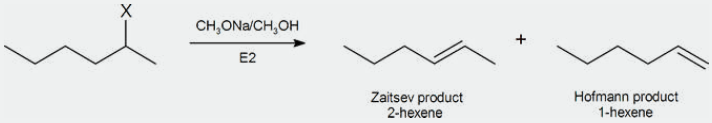


Elimination Reactions

Like alcohols, amines can be converted into alkenes by an elimination reaction. Amine functions seldom serve as leaving groups in nucleophilic substitution or base-catalyzed elimination reactions. Unlike what happens in other E2 reactions, the major product of Hofmann elimination is the less highly substituted alkene rather than the more highly substituted one.

Elimination Stereoselectivity

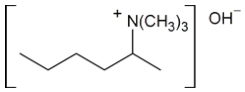
For the best-leaving groups, Zaitsev elimination is the major product. One explanation for Hofmann elimination is based on the consideration of the structures of the possible transition states; suggested by Joseph Bunnett and widely accepted. We can begin to understand Bunnett's reasoning by considering the elimination products formed by the dehydrohalogenation of a number of substituted hexanes in the reaction:



The table below describes the proportion of each product you would expect when X in the above reaction represents a given halogen.

X	% 2-hexene	% hexene
I	81	19
Br	72	28
Cl	67	33
F	30	70

As we descend this table, the electron-withdrawing ability of X increases, and the percentage of Hofmann product also increases. Given that the $(CH_3)_3N^+$ group is strongly electron-withdrawing, it is quite consistent for a compound of the type



to give 96% Hofmann product and 4% Zaitsev product in an E2 elimination reaction. But why does the proportion of Hofmann product increase as the electron-withdrawing ability of X increases? Bunnett suggests that the transition state in an E2 process can vary from being "carbocation-like" on one hand to "carbanion-like" on the other.

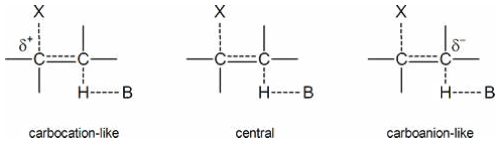


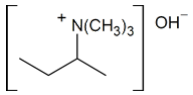
Figure 10.8.1 Various transition states for an E2 elimination reaction

In a carbocation-like transition state, the C-X bond is broken to a greater extent than the C-H bond; in the central transition state both, the C-X bond and the C-H bond are broken to an equal extent; and in the carbanion-like transition state, the C-H bond is broken to a greater extent than the C-X bond. In the latter case, a partial negative charge will develop on the carbon atom to which the hydrogen is attached, hence the term "carbanion-like." As we already know, any

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species or transition state bearing a full or partial negative charge is stabilized by the presence of electron-withdrawing groups and destabilized by the presence of electron-releasing groups.

Let us now consider the two possible transition states for an E2 elimination of $(CH_3)_3NH^+$ from a quaternary ammonium hydroxide,



One transition state leads to Zaitsev elimination, the other to Hofmann elimination.

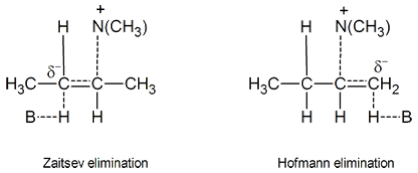
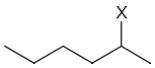


Figure 10.8.2 Possible carbanion-like transition states

In the transition state leading to the Zaitsev product, the carbon atom carrying the partial negative charge is bonded to an electron-releasing methyl group. This is clearly a less favourable situation than the one that exists in the transition state leading to Hofmann elimination, where there are no electron-releasing groups attached to the carbon atom bearing the partial negative charge. Bunnett's argument is that carbanion-like transition states are much more likely when the atom or group X in a compound such as



is strongly electron-withdrawing because the C–X bond becomes stronger as the electron-withdrawing ability of X increases.

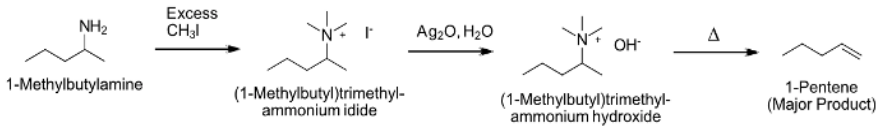
Thus, as we go along the series X = I, Br, Cl, F, $(CH_3)_3N^+$, the electron-withdrawing ability of X increases, the C-X bond becomes more difficult to break, the transition state becomes more carbanion-like in character, and Hofmann elimination becomes more pronounced.

Hofmann Elimination

Amine functions seldom serve as leaving groups in nucleophilic substitution or base-catalyzed elimination reactions. Indeed, they are even less effective in this role than are hydroxyl and alkoxyl groups. As noted earlier, 1º and 2º-amines are much weaker acids than alcohols, so it is not surprising that it is difficult to force the nitrogen function to assume the role of a leaving group. In this context we note that the acidity of the potential ammonium leaving group is at least ten powers of ten less than that of an analogous oxonium species. However, amines can be turned into a good leaving group by alkylation with an alkyl halide to form a quarternary ammonium salt. Upon elimination the quarternary ammonium salt produces a stable 3º amine as a leaving group.

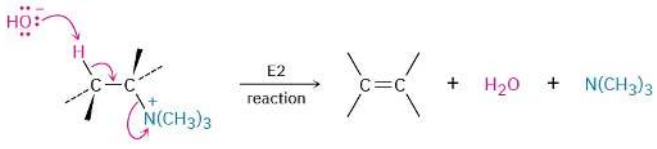
Elimination reactions of 4º-ammonium salts are termed **Hofmann eliminations**. Since the counter anion in most 4º-ammonium salts is halide, this is often replaced by the more basic hydroxide ion through reaction with silver hydroxide (or silver oxide). The resulting hydroxide salt must then be heated (100 - 200 ºC) to affect the E2-like elimination of a 3º-amine. For an elimination to occur one of the alkyl substituents on nitrogen must have one or more beta-hydrogens, which is similar to elimination reactions of alkyl halides. Simple amines are easily converted to the necessary 4º-ammonium salts by exhaustive alkylation, usually with methyl iodide (methyl has no beta-hydrogens and cannot compete in the elimination reaction).

General Reaction



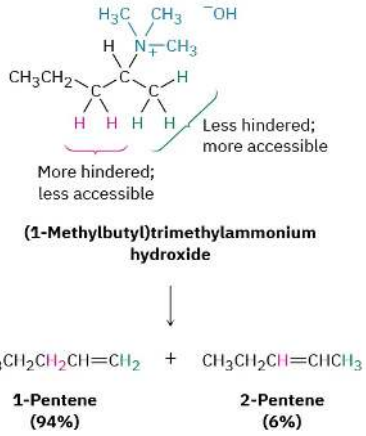
Mechanism

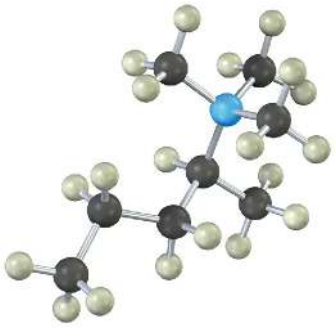
During the Hofmann elimination, the hydroxide counter ion acts as a base to remove a beta-hydrogen and cause an E2 elimination to form an alkene. A trialkyl amine is eliminated as a leaving group during this reaction.



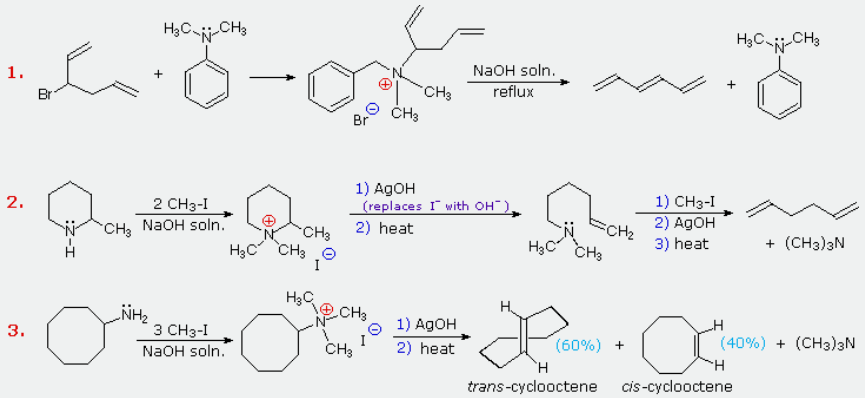
When predicting the products of an E2 elimination, the more substituted alkene is expected to be the preferred product based on Zaitsev's rule. The tendency of Hofmann eliminations to give the less-substituted double bond isomer is commonly referred to as the **Hofmann Rule**. To understand why the base-induced elimination of 4º-ammonium salts behaves differently from that of alkyl halides it is necessary to reexamine the nature of the E2 transition state.

The reason for the difference in products in a Hofmann elimination is most likely due to steric hindrance of the base. The large size of of the quaternary ammonium group forces the base to remove a hydrogen from the least sterically hindered position. This correspondingly leads to the alkene with the least number of substituents to be preferred.





Examples

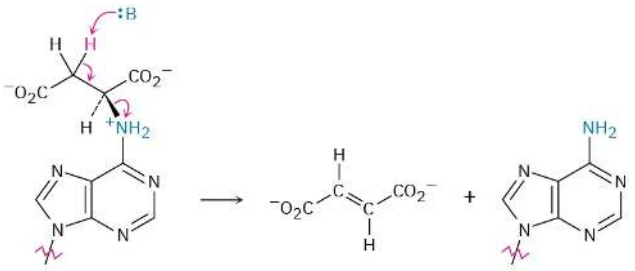


Example #1 is interesting in two respects. First, it generates a 4º-ammonium halide salt in a manner different from exhaustive methylation. Second, this salt is not converted to its hydroxide analog prior to elimination. A concentrated aqueous solution of the halide salt is simply dropped into a refluxing sodium hydroxide solution, and the volatile hydrocarbon product is isolated by distillation.

Example #2 illustrates an important aspect of the Hofmann elimination. If the nitrogen atom is part of a ring, then a single application of this elimination procedure does not remove the nitrogen as a separate 3º-amine product. In order to sever the nitrogen function from the molecule, a second Hofmann elimination must be carried out. Indeed, if the nitrogen atom was a member of two rings (fused or spiro), then three repetitions of the Hofmann elimination would be required to remove the nitrogen from the remaining molecular framework.

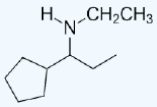
Example #3 is noteworthy because the less stable trans-cyclooctene is the chief product, accompanied by the cis-isomer. An anti-E2-transition state would necessarily give the cis-cycloalkene, so the trans-isomer must be generated by a syn-elimination. The cis-cyclooctene produced in this reaction could also be formed by a syn-elimination. Cyclooctane is a conformationally complex structure. Several puckered conformations that avoid angle strain are possible, and one of the most stable of these is shown on the right. Some eclipsed bonds occur in all these conformers, and transannular hydrogen crowding is unavoidable. Since the trimethylammonium substituent is large (about the size of tert-butyl) it will probably assume an equatorial-like orientation to avoid steric crowding. An anti-E2 transition state is likely to require an axial-like orientation of this bulky group, making this an unfavorable path.

Eliminations analogous to the Hofmann elimination are often seen in biological systems. In these cases, ammonium ions (protonated amines) are used instead of quaternary ammonium salts. An example is seen in the biosynthesis of nucleic acids where a biological base causes a Hofmann-like elimination of protonated adenylosuccinate to produce the alkene containing fumarate and adenosine monophosphate.



Worked Exercise 10.6.2

Predict the preferred product of a Hofmann elimination with the following molecule.



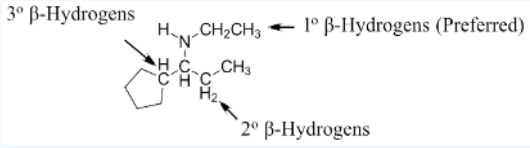
Strategy

The Hofmann elimination is an E2 reaction that converts an amine into an alkene and occurs with non-Zaitsev regiochemistry to form the less highly substituted double bond. To predict the product, look at the reactant and identify the positions from which elimination might occur (the positions two carbons away from nitrogen). Then, carry out an elimination using the most accessible hydrogen. In the present instance, there are three possible positions from which elimination might occur—one primary, one secondary, and one tertiary. The primary position is the most accessible and leads to the least highly substituted alkene, ethylene.

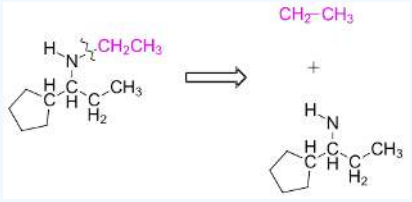
Answer

Predicting the product of a Hofmann elimination can be difficult so it is best done stepwise.

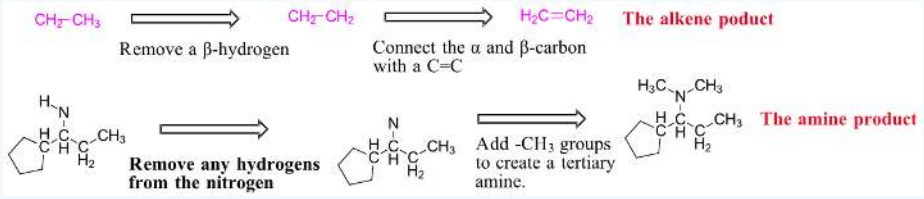
Step 1: Find the least sterically hindered beta hydrogens. Beta hydrogens are on the second carbon away from the nitrogen. The order of preferred hydrogens are $1^o > 2^o > 3^o$. If the molecule is presented as a line structure it is usually beneficial to convert to a condensed structure first.



Step 2: Break the C-N bond of the alkyl group which contains the preferred hydrogens. This will form two fragments.



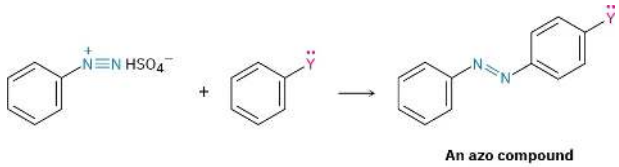
Step 3: Remove one of the original beta hydrogens in the alkyl fragment then draw a C=C between the alpha and beta carbon. This produces the alkene product of the Hofmann elimination. Sometimes the amine fragment of a Hofmann elimination is of interest. Remember that prior to elimination the amine is exhaustively alkylated with CH_3I. This means any hydrogens attached to amine will starting material will be removed and the amine product will have enough methyl ($-CH_3$) groups added to become a tertiary amine. In this case two methyl groups are added to the nitrogen. The end result are the two products of a Hofmann elimination.



Diazonium Coupling Reactions

A resonance description of diazonium ions shows that the positive charge is delocalized over the two nitrogen atoms. It is not possible for nucleophiles to bond to the inner nitrogen, but bonding (or coupling) of negative nucleophiles to the terminal nitrogen gives neutral azo compounds. As shown in the following equation, this coupling to the terminal nitrogen should be relatively fast and reversible. The azo products may exist as E / Z stereoisomers. In practice it is found that the E-isomer predominates at equilibrium.

Arenediazonium salts undergo a coupling reaction with activated aromatic rings such as phenols and arylamines to yield brightly colored azo compounds, $\mathbf{Ar–N=N–Ar'}$.



An azo compound

where Y = −OH or $-NR_2$

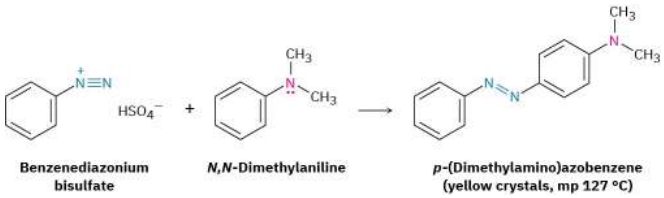
Unless these azo products are trapped or stabilized in some manner, reversal to the diazonium ion and slow nucleophilic substitution at carbon (with irreversible nitrogen loss) will be the ultimate course of reaction, as described in the previous section. For example, if phenyldiazonium bisulfate is added rapidly to a cold solution of sodium hydroxide a relatively stable solution of sodium phenyldiazoate (the conjugate base of the initially formed diazoic acid) is obtained. Lowering the pH of this solution regenerates phenyldiazoic acid (pK_a ca. 7), which disassociates back to the diazonium ion and eventually undergoes substitution, generating phenol.

$C_6H_5N_2^{(+)}\ HSO_4^{(-)}$ + NaOH (cold solution)	⇌	C
phenyldiazonium bisulfate		s o p h e n y l d i a z o a t e

Aryl diazonium salts may be reduced to the corresponding hydrazines by mild reducing agents such as sodium bisulfite, stannous chloride or zinc dust. The bisulfite reduction may proceed by an initial sulfur-nitrogen coupling, as shown in the following equation.

$Ar\text{-}N_2^{(+)}\ X^{(-)}$	$\xrightarrow{NaHSO_3}$	Ar-N=N-SO_3H	$\xrightarrow{NaHSO_3}$	Ar-NH-NH-SO_3H	$\xrightarrow{H_2O}$	Ar-NH_2 + H_2SO_4

The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles. The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes. Azobenzene (Y=Z=H) is light orange; however, the color of other azo compounds may range from red to deep blue depending on the nature of the aromatic rings and the substituents they carry. Azo compounds may exist as cis/trans isomer pairs, but most of the well-characterized and stable compounds are trans.



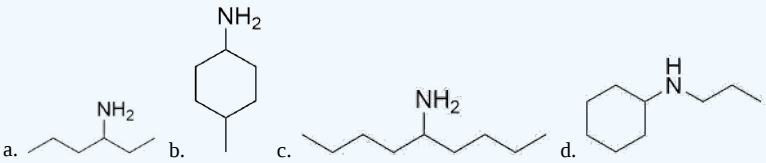
Some examples of azo coupling reactions are shown below. A few simple rules are helpful in predicting the course of such reactions:

I. At acid pH (< 6) an amino group is a stronger activating substituent than a hydroxyl group (i.e. a phenol). At alkaline pH (> 7.5) phenolic functions are stronger activators, due to increased phenoxide base concentration.
II. Coupling to an activated benzene ring occurs preferentially para to the activating group if that location is free. Otherwise ortho-coupling will occur.
III. Naphthalene normally undergoes electrophilic substitution at an alpha-location more rapidly than at beta-sites; however, ortho-coupling is preferred. See the diagram for examples of α / β notation in naphthalenes.

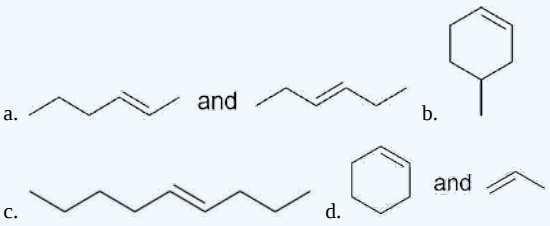
Exercises

Exercise 10.6.1

Draw the product for a Hofmann elimination for each of the following molecules.

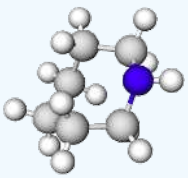


Answer

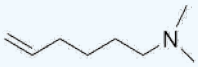


Exercise 10.6.2

Draw the product of a Hofmann elimination for the following molecule.


Azepane

Answer



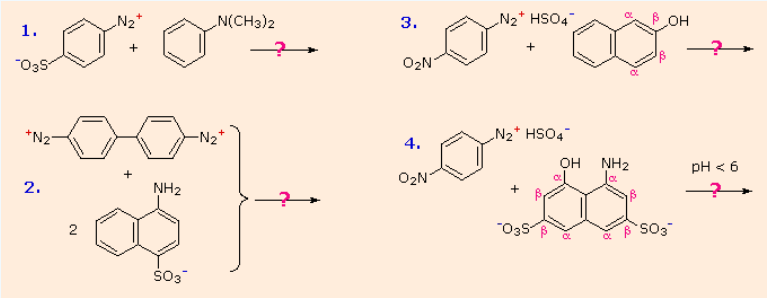
Exercise 10.6.3

Propose a synthesis of *p*-(dimethylamino)azobenzene with benzene as your only organic starting material.

Answer

1. HNO_3, H_2SO_4; 2. $SnCl_2$; 3a. 2 equiv. CH_3I; 3b. $NaNO_2$, H_2SO_4; 4. product of 3a + product of 3b

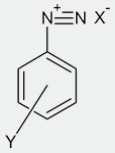
Exercise 10.6.4



Study Notes

The general process of reacting an aromatic amine with acetic anhydride, substituting it, and then hydrolyzing it is known as “protecting the amino group.”

An “arenediazonium salt”, often simply referred to as diazonium salts, is formed by the reaction of an aromatic amine with nitrous acid at 0–5°C, and has the structure shown below.



As mentioned in the textbook, arenediazonium salts are very useful intermediates from which a wide variety of aromatic compounds can be prepared. You should be thoroughly familiar with the use of diazonium salts to prepare each of the classes of compounds.

The presence of the letters “azo” in a compound’s name usually implies that a nitrogen-nitrogen double bond is present in its structure. Azo compounds t in which two aryl groups are joined by a –N=N– linkage are usually very colorful.

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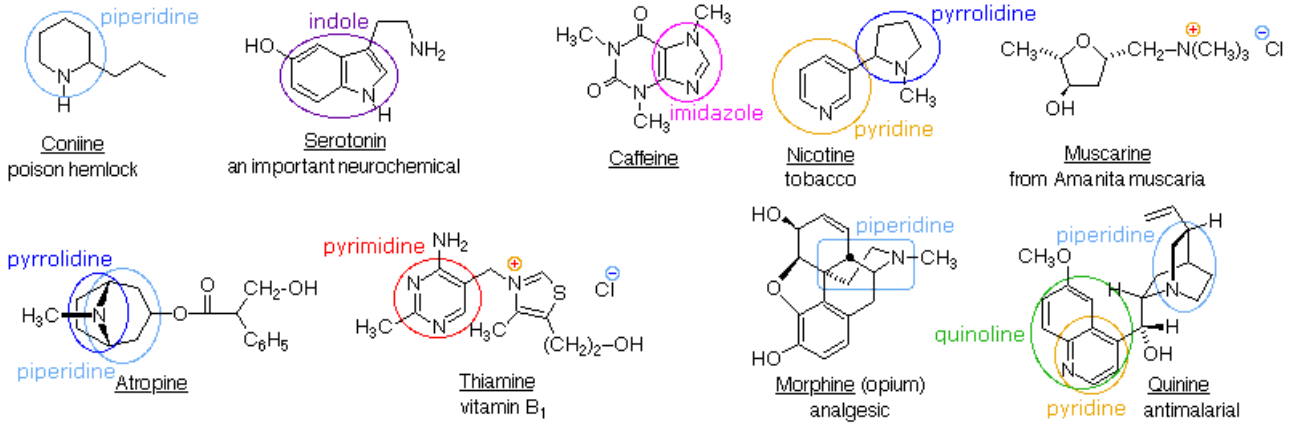
10.7: Heterocyclic Amines

Objectives

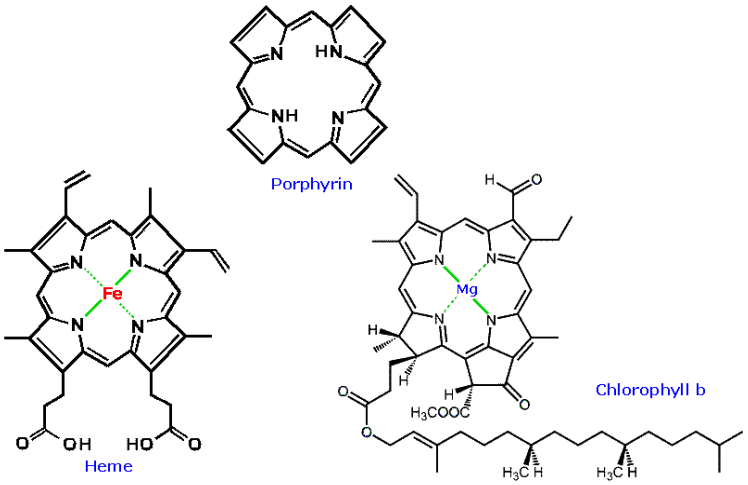
After completing this section, you should be able to

1. draw the structure of furan, pyrrole and imidazole.
2. use the Hückel $2n + 4$ rule to explain the aromaticity of pyrrole.
3. predict the product formed when pyrrole is subjected to an aromatic electrophilic substitution, such as nitration, etc.
4. write the detailed mechanism for the electrophilic aromatic substitution of pyrrole to account for the fact that substitution takes place at C2 rather than C3.
5. describe the geometry of the pyridine molecule.
6. account for the difference in basicity between pyridine, pyrrole and other amines.
7. explain why pyridine undergoes electrophilic substitution much less readily than does benzene.
8. identify the presence of a fused-ring heterocycle in a given structure.
9. make predictions about the chemical behaviour of the fused-ring heterocycle based on what you have learned about pyrrole, imidazole, pyridine and pyrimidine.

Heterocyclic structures containing nitrogen are found in many natural products. Examples of some nitrogen compounds, known as alkaloids because of their basic properties, were given in the amine chapter.

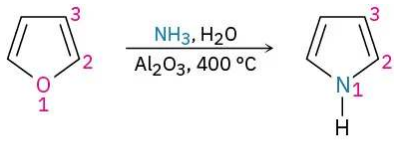


The porphyrin aromatic heterocycle contains multiple pyrrole ring strictures. The porphyrines, heme and chlorophyll b play vital parts in the metabolism of plants and animals.



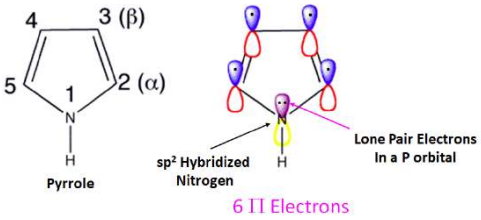
Pyrrole

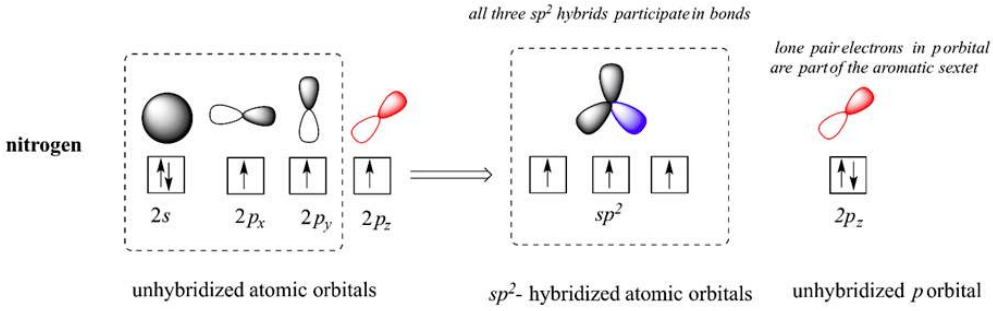
Pyrrole, the simplest five-membered unsaturated heterocyclic amine, is obtained commercially by treatment of furan with ammonia over an alumina catalyst at 400 °C. Furan, the oxygen-containing analog of pyrrole, is obtained by acid-catalyzed dehydration of the five-carbon sugars found in oat hulls and corncobs.



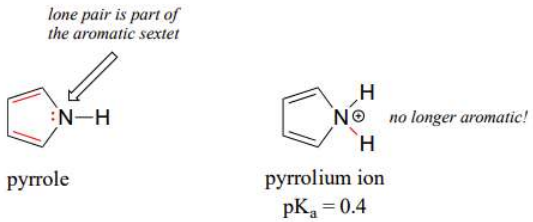
Furan **Pyrrole**

As discussed in **Section 2.6**, pyrrole has six pi electrons contributing to its aromaticity. Each carbon in pyrrole contributes one pi electron. The nitrogen in pyrrole contributes two pi electron by becoming sp^2 hybridized and placing its lone pair electrons into a p orbital.

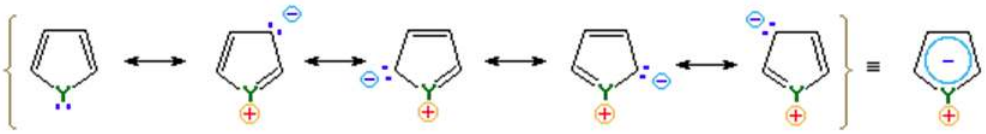


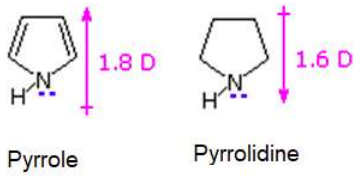


Because the nitrogen lone pair *is* part of the aromatic sextet, the electrons are very stable and are much less available for bonding to a proton (and if they *do* pick up a proton, the aromatic system is destroyed). For these reasons, pyrrole nitrogens are not strongly basic. Pyrrole is a very weak base: the conjugate acid is a strong acid with a pK_a of 0.4.

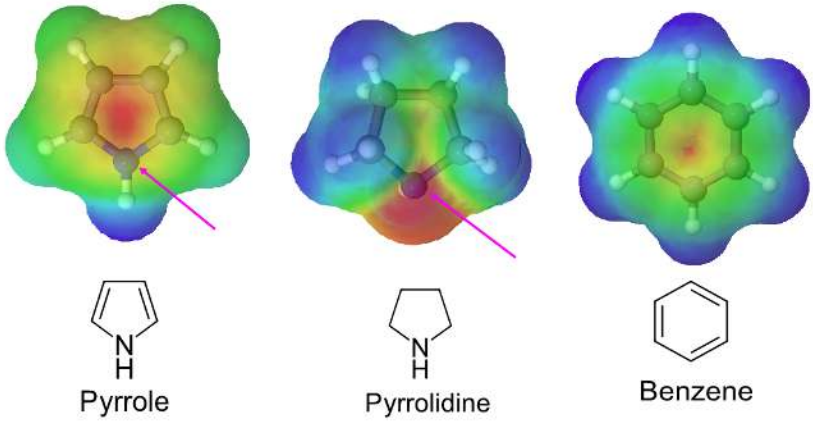


The involvement of the nitrogen lone pair electrons in pyrrole's aromatic conjugation creates charge separated structures not normally found for benzene. The combination of these resonance forms creates an overall separation of charge which increases the electron density around the ring carbons and decreases the electron density on the nitrogen. This effect has a number of ramifications. First is that pyrrole has a large dipole moment (1.8 D) pointing away from the ring nitrogen. This is in sharp contrast to the non-aromatic heterocycle pyrrolidine where the dipole moment (1.5 D) points towards the ring nitrogen.

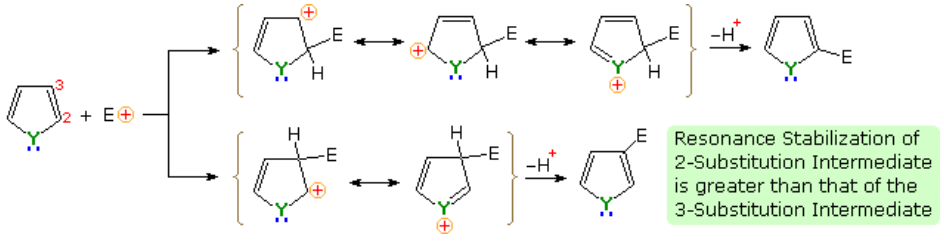




Due to the resonance forms, pyrrole has less electron density around it than the nitrogen in a typical alkyl amine. This agrees with fact that that pyrrole is a much weaker base than pyrrolidine. The electrostatic potential map of pyrrole (Shown Below) shows less electron density (shown as a red color) on the ring nitrogen when compared to its aliphatic equivalent, pyrrolidine. The map of pyrrole also shows that the resonance forms increase the electron density of pyrrole's ring carbons when compared to the ring carbons of benzene. The involvement of nitrogen's lone pair electrons in the aromaticity of pyrrole makes the ring activated towards electrophilic aromatic substitution.



Pyrrole can undergo many of the same electrophilic aromatic substitution reactions as benzene. Because of the activation of pyrrole's aromatic ring, many of these reactions are performed under a reduced temperature compared to a similar reaction with benzene. There is a clear preference for substitution at the 2-position (α) of the pyrrole ring. An explanation for the general α-selectivity of these substitution reactions is apparent from the mechanism outlined below. The intermediate formed by electrophile attack at C-2 is stabilized by charge delocalization to a greater degree than the intermediate from C-3 attack. From the Hammond postulate, we may then infer that the activation energy for substitution at the former position is less than that of the latter substitution.



Examples

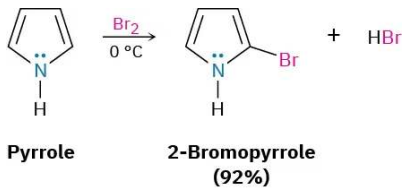


Figure 10.7.1: Electrophilic bromination of pyrrole. The intermediate produced by the reaction at C2.

Electrophilic substitutions normally occur at C2, the position next to the nitrogen, because reaction at this position leads to a more stable intermediate cation having three resonance forms, whereas reaction at C3 gives a less stable cation with only two resonance forms (Figure 10.7.1).

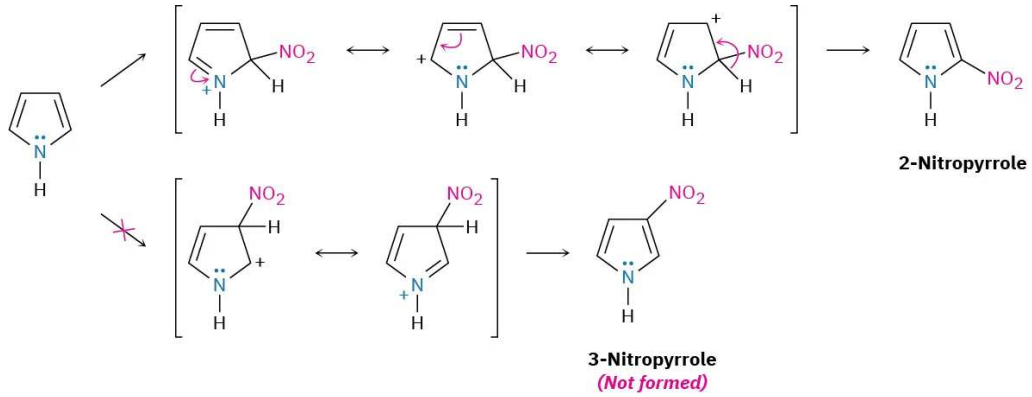
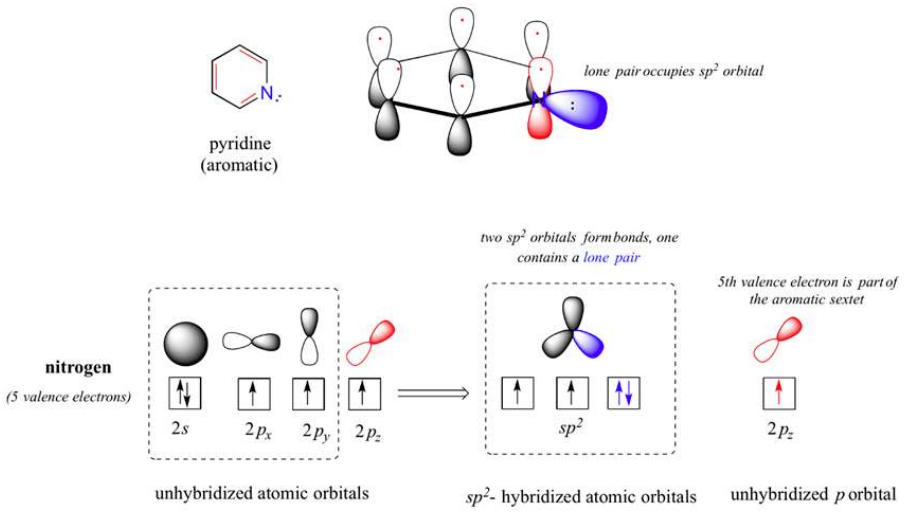


Figure 10.7.2: Electrophilic nitration of pyrrole. The intermediate produced by the reaction at C2 is more stable than that produced by the reaction at C3.

Pyridine

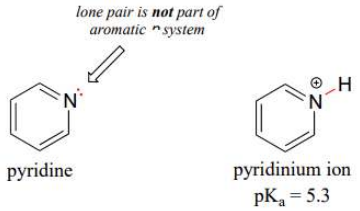
Pyridine is an example of a six-membered aromatic heterocycle. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair. The unhybridized *p* orbital contains a single electron, which is part of the 6 pi-electron aromatic system delocalized around the ring.



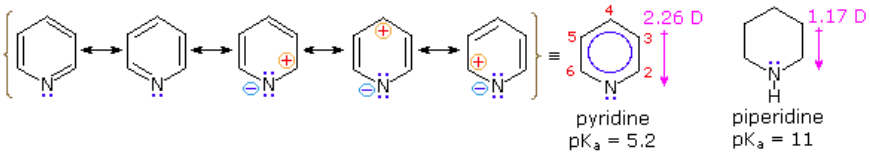
Pyridine's nitrogen lone pair occupies an sp^2-hybrid orbital, and *is not* part of the aromatic sextet. Thus, its electron pair is available for forming a bond to a proton, making pyridine's nitrogen atom (conjugate acid $pK_a = 5.25$) more basic than pyrrole's ($pK_a = 0.4$). However, pyridine is is less basic than a typical alkylamine (pK_a ~ 10-11). The difference is due to nitrogen hybridization. The lone

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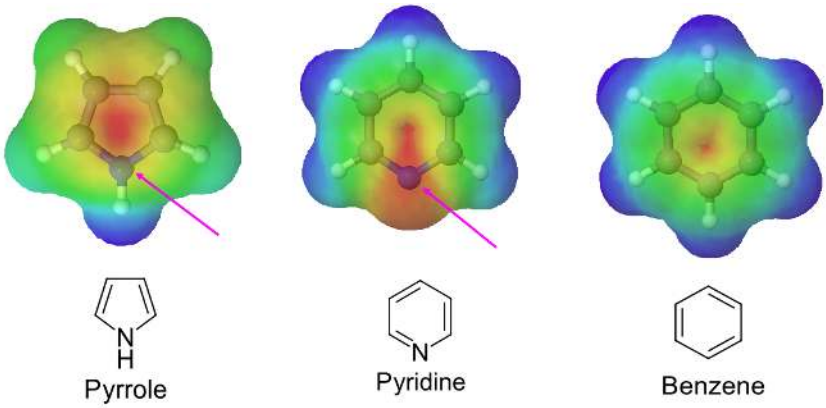
pair electrons on a pyridine nitrogen occupy an sp^2 hybrid orbital, while the lone pair electrons on an amine nitrogen occupy an sp^3 hybrid orbital. sp^2 orbitals are composed of one part *s* and two parts *p* atomic orbitals, meaning that they have about 33% *s* character. sp^3 orbitals, conversely, are only 25% *s* character (one part *s*, three parts *p)* . An *s* atomic orbital holds electrons closer to the nucleus than a *p* orbital, thus *s* orbitals are more electronegative than *p* orbitals. Therefore, sp^2 hybrid orbitals, with their higher s-character, are more electronegative than sp^3 hybrid orbitals. Lone pair electrons in the more electronegative sp^2 hybrid orbitals of pyridine are held more tightly to the nitrogen nucleus, and are therefore less 'free' to break away and form a bond to a proton - in other words, they are less basic.



The lack of involvement of pyrrole's nitrogen lone pair electrons in the aromatic conjugation creates charge separated structures not normally found for benzene. The combination of the resonance forms creates an overall charge separation which increases the electron density around the ring's nitrogen and decreases the electron density on the ring carbons. This causes pyridine to have a larger dipole moment (2.26 D) than its non-aromatic equivalent piperidine where the dipole moment (1.17 D). In both cases the dipole moment points towards the ring nitrogen.

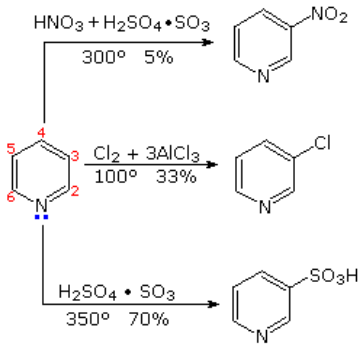


Due to the resonance forms, pyridine has more electron density around its nitrogen than in a typical alkyl amine. The electrostatic potential map of pyridine (Shown Below) shows more electron density (shown as a red color) on the ring nitrogen of pyridine when compared to pyrrole. The map of pyridine also shows that the resonance forms decrease the electron density of pyridine's ring carbons (Show as a blue/green color) when compared to those of benzene. The involvement of the nitrogen's lone pair electrons in the aromaticity of pyridine makes the ring deactivated towards electrophilic aromatic substitution.



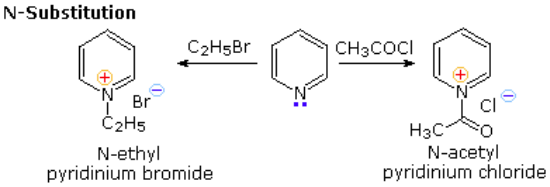
From the previous resonance description of pyridine, we expect this aromatic amine to undergo electrophilic substitution reactions far less easily than does benzene. Furthermore, the electrophilic reagents and catalysts employed in these reactions coordinate with the nitrogen electron pair, exacerbating the positive charge at positions 2,4 & 6 of the pyridine ring. When these reactions do occur then tend to produce the 3-substituted product. Three examples of the extreme conditions required for electrophilic substitution are shown below.

Example

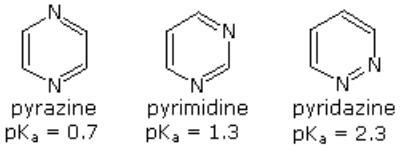


Friedel-Crafts reactions are not feasible because alkyl halides and acid halides prefer to react with pyridine nucleophilic ring nitrogen to provide a N-substituted product. As shown below, N-alkylation and N-acylation products may be prepared as stable crystalline solids in the absence of water or other reactive nucleophiles. Pyridine is a modest base (pK_a=5.2). Since the lone pair electrons on pyridine's nitrogen are not part of the aromatic sextet, the pyridinium species produced by N-substitution retains the aromaticity of pyridine.

Example



Other six-membered nitrogen contain aromatic heterocycles include pyrazine, pyrimidine, and pyridazine. The inductive effect of a second nitrogen makes all three of these heterocycles less basic than pyridine.

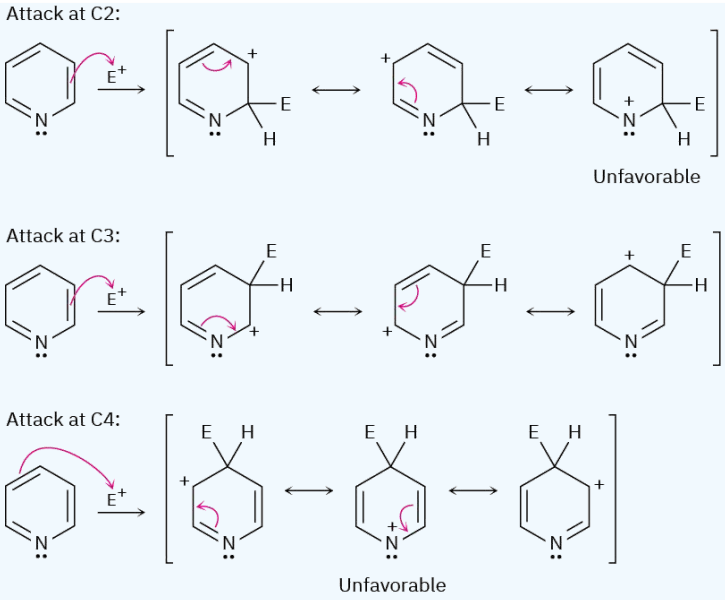


? Exercise 10.7.3

Pyridine reacts with electrophiles to product a 3-substituted product rather than a 2-substituted product or a 4-substituted product. Write a series of resonance forms for the cation intermediate formed during the reaction. Use these structures to explain the experimental result.

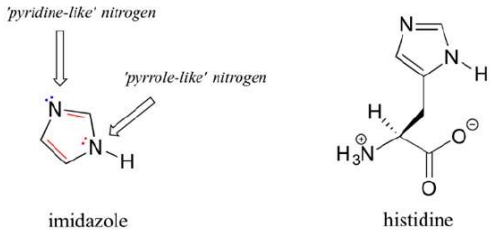
Answer

The resonance forms of 2-substitution places a positive charge on the ring nitrogen. The resonance forms of 3-substitution do not place a positive charge on the ring nitrogen. Having a positive charge on a nitrogen is less stable than on a carbon. Nitrogen is more electronegative than carbon making it less able to stabilize the positive charge. The 3-substituted product is preferred because it causes resonance forms which are more stable.



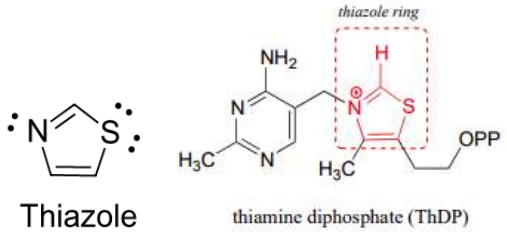
Imidazole

Imidazole is another important example of an aromatic heterocycle found in biomolecules - the side chain of the amino acid histidine contains an imidazole ring. The two nitrogens in imidazole are quite different. One nitrogen is pyrrole-like and donates its lone pair electrons, like pyrrole, to make imidazole aromatic. The other nitrogen is pyridine like and its lone pair electrons are contained is a sp^2 hybridized orbital. These lone pair electrons are readily available for bonding which imidazole (pK_a = 6.95) much more basic than pyrrole (pK_a = 0.4).



Thiazole

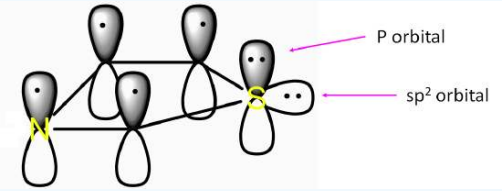
Thiazole is a five-membered sulfur containing aromatic ring system which is found in biological systems, such as thiamine diphosphate. Thiamine diphosphate (ThDP, sometimes also abbreviated TPP or ThPP) is a coenzyme which, like PLP, acts as an electron sink to stabilize key carbanion intermediates. The most important part of the ThDP molecule from a catalytic standpoint is its thiazole ring. The presence of sulfur in thiazole's aromatic ring makes its nitrogen less basic (pK_a = 2.44) than imidazole.



Exercise 10.7.1

Describe how thiazole is aromatic. Use an orbital picture and include the lone pair electrons on sulfur. Assume the sulfur is sp^2 hybridized.

Answer



Exercise 10.7.2

Would you expect a thiazole ring to be protonated at the physiological pH of 7.3 **(Section 10-6)**?

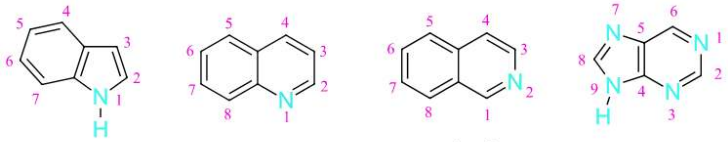
Answer

$7.3 = 2.44 + \log([RNH_2] / [RNH_3^+])$

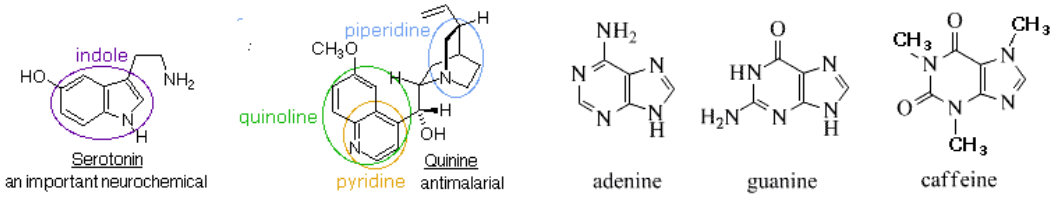
$([RNH_2] / [RNH_3^+]) = 7.2 \times 10^4$

. . . so, $[RNH_2] >> [RNH_3^+]$ so thiazole would be almost completely unprotonated at pH = 7.3.

Polycyclic Heterocycles



Indole, quinoline, isoquinoline, and purine are all polycyclic aromatic heterocycles commonly found in nature. Indole, quinoline, and isoquinoline all contain a hetrocyclic ring fused to benzene. Purine is made up to two heterocyclic rings, imidazole and pyrimidine, fused together. Quinoline is found in the antimalarial drug quinine. Indole is found in the neurotransmitter serotonin. The purine ring structure is found in adenine and guanine, two important parts of DNA and in the stimulant caffeine.



The pyridine-like nitrogen atom in quinoline and isoquinoline withdraws electrons making them both less reactive to electrophilic substitution than benzene. Likewise, quinoline (pK_a = 4.9) and isoquinoline (pK_a = 5.4) are less basic that a typical amine (pK_a ~10-11). Quinoline and isoquinoline can both undergo electrophilic aromatic substitution but substitution on the pyridine-like ring is avoided. Quinoline usually makes a roughly equal mixture of 5 and 8 substituted products. Isoquinoline favors making the 5 substituted product with a small amount of an 8 substituted side product.

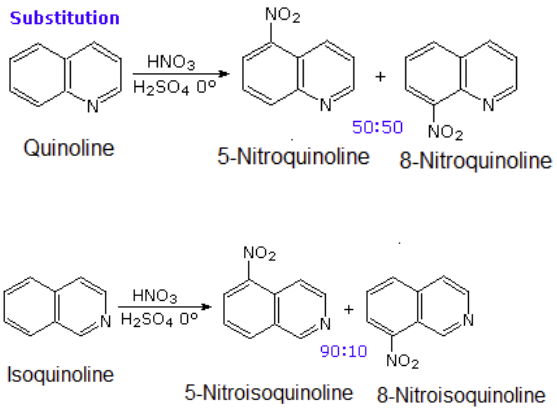


Figure 10.7.3: Electrophilic Aromatic Substitution of Quinoline vs Isoquinoline.

Indole has a ring nitrogen similar to to pyrrole. The lone pair electrons for this nitrogen are contained in a p orbital and are part of indole's 10 pi aromaticity. This makes indole relatively non-basic (pK_a = -2) and activated toward electrophilic substitution. Indole undergo electrophilic substitution more easily than benzene and substitution typically occurs at the 3 position on the pyrrole ring.

Example

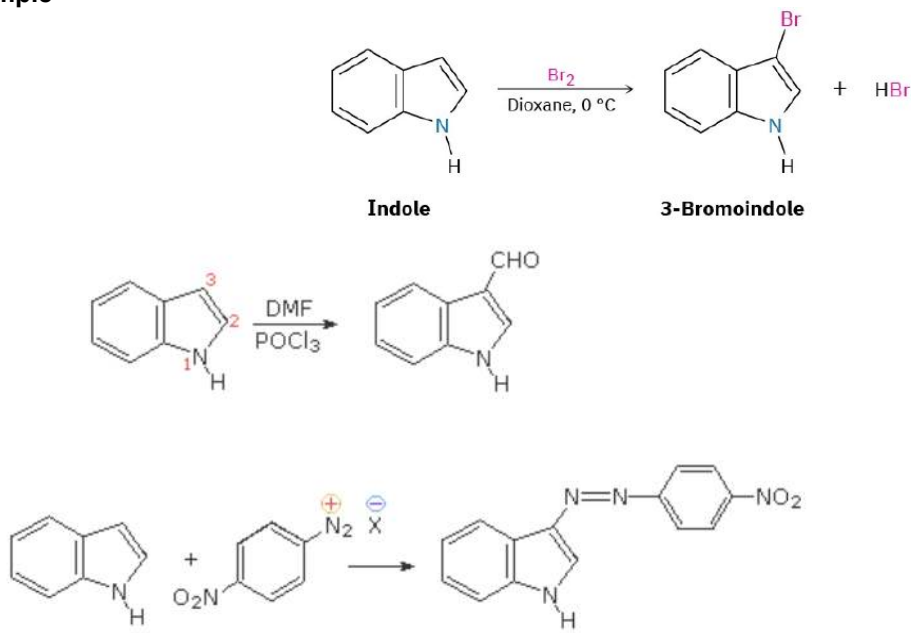
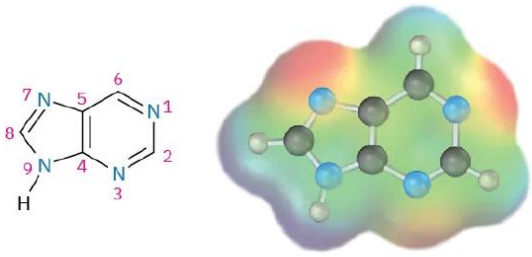


Figure 10.7.4: Electrophilic Aromatic Substitution of Indole. The intermediate produced by the reaction at C3 is more stable than that produced by the reaction at C2.

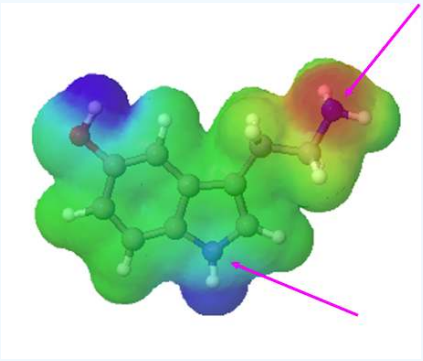
The purine ring system contain three pyridine-like nitrogens. This lone pair electrons of theses nitrogen are contained in sp^2 hybrid orbitals, making them not not part of purine's 10 pi aromaticity, allowing them to retain base-like characteristics. The lone pair electrons for the remaining, pyrrole-like, nitrogen are contained in a p orbital and are part of purine's 10 pi aromaticity. This makes the remaining nitrogen relatively non-basic.



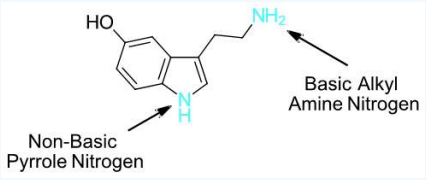
Purine

Exercise 10.7.4

Which nitrogen atom in the neurotransmitter serotonin is expected to be the most basic? Please explain your answer.



Answer

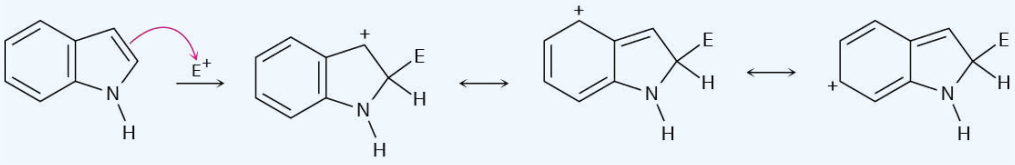


Exercise 10.7.5

Indole reacts with electrophiles at C3 rather than at C2. Draw resonance forms of the intermediate cations resulting from reaction at C2 and C3, and explain the observed results.

Answer

Reaction at C2 is disfavored because the aromaticity of the benzene ring is lost.



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10.8: Spectroscopy of Amines

Objectives

After completing this section, you should be able to

1. identify the region of the infrared spectrum that shows absorptions resulting from the N–H bonds of primary and secondary amines.
2. describe a characteristic change that occurs in the infrared spectrum of an amine when a small amount of mineral acid is added to the sample.
3. use ^{1}H NMR spectra in determining the structure of an unknown amine.
4. use the “nitrogen rule” of mass spectrometry to determine whether a compound has an odd or even number of nitrogen atoms in its structure.
5. predict the prominent peaks in the mass spectrum of a given amine.
6. use the mass spectrum of an unknown amine in determining its structure.

Key Terms

Make certain that you can define, and use in context, the key term below.

- nitrogen rule

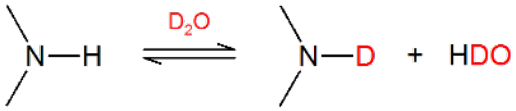
Study Notes

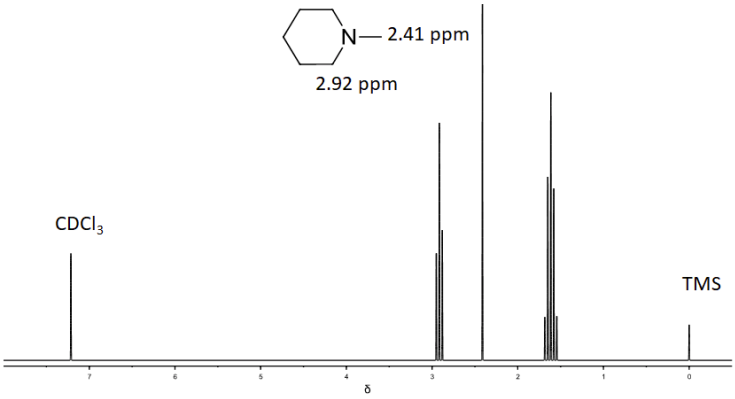
You should note the spectroscopic similarities between amines and alcohols: both have infrared absorptions in the 3300–3360 cm^{-1} region, and in both cases, the proton that is attached to the heteroatom gives rise to an often indistinct signal in the ^{1}H NMR spectrum.

^{1}H NMR of Amines

The hydrogens attached to an amine show up ~ 0.5-5.0 ppm. The location is dependent on the amount of hydrogen bonding and the sample's concentration. The hydrogens on carbons directly bonded to an amine typically appear ~2.3-3.0 ppm. These hydrogens are deshielded by the electron-withdrawing effects of nitrogen and appear downfield in an NMR spectra compared to alkane hydrogens.

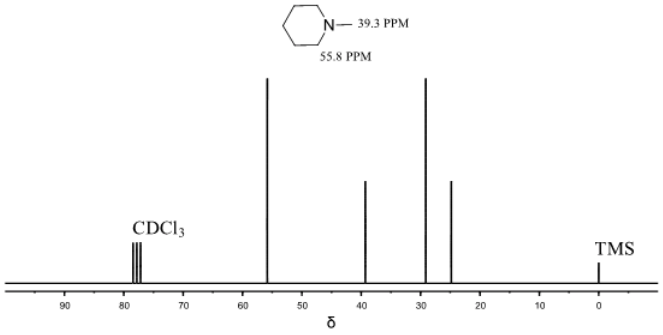
Addition of D_2O will normally cause all hydrogens on non-carbon atoms to exchange with deuterium, thus making these resonances "disappear." Addition of a few drops of D_2O causing a signal to vanish can help confirm the presence of -NH.





^{13}C NMR of Amines

Carbons directly attached to the nitrogen appear in 10-65 ppm region of a ^{13}C NMR spectra. They are shifted slightly downfield compared to alkane carbons due to the electron-withdrawing effect of nitrogen again causing deshielding.



IR of Amines

The infrared spectra of several amines are shown in the following table. Some characteristic absorptions for C-H stretching and aromatic ring substitution are also marked, but not colored.

Amine Class	Stretching Vibrations	Bending Vibrations
Primary (1°)	The N-H stretching absorption is less sensitive to hydrogen bonding than are O-H absorptions. In the gas phase and in dilute CCl_4 solution free N-H absorption is observed in the 3400 to 3500 cm^{-1} region. Primary aliphatic amines display two well-defined peaks due to asymmetric (higher frequency) and symmetric N-H stretching, separated by 80 to 100 cm^{-1}. In aromatic amines these absorptions are usually 40 to 70 cm^{-1} higher in frequency. A smaller absorption near 3200 cm^{-1} (shaded orange in the spectra) is considered to be the result of interaction between an overtone of the 1600 cm^{-1} band with the symmetric N-H stretching band. C-N stretching absorptions are found at 1200 to 1350 cm^{-1} for aromatic amines, and at 1000 to 1250 cm^{-1} for aliphatic amines.	Strong in-plane NH_2 scissoring absorptions at 1550 to 1650 cm^{-1}, and out-of-plane wagging at 650 to 900 cm^{-1} (usually broad) are characteristic of 1°-amines.
Secondary (2°)	Secondary amines exhibit only one absorption near 3420 cm^{-1}. Hydrogen bonding in concentrated liquids shifts these absorptions to lower frequencies by about 100 cm^{-1}. Again, this absorption appears at slightly higher frequency when the nitrogen atom is bonded to an aromatic ring. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1}(aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	A weak N-H bending absorption is sometimes visible at 1500 to 1600 cm^{-1}. A broad wagging absorption at 650 to 900 cm^{-1} may be discerned in liquid film samples.
Tertiary (3°)	No N-H absorptions. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1} (aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	Aside from the C-N stretch noted on the left, these compounds have spectra characteristic of their alkyl and aryl substituents.

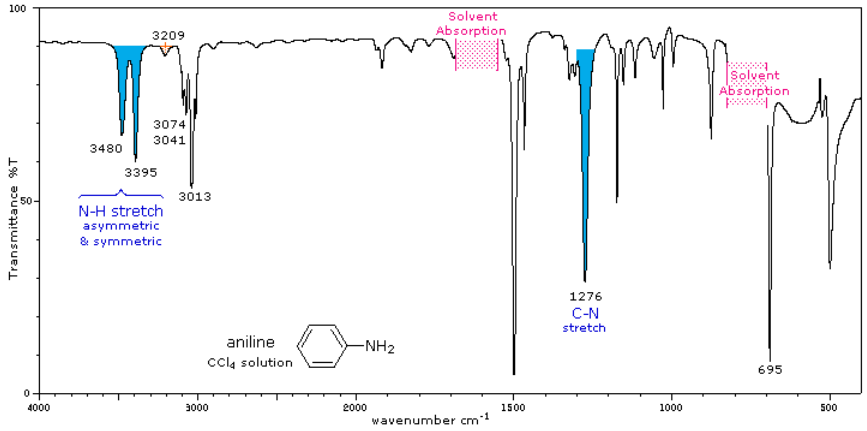


Figure 1: IR spectrum of a Primary Amine "cyclohexylamine".

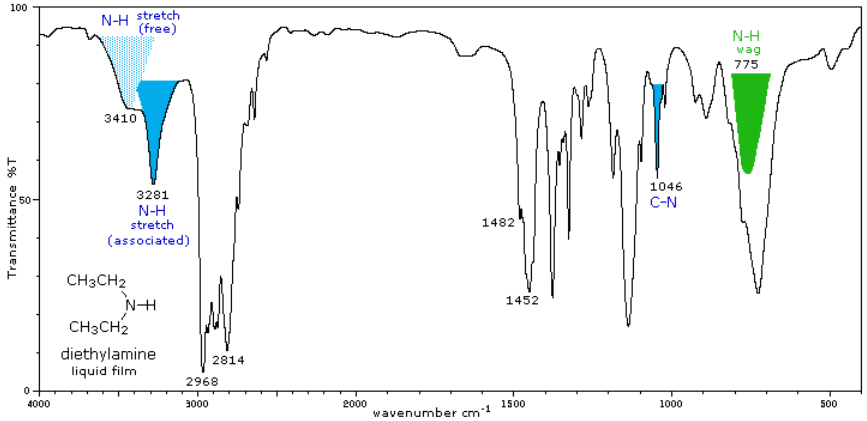


Figure 2: IR spectrum of a Secondary Amine "diethylamine".

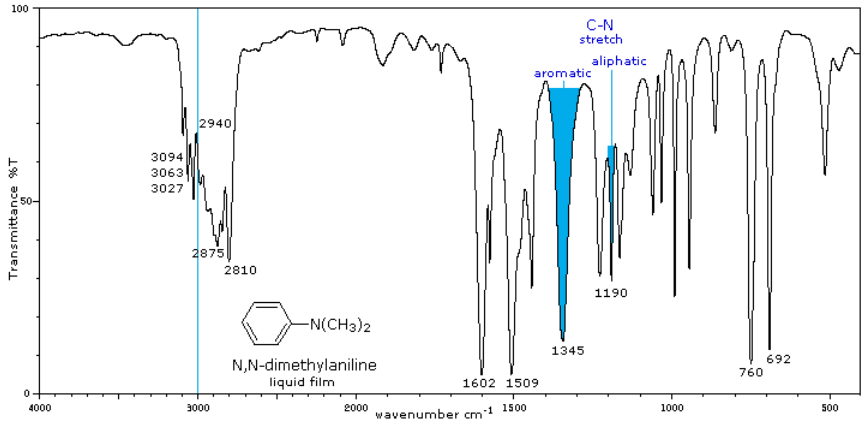


Figure 3: IR spectrum of a Terciary Amine "N,N-dimethylamine".

UV/Vis Spectra of Amines

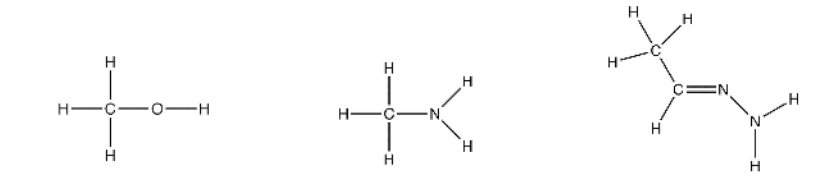
Alky Amines absorb in the region around 200 nm, which makes them of little value. In arylamines, the lone pair electron on the nitrogen interacts with the pi electron system of the aromatic ring, shifting the ring's absorption to longer wavelengths. An example is benzene's lambda max of 256 nm, while aniline's lambda max of 280 nm.

Mass Spectra of Amines

Nitrogen Rule

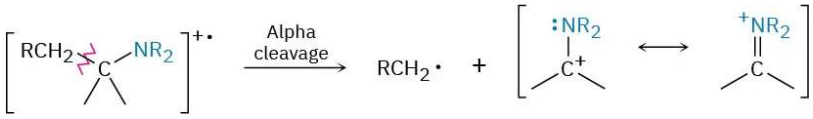
The nitrogen rule states that a molecule that has no or even number of nitrogen atoms has an even nominal mass, whereas a molecule that has an odd number of nitrogen atoms has an odd nominal mass.

Example



Fragmentation Patterns

The molecular ion peak is an odd number any time there is an odd number of nitrogen atoms in a molecule. The mass spectra of amines is dominated by alpha-cleavage which produces an alkyl radical on a resonance stabilized nitrogen containing cation. Secondary and tertiary amines have the possibility of multiple alpha-cleavages.



As an example of a primary amine, the mass spectrum of N-Butylamine ($C_4H_{11}N$, MW = 73.13) shows a peak at m/z = 73 corresponding to the molecular ion which is an odd number; and at *m*/*z* = 30, corresponding to the *α* cleavage.

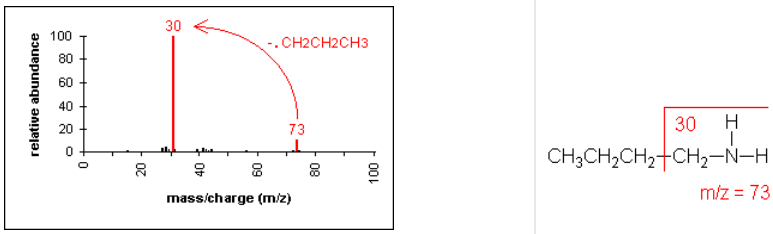


Figure 10.8.4: Mass spectrum of a primary amine "*N*-butylamine". The *α* cleavage leads to the observed fragment ion at *m*/*z* = 30.

As an example, the mass spectrum of *N*-ethylpropylamine shown in Figure 10.8.4 has peaks at *m*/*z* = 58 and *m*/*z* = 72, corresponding to the two possible modes of *α* cleavage.

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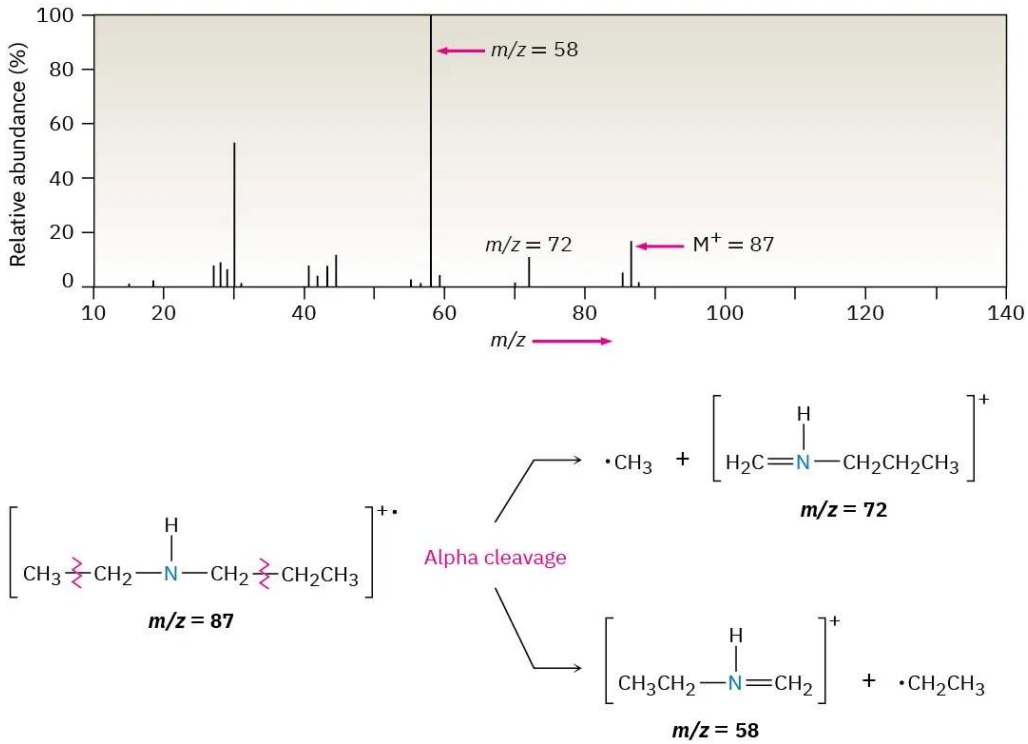


Figure 10.8.5: Mass spectrum of a secondary amine "*N*-ethylpropylamine". The two possible modes of α cleavage lead to the observed fragment ions at *m*/*z* = 58 and *m*/*z* = 72.

Another example of a secondary amine N-Methylbenzylamine ($C_8H_{11}N$) with MW = 121.18. Again, the molecular ion peak is an odd number. The base peak (m/z = 44) is from the C-C cleavage adjacent to the C-N bond. Other important peaks come from the cleavage of the N-H bond (m/z = 120) and cleavage at the benzylic position (m/z = 91).

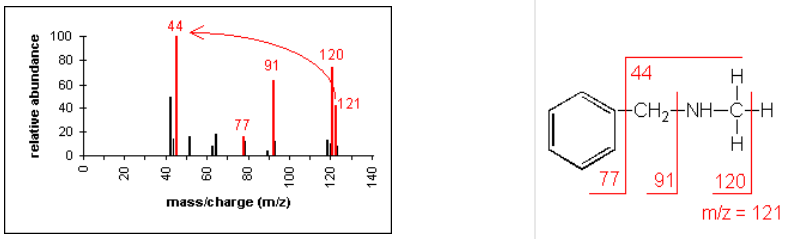
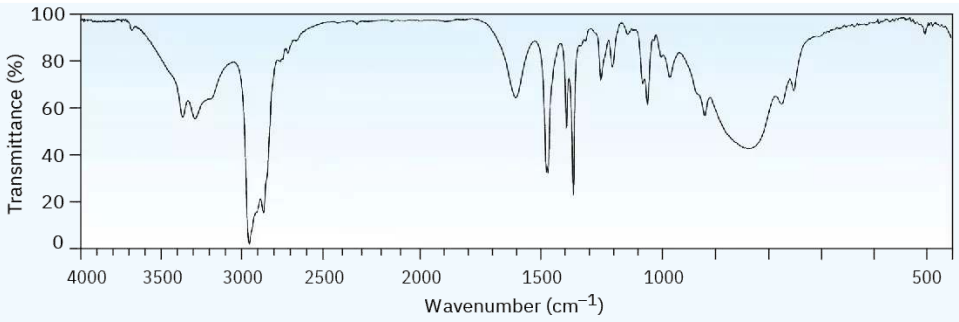
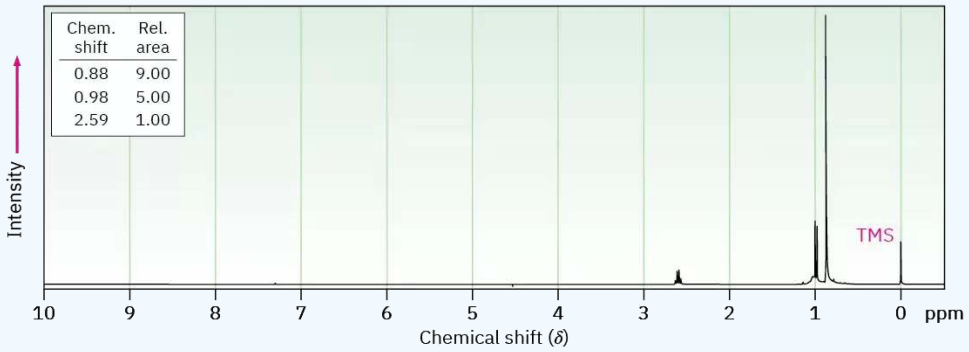


Figure 10.8.6: Mass spectrum of a secondary amine "*N*-Methylbenzylamine". The observed fragment ions are produced by α cleavage, cleavage of the N-H bond, and the cleavage at the benzylic position.

? Exercise 10.8.1

Compound **A**, $C_6H_{12}O$, has an IR absorption at 1715 cm^{-1} and gives compound **B**, $C_6H_{15}N$, when treated with ammonia and $NaBH_4$. The IR and ^1H NMR spectra of **B** are shown. What are the structures of **A** and **B**?





Answer

$(CH_3)_3CCOCH_3 \longrightarrow (CH_3)_3CCH(NH_2)CH_3$

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10.9: Drugs and the Mind

Learning Objectives

- Describe how neurotransmitters work.
- Know the different types of drugs and their functions.

Art in a Cup

Who knew that a cup of coffee could also be a work of art? A talented barista can make coffee look as good as it tastes. If you are a coffee drinker, you probably know that coffee can also affect your mental state. It can make you more alert and may improve your concentration. That's because the caffeine in coffee is a psychoactive drug. In fact, caffeine is the most widely consumed psychoactive substance in the world. In North America, for example, 90 percent of adults consume caffeine daily.



Figure 10.9.1: Murano Coffee with decoration on the surface.

Psychoactive drugs are substances that change the function of the brain and result in alterations of mood, thinking, perception, and/or behavior. Psychoactive drugs may be used for many purposes, including therapeutic, ritual, or recreational purposes. Besides caffeine, other examples of psychoactive drugs include cocaine, LSD, alcohol, tobacco, codeine, and morphine. Psychoactive drugs may be legal prescription medications (e.g., codeine and morphine), legal nonprescription drugs (e.g., alcohol and tobacco), or illegal drugs (cocaine and LSD).



Figure 10.9.2: Advertising for legal psychoactive drugs is ubiquitous.

Cannabis (or marijuana) is also a psychoactive drug, but its status is in flux, at least in the United States. Depending on the jurisdiction, cannabis may be used recreationally and/or medically, and it may be either legal or illegal. Legal prescription medications such as opioids are also used illegally by increasingly large numbers of people. Some legal drugs, such as alcohol and nicotine, are readily available almost everywhere, as illustrated by the sign pictured in Figure 10.9.2.

Classes of Psychoactive Drugs

Psychoactive drugs are divided into different classes according to their pharmacological effects. Several classes are listed below, along with examples of commonly used drugs in each class.

- Stimulants are drugs that stimulate the brain and increase alertness and wakefulness. Examples of stimulants include caffeine, nicotine, cocaine, and amphetamines such as Adderall.
- Depressants are drugs that calm the brain, reduce anxious feelings, and induce sleepiness. Examples of depressants include ethanol (in alcoholic beverages) and opioids such as codeine and heroin.
- Anxiolytics are drugs that have a tranquilizing effect and inhibit anxiety. Examples of anxiolytic drugs include benzodiazepines such as diazepam (Valium), barbiturates such as phenobarbital, opioids, and antidepressant drugs such as sertraline (Zoloft).
- Euphoriants are drugs that bring about a state of euphoria, or intense feelings of well-being and happiness. Examples of euphoriants include the so-called club drug MDMA (ecstasy), amphetamines, ethanol, and opioids such as morphine.
- Hallucinogens are drugs that can cause hallucinations and other perceptual anomalies. They also cause subjective changes in thoughts, emotions, and consciousness. Examples of hallucinogens include LSD, mescaline, nitrous oxide, and psilocybin.
- Empathogens are drugs that produce feelings of empathy, or sympathy with other people. Examples of empathogens include amphetamines and MDMA.



Figure 10.9.3: Ecstasy (MDMA) is most commonly taken in tablet form, like the colorful and decorated tablets shown here.

Many psychoactive drugs have multiple effects so they may be placed in more than one class. An example is MDMA, pictured below, which may act both as a euphoriant and as an empathogen. In some people, MDMA may also have stimulant or hallucinogenic effects. As of 2016, MDMA had no accepted medical uses, but it was undergoing testing for use in the treatment of post-traumatic stress disorder and certain other types of anxiety disorders.

Mechanisms of Action

Psychoactive drugs generally produce their effects by affecting brain chemistry, which in turn may cause changes in a person's mood, thinking, perception, and/or behavior. Each drug tends to have a specific action on one or more neurotransmitters or neurotransmitter receptors in the brain. Generally, they act as either agonists or antagonists.

- **Agonists** are drugs that increase the activity of particular neurotransmitters. They might act by promoting the synthesis of the neurotransmitters, reducing their reuptake from synapses, or mimicking their action by binding to receptors for the neurotransmitters.
- **Antagonists** are drugs that decrease the activity of particular neurotransmitters. They might act by interfering with the synthesis of the neurotransmitters or by blocking their receptors so the neurotransmitters cannot bind to them.

Consider the example of the neurotransmitter GABA. This is one of the most common neurotransmitters in the brain, and it normally has an inhibitory effect on cells. GABA agonists, which increase its activity, include ethanol, barbiturates, and benzodiazepines, among other psychoactive drugs. All of these drugs work by promoting the activity of GABA receptors in the brain.

Chemistry of the Nervous System

Neurons, also called nerve cells, are electrically excitable cells that are the main functional units of the nervous system. Their function is to transmit nerve impulses. They are the only type of human cells that can carry out this function.

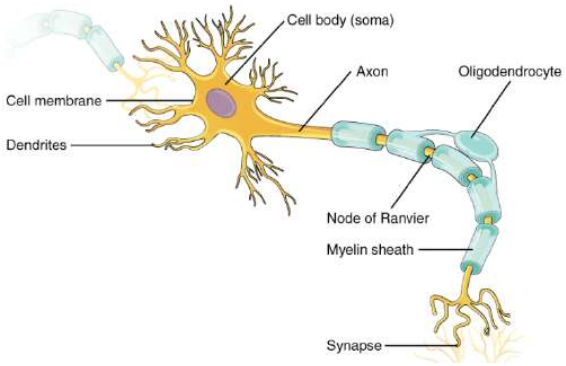


Figure 10.9.4 Parts of a neuron.

The main parts of a neuron are labeled in Figure 10.9.4 and described below.

- The **cell body** is the part of a neuron that contains the cell nucleus and other cell organelles. It is usually quite compact, and may not be much wider than the nucleus.
- **Dendrites** are thin structures that are extensions of the cell body. Their function is to receive nerve impulses from other cells and carry them to the cell body. A neuron may have many dendrites, and each dendrite may branch repeatedly to form a dendrite "tree" with more than 1,000 "branches." The end of each branch can receive nerve impulses from another cell, allowing a given neuron to communicate with tens of thousands of other cells.
- The **axon** is a long, thin extension of the cell body. It transmits nerve impulses away from the cell body and toward other cells. The axon branches at the end, forming multiple axon terminals. These are the points where nerve impulses are transmitted to other cells, often to the dendrites of other neurons. An area called a synapse occurs at each axon terminal. Synapses are complex membrane junctions that transmit signals to other cells. An axon may branch hundreds of times, but there is never more than one axon per neuron.
- Spread out along axons, especially the long axons of nerves, are many sections of the **myelin sheath.** These are lipid layers that cover sections of the axon. The myelin sheath is a very good electrical insulator, similar to the plastic or rubber that encases an electrical cord.
- Regularly spaced gaps between sections of myelin sheath occur along the axon. These gaps are called **nodes of Ranvier**, and they allow the transmission of nerve impulses along the axon. Nerve impulses skip from node to node, allowing nerve impulses to travel along the axon very rapidly.
- A Schwann cell (also on an axon) is a type of glial cell. Its function is to produce the myelin sheath that insulates axons in the peripheral nervous system. In the central nervous system, a different type of glial cell, called an oligodendrocyte, produces the myelin sheath.

Neurotransmission is the process by which signaling molecules called neurotransmitters are released by the axon terminal of a neuron (the presynaptic neuron), and bind to and react with the receptors on the dendrites of another neuron (the postsynaptic neuron) a short distance away. Synapses are functional connections between neurons, or between neurons and other types of cells. The **synaptic cleft** —also called **synaptic gap**— is a gap between the pre- and postsynaptic cells that is about 20 nm (0.02 μ) wide. The small volume of the cleft allows neurotransmitter concentration to be raised and lowered rapidly.

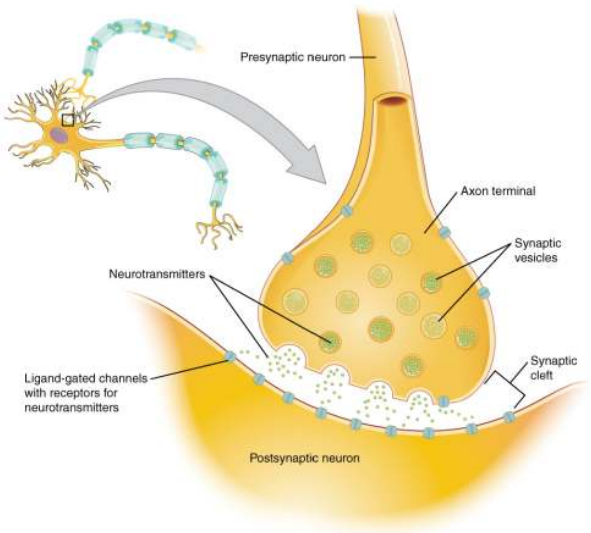


Figure 10.9.5 The synapse. The synapse is a connection between a neuron and its target cell (which is not necessarily a neuron).

Neurotransmiters

Neurotransmitters are endogenous chemicals that enable neurotransmission. It is a type of chemical messenger which transmits signals across a chemical synapse, such as a neuromuscular junction, from one neuron (nerve cell) to another "target" neuron, muscle cell, or gland cell.

Biochemical Theories of Brain Diseases

One theory that explains mental illness incorporates the various amounts of neurotransmitters. Using this theory, the lack or excess of specific neurotransmitters can be associated with depression, anxiety, bipolar disorder, or schizophrenia. Other disorders or health conditions, namely Attention Deficient Hyperactivity Disorder (ADHD) and Parkinson's Disease have also been linked with varying levels of neurotransmitters.

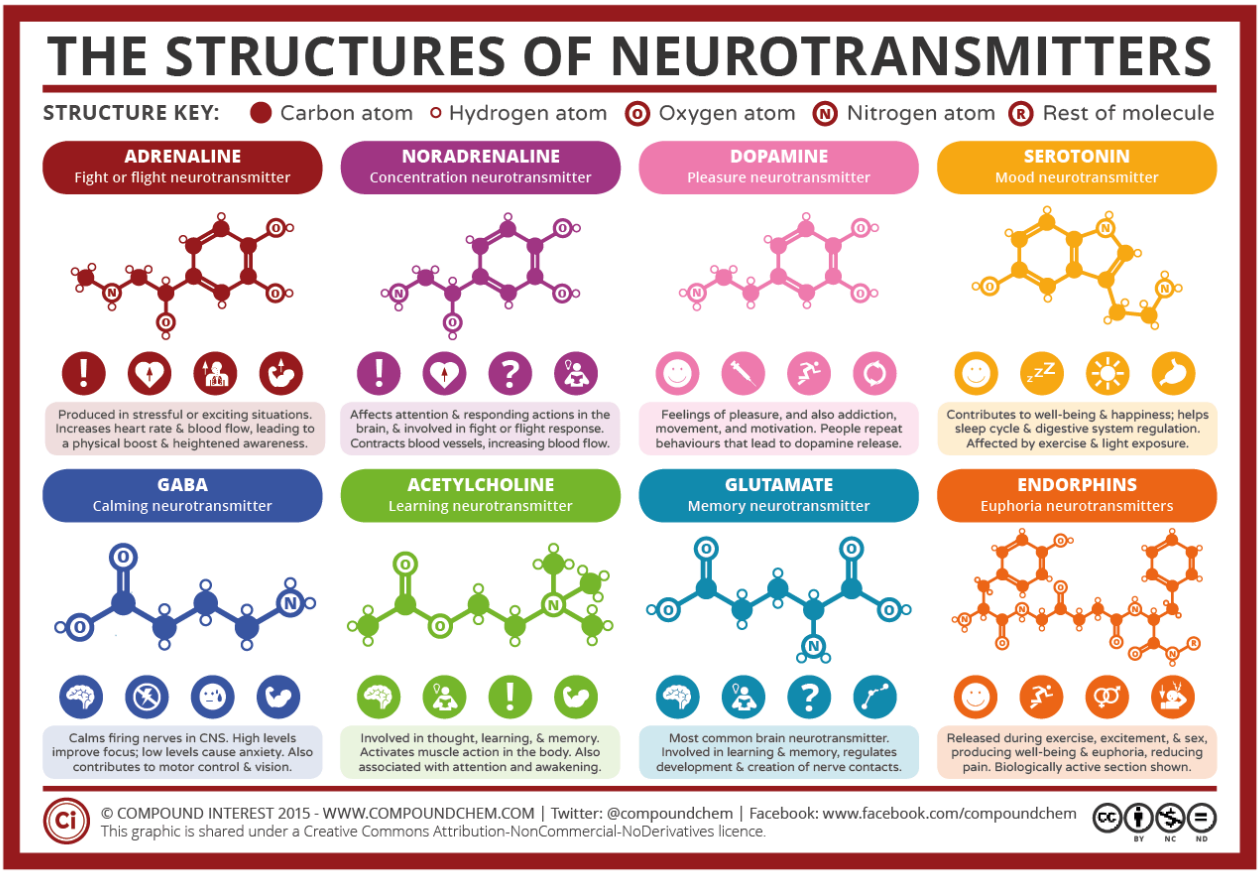


Figure 10.9.6: The Structures of Neurotransmitters.(CC BY-NC-ND; Andy Brunning)

The Noradrenaline neurotransmitter is also called norepinephrine. When evaluating antidepressants or other mental health medications, it is important to be aware of this terminology. For a brief overview of the correlation between neurotransmitters and mental health, watch the video below.



Mental health conditions can result from a person's life experiences and/or genetics. Sometimes, drug usage or brain trauma can trigger mental illness. It is important to note all health conditions that are present in your family tree (biological). Also, recognizing emotional trauma and then seeking counseling/medical treatment is important for navigating a mental health condition.



Figure 10.9.7: Nason family picture circa 1905. Image courtesy of Elizabeth R. Gordon

Depression symptoms

Can be short or long-term. Experience-sadness, sleeping and eating issues, withdrawal, feelings of hopelessness, loss of interest/pleasure, lack of energy, feelings of worthlessness/guilt, slowed processing, trouble concentrating, frequent thought of suicide/death, anxiety, and unexplained health problems.

Treatments for depression

psychotherapy, brain stimulation, medication, exercise, light therapy. Discussions to have with dr: meds/vitamins you are on, self-medication is not answer, stopping antidepressants without assistance, and report problems with meds. Limit alcohol and refrain from illicit and scheduled drugs. FDA black-box warning for antidepressants in people under 25.

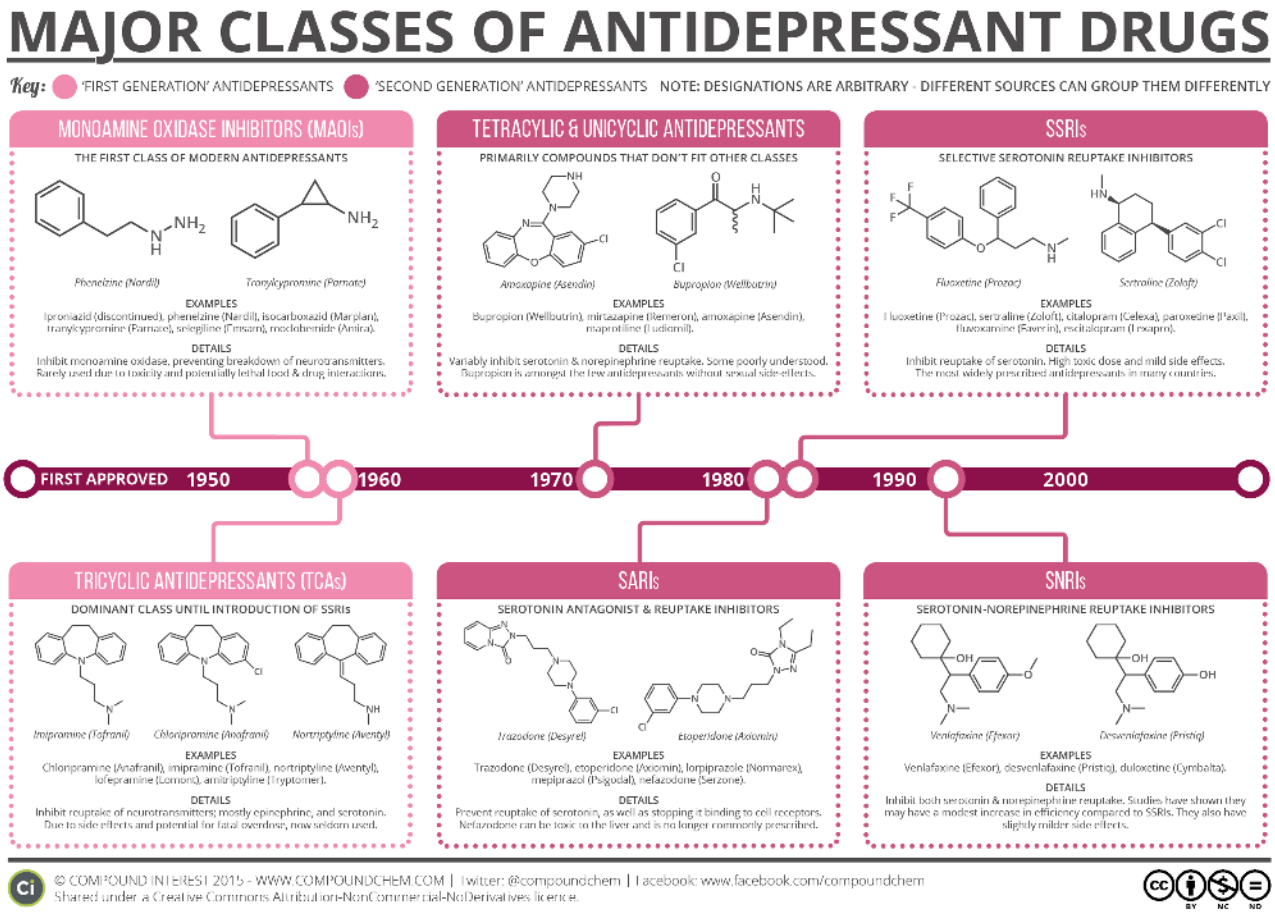


Figure 10.9.8: Major Classes of Antidepressant Drugs.(CC BY-NC-ND; Andy Brunning)

Finding the correct antidepressant

Trial and Error-take for six weeks, then wean, and start another. Since the early 2000's, Mayo Clinic has been researching gene technology. Test is now offered by Assurex Health and called Genesight.

https://genesight.com/gene-test-for-...surex%20Health

Common Side Effects of Antidepressants

This carry varies with the patient and type of medicine. Most common include weight gain, fatigue, dizziness, loss of sexual desire, nausea, dry mouth, blurred vision, agitation, insomnia, and constipation.

Support and information regarding mental health conditions.

National Alliance on Mental Illness

Figure 10.9.9: Official logo of the National Alliance on Mental Illness. (National Alliance on Mental Illness, http://www.nami.org/Template.cfm?Sec...ntentID=121014)

Anesthetics

An **anesthetic** or **anaesthetic** is a drug used to induce anesthesia - in other words, to result in a temporary loss of sensation or awareness. They may be divided into two broad classes: general anesthetics, which result in a reversible loss of consciousness, and local anesthetics, which cause a reversible loss of sensation for a limited region of the body without necessarily affecting consciousness.

A wide variety of drugs are used in modern anesthetic practice. Many are rarely used outside anesthesiology, but others are used commonly in various fields of healthcare. Combinations of anesthetics are sometimes used for their synergistic and additive therapeutic effects. Adverse effects, however, may also be increased. Anesthetics are distinct from analgesics, which block only sensation of painful stimuli.

General Anesthetics

General anesthetics are often defined as compounds that induce a loss of consciousness in humans or loss of righting reflex in animals. Clinical definitions are also extended to include the lack of awareness to painful stimuli, sufficient to facilitate surgical applications in clinical and veterinary practice. General anesthetics do not act as analgesics and should also not be confused with sedatives. General anesthetics are a structurally diverse group of compounds whose mechanisms encompasses multiple biological targets involved in the control of neuronal pathways. The precise workings are the subject of some debate and ongoing research.

General anesthetics elicit a state of general anesthesia. It remains somewhat controversial regarding how this state should be defined. General anesthetics, however, typically elicit several key reversible effects: immobility, analgesia, amnesia, unconsciousness, and reduced autonomic responsiveness to noxious stimuli.

Mode of administration

Drugs given to induce general anesthesia can be either as gases or vapors (inhalational anesthetics), or as injections (intravenous anesthetics or even intramuscular). All of these agents share the property of being quite hydrophobic (i.e., as liquids, they are not freely miscible—or mixable—in water, and as gases they dissolve in oils better than in water). It is possible to deliver anesthesia solely by inhalation or injection, but most commonly the two forms are combined, with an injection given to induce anesthesia and a gas used to maintain it.

Inhalation

General anesthetics are frequently administered as volatile liquids or gases (Figure 10.9.6). Inhalational anesthetic substances are either volatile liquids or gases, and are usually delivered using an anesthesia machine. An anesthesia machine allows composing a mixture of oxygen, anesthetics and ambient air, delivering it to the patient and monitoring patient and machine parameters. Liquid anesthetics are vaporized in the machine.

Many compounds have been used for inhalation anesthesia, but only a few are still in widespread use. Desflurane, isoflurane and sevoflurane are the most widely used volatile anesthetics today. They are often combined with nitrous oxide. Older, less popular, volatile anesthetics, include halothane, enflurane, and methoxyflurane. Researchers are also actively exploring the use of xenon as an anesthetic.

Figure 10.9.10 General anesthetics are frequently administered as volatile liquids or gases.

Injection

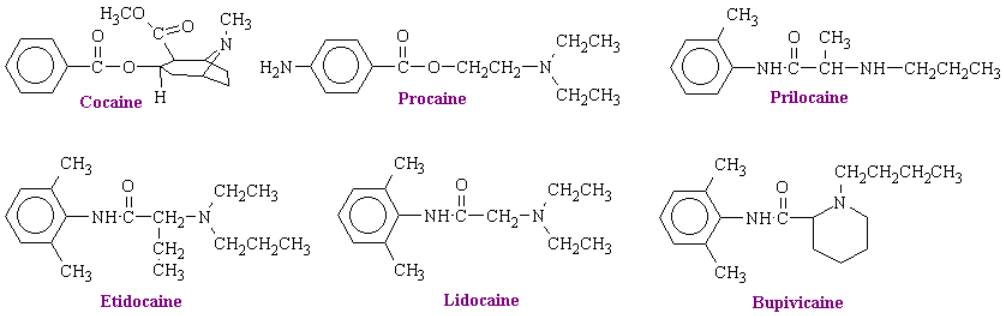
Injectable anesthetics are used for the induction and maintenance of a state of unconsciousness. Anesthetists prefer to use intravenous injections, as they are faster, generally less painful and more reliable than intramuscular or subcutaneous injections. Among the most widely used drugs are propofol, etomidate, barbiturates such as methohexital and thiopentone/thiopenta, Benzodiazepines such as midazolam, Ketamine is used in the UK as "field anaesthesia", for instance in road traffic incidents or similar situations where an operation must be conducted at the scene or when there is not enough time to move to an operating room, while preferring other anesthetics where conditions allow their use. It is more frequently used in the operative setting in the US. Benzodiazepines are sedatives and are used in combinations with other general anesthetics.

Local Anesthetics

The first local anesthetic to be discovered was cocaine, an alkaloid contained in large amounts in the leaves of *Erythroxylon coca*, a shrub growing in the Andes Mountains. Over 9 million kilograms of these leaves are consumed annually by the 2 million inhabitants of the highlands of Peru, who chew or suck the leaves for the sense of wellbeing it produces.

Local anesthetics are drugs that block nerve conduction when applied locally to nerve conduction when applied locally to nerve tissue in appropriate concentrations. They act on any part of the nervous system and on every type of nerve fiber. For example, when they are applied to the motor cortex impulse transmission from that area stops, and when they are injected into the skin they prevent the initiation and the transmission of sensory impulses. A local anesthetic in contact with a nerve trunk can cause both sensory and motor paralysis in the area innervated. The great practical advantage of the local anesthetic is that their action is reversible: their use is followed by complete recovery in nerve function with no evidence of structural damage to nerve fibers of cells.

The structures some of the typical anesthetics are shown below.



These structures contain hydrophilic and hydrophobic domains that are separated by an intermediate alkyl chain. Linkage of these two domains is of either the ester or amide type. the ester link is important because this bond is readily hydrolyzed during metabolic degradation and inactivation in the body. Procaine, for example, can be divided into three main portions: the aromatic acid (para-aminobenzoic), the alcohol (ethanol), and the tertiary amino group (diethylamino). Changes in any part of the molecule alter the anesthetic potency and the toxicity of the compound. Increasing the length of the alcohol group leads to a greater anesthetic potency. It also leads to an increase in toxicity.

Depressants

A **depressant**, or **central depressant**, is a drug that lowers neurotransmission levels, which is to depress or reduce arousal or stimulation, in various areas of the brain. Depressants are also occasionally referred to as **"downers"** as they lower the level of arousal when taken. Stimulants or "uppers" increase mental and/or physical function, hence the opposite drug class of depressants is stimulants, not antidepressants.

Depressants are widely used throughout the world as prescription medicines and as illicit substances. When depressants are used, effects often include ataxia, anxiolysis, pain relief, sedation or somnolence, and cognitive/memory impairment, as well as in some instances euphoria, dissociation, muscle relaxation, lowered blood pressure or heart rate, respiratory depression, and anticonvulsant effects. Depressants also act to produce anesthesia. Cannabis may sometimes be considered a depressant due to one of its components, cannabidiol. The latter is known to treat insomnia, anxiety and muscle spasms similar to other depressive drugs. However, tetrahydrocannabinol, another component, may slow brain function to a small degree while reducing reaction to stimuli, it is generally considered to be a stimulant and main psychoactive agent to sometimes cause anxiety, panic and psychosis instead. Other depressants can include drugs like Xanax (a benzodiazepine) and a number of opiates.

Depressants exert their effects through a number of different pharmacological mechanisms, the most prominent of which include facilitation of GABA, and inhibition of glutamatergic or monoaminergic activity. Other examples are chemicals that modify the electrical signaling inside the body, the most prominent of these being bromides and body blockers.

Alcohol

Alcohol is a very prominent depressant. Alcohol can be and is more likely to be a large problem among teenagers and young adults. Symptoms of alcohol consumption at lower doses may include mild sedation and poor coordination. At higher doses, there may be slurred speech, trouble walking, and vomiting. Extreme doses may result in a respiratory depression, coma, or death. Complications may include seizures, aspiration pneumonia, injuries including suicide, and low blood sugar. Alcohol intoxication can lead to alcohol-related crime with perpetrators more likely to be intoxicated than victims.

Alcohol intoxication typically begins after two or more alcoholic drinks. Risk factors include a social situation where heavy drinking is common and a person having an impulsive personality. Diagnosis is usually based on the history of events and physical examination. Verification of events by witnesses may be useful. Legally, alcohol intoxication is often defined as a blood alcohol concentration (BAC) of greater than 5.4–17.4 mmol/L (25–80 mg/dL or 0.025–0.080%). This can be measured by blood or breath testing. Alcohol is broken down in human body at a rate of about 3.3 mmol/L (15 mg/dL) per hour.

Alcohol intoxication is very common, especially in the Western world. Most people who drink alcohol have at some time been intoxicated. In the United States acute intoxication directly results in about 2,200 deaths per year, and indirectly more than 30,000 deaths per year. Acute intoxication has been documented throughout history and alcohol remains one of the world's most widespread recreational drugs. Some religions consider alcohol intoxication to be a sin.

Barbiturates

Barbiturates are CNS depressants and are similar, in many ways, to the depressant effects of alcohol. To date, there are about 2,500 derivatives of barbituric acid of which only 15 are used medically. The first barbiturate was synthesized from barbituric acid in 1864.

The original use of barbiturates was to replace drugs such as opiates, bromides, and alcohol to induce sleep. Barbiturates are effective as anxiolytics, hypnotics, and anticonvulsants, but have physical and psychological addiction potential as well as overdose potential among other possible adverse effects. They have largely been replaced by benzodiazepines (discussed below) and nonbenzodiazepines ("Z-drugs") in routine medical practice, particularly in the treatment of anxiety and insomnia, due to the significantly lower risk of addiction and overdose and the lack of an antidote for barbiturate overdose. Despite this, barbiturates are still in use for various purposes: in general anesthesia, epilepsy, treatment of acute migraines or cluster headaches, euthanasia, capital punishment, and assisted suicide.

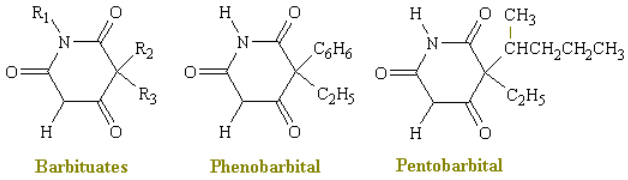


Figure 10.9.11 Barbitutrates.

Some symptoms of an overdose typically include sluggishness, incoordination, difficulty in thinking, slowness of speech, faulty judgement, drowsiness, shallow breathing, staggering, and, in severe cases, coma or death. The lethal dosage of barbiturates varies greatly with tolerance and from one individual to another.

Barbiturates in overdose with other CNS (central nervous system) depressants (e.g. alcohol, opiates, benzodiazepines) are even more dangerous due to additive CNS and respiratory depressant effects. In the case of benzodiazepines, not only do they have additive effects, barbiturates also increase the binding affinity of the benzodiazepine binding site, leading to exaggerated benzodiazepine effects. (ex. If a benzodiazepine increases the frequency of channel opening by 300%, and a barbiturate increases the duration of their opening by 300%, then the combined effects of the drugs increase the channels overall function by 900%, not 600%).

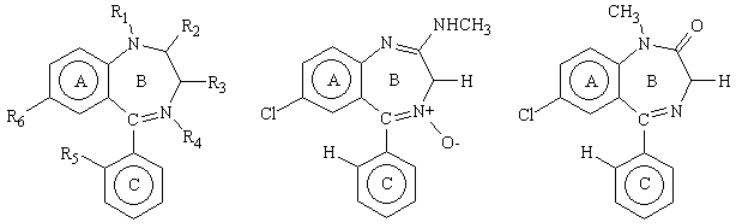
Anti-anxiety Agents

Anti-anxiety medications help reduce the symptoms of anxiety, such as panic attacks, or extreme fear and worry.

Benzodiazepines are prescribed to quell panic attacks. Benzodiazepines are also prescribed in tandem with an antidepressant for the latent period of efficacy associated with many antidepressants for anxiety disorder. The effects of the benzodiazepines virtually all result from action of these drugs on the central nervous system, even when lethal doses are used. The most prominent of these effects are sedation, hypnosis, decreased anxiety, muscle relaxation, and anticonvulsant activity. As the dose of a benzodiazepine is increased, sedation progresses to hypnosis and hypnosis to stupor. They are used as sedatives, hypnotics, antianxiety agents (in panic disorder), anticonvulsants, muscle relaxants, in anesthesia and in alcoholism.

There is risk of benzodiazepine withdrawal and rebound syndrome if BZDs are rapidly discontinued. Tolerance and dependence may occur. The risk of abuse in this class of medication is smaller than in that of barbiturates. Cognitive and behavioral adverse effects are possible.

There are several useful benzodiazepines available. The skeletal structure and two examples are shown below.



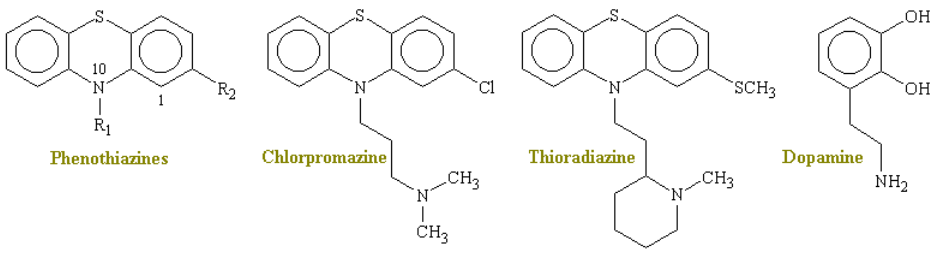
Benzodiazepine include: Alprazolam (Xanax), Bromazepam, Chlordiazepoxide (Librium), Clonazepam (Klonopin), Diazepam (Valium), Lorazepam (Ativan), Oxazepam, Temazepam, and Triazolam. Short half-life (or short-acting) benzodiazepines (such as Lorazepam) and beta-blockers are used to treat the short-term symptoms of anxiety. Beta-blockers help manage physical symptoms of anxiety, such as trembling, rapid heartbeat, and sweating that people with phobias (an overwhelming and unreasonable fear of an object or situation, such as public speaking) experience in difficult situations. Taking these medications for a short period of time can help the person keep physical symptoms under control and can be used “as needed” to reduce acute anxiety.

Antipsychotics, also known as neuroleptics, are a class of psychotropic medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia but also in a range of other psychotic disorders. They are also the mainstay together with mood stabilizers in the treatment of bipolar disorder.

The **phenothiazines** as a class, and especially chlorpromazine, the prototype, are among the most widely used drugs in medical practice and are primarily employed in the management of patients with serious psychiatric illnesses. In addition, many members of the group have other clinically useful properties, including antiemetic, antinausea, and antihistaminic effects and the ability to potentiate analgesics, sedatives and general anesthetics.

It was noted that chlorpromazine by itself did not cause a loss of consciousness but produced only a tendency to sleep and a lack of interest in what was going on. These central actions became known as neuroleptic soon after.

Phenothiazine has a tricyclic structure in which two benzene rings are linked by a sulfur and a nitrogen atom (see figures below). Substitution of an electron-withdrawing group at R2 (but not at position 3 or 4) increases the efficacy of phenothiazines and other tricyclic congeners.

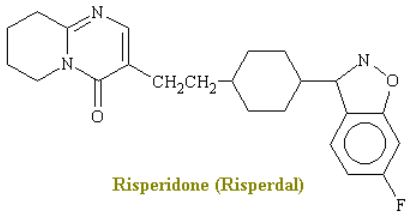


Neuroleptic drugs reduce initiative and interest in the environment, and they reduce displays of emotion or affect. Initially there may be some slowness in response to external stimuli and drowsiness. However subject are easily aroused, capable of giving

appropriate answers to direct questions, and seem to have intact intellectual functions; there is no ataxia, incoordination, or dysathria at ordinary doses. Psychotic patients become less agitated and restless, and withdrawn or autistic patients sometimes become more responsive and communicative. Aggressive and impulsive behavior diminishes. Gradually (over a period of days). psychotic symptoms of hallucinations, delusions, and disorganized or incoherent thinking tend to disappear.

The most prominent observable effects of typical neuroleptic agents are strikingly similar. In low doses, operant behavior is reduced but spinal reflexes are unchanged. Exploratory behavior is diminished, and responses to a a variety of stimuli are fewer, slower, and smaller, although the ability to discriminate stimuli is retained. Conditioned avoidance behaviors are selectively inhibited, while unconditioned escape or avoidance responses are not.

In 1994 an addition tot he antipsychotic drugs is **risperidone** (Risperdal). This drug antagonises D2 and serotonin type 2 receptors. The drug also antagonizes for other receptors such as a adrenergic and histaminergic H1 receptors.



Risperidone (Risperdal)

Anti Depressants

Major depression is the most common of the major mental illnesses, and it must be distinguished from normal grief, sadness, and disappointment. Major depression is characterized by feelings of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, agitation, and self-depreciation. Physical changes also occur, such as weight loss, decreased libido, and disruption of hormonal circadian rhythms.

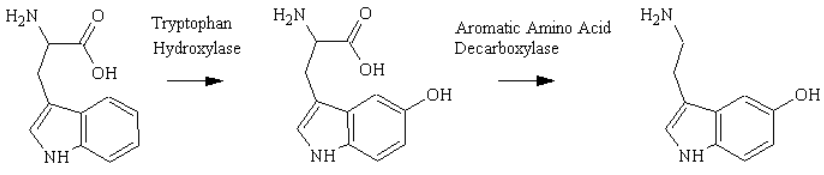
Before the advent of psychotherapy in the 1950s, treatment of depression consisted of stimulants such as caffeine and amphetamines to ameliorate the depressive phases and barbiturates to allay agitation, anxiety, and insomnia. At best, such attempts at therapy may have offered transient relief to some patients. Suffering usually decreased little.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) were the first effective antidepressants used. The monoamine oxidase inhibitors comprise a chemically heterogeneous group of drugs that have in common the ability to block oxidative deamination of naturally occurring monoamines. These drugs have numerous other effects, many of which are still poorly understood. For example, they lower blood pressure and were at one time used to treat hypertension. Their use in psychiatry has also become very limited as the tricyclic antidepressants have come to dominate the treatment of depression and allied conditions. Thus, MAOIs are used most often when tricyclic antidepressants give unsatisfactory results. In addition, whereas severe depression may not be the primary indication for these agents, certain neurotic illnesses with depressive features, and also with anxiety and phobias, may respond especially favorably.

Serotonin

Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine neurotransmitter found in cardiovascular tissue, in endothelial cells, in blood cells, and in the central nervous system. The role of serotonin in neurological function is diverse, and there is little doubt that serotonin is an important CNS neurotransmitter.



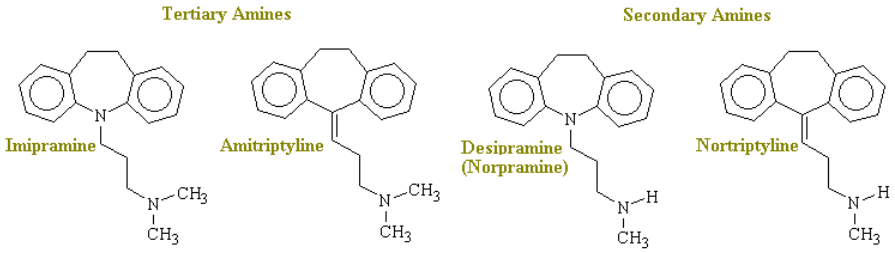
Tryptophan 5-Hydroxytryptophan 5-Hydroxytryptomine

The monoamine serotonin is itself a precursor for melatonin production in the pineal gland. The biosynthesis of serotonin from the amino acid tryptophan is similar to that found for the catecholamines, and 5-hydroxytryptophan can cross the BBB to increase central levels of 5-HT. Although some of the serotonin is metabolized by monoamine oxidase to 5-hydroxyindole acetic acid, most of the serotonin released into the post-synaptic space is removed by the neuron through a reuptake mechanism inhibited by the tricyclic antidepressants and the newer, more selective antidepressants such as fluoxetine and sertraline.

Serotonin receptors are diverse and numerous. Over the past several years, over fourteen different serotonin receptors have been cloned and sequenced through molecular biological techniques. Overall, there are seven distinct families of 5-HT receptors, with as many as five within a particular family. Only one of the 5-HT receptors is a ligand-gated ion channel (the 5-HT3 receptor), and the other six families are all G protein-coupled receptors.

Tricyclic Anti-depressants

Imipramine, amitriptylin, and other closely related drugs are among the drugs currently most widely used for the treatment of major depression. Because of there structure (see below). They are often referred to as the tricyclic antidepressants. Although these compounds seem to be similar to the phenothiazines chemically, the ethylene group of imiprimine's middle ring imparts dissimilar stereochemical properties and prevents conjegation of the rings, as occurs with the phenothiazines.



One might expect an effective antidepressant drug to have a stimulating or mood-elevating effect when given to a normal subject. Although this may occur with the MAOIs, it is not true of the tricyclic antidepressants. If a dose of imipramine given to a normal subject, he feels sleepy and tends to be quieter, his blood pressure falls slightly, and he feels light headed. These drug effects are usually perceived to be unpleasant, and cause a feeling of unhappiness and increased anxiety. Repeated administration for several days may lead to accentuation of these symptoms and, in addition, to difficulty in concentrating and thinking. In contrast, if the drug is given over a period of time (two to three weeks) to depressed patients an elevated mood occurs. For this reason, the tricyclics are not prescribed on an "as-needed" basis.

Selective Serotonin Reuptake Inhibitors

In recent years, selective serotonin reuptake inhibitors (SSRIs) have been introduced for the treatment of depression. Prozac is the most famous drug in this class. Lilly's sales of Prozac in 1993 exceeded 1 billion US dollars. Clomiprimine, fluoxetine (Prozac), sertraline and paroxetine selectively block the reuptake of serotonin, thereby increasing the levels of serotonin in the central nervous system. Note the similarities and differences between the tricyclic antidepressants and the selective serotonin reuptake inhibitors. The SSRIs generally have fewer anticholinergic side effects, but caution is still necessary when co-administering any drugs that affect serotonergic systems (e.g., monoamine oxidase inhibitors). Some of the newer, SSRIs (e.g., clomipramine) have been useful in the treatment of obsessive-compulsive disorders.

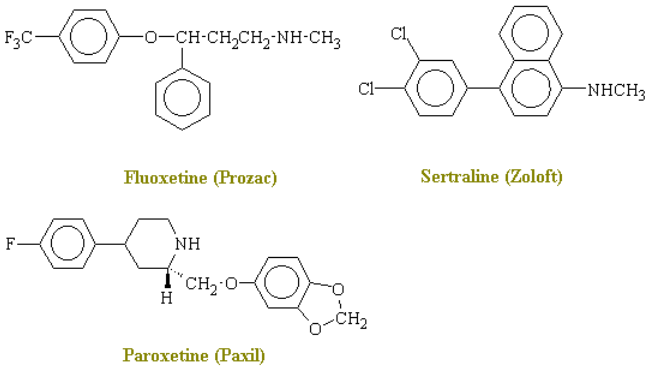


Figure 10.9.12 Examples of SSRIs.

Stimulants

These classes of chemicals induce alertness and stimulant the brain and nervous system. Side effects of stimulant use include wakefulness, increased speech, and motor activity, and decreased appetite. Amphetamines are a type of stimulant that incorporates a nitrogen-containing organic functional group. These compounds have been noted to block the reuptake of dopamine.

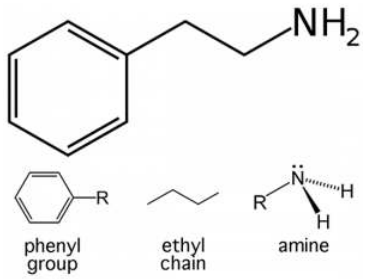


Figure 10.9.13: The skeletal structure of phenethylamine. (Copyright, http://countyourculture.com/2010/11/02/phenethylamine-and-amphetamine/)

Early Stimulant Use

For over 5000 years, the Chinese have extracted the compound Ephedrine from locally grown Ephedra plants. Native peoples of the United States were known to isolate this compound as well. Both cultures used Ephedrine to treat asthma, hay fever, and congestion. Ephedrine was noted to have a stimulant effect on its users. Chemically similar to adrenaline, ephedrine was a more stable compound and could be taken orally. By the mid-1920s, the pharmaceutical company, Eli Lily, synthesized ephedrine and introduced it into western medicine.

Figure 10.9.14: : https://commons.wikimedia.org/wiki/C...phedra_viridis. (Copyright, https://commons.wikimedia.org/wiki/User:Dcrjsr)

Ephedrine can decrease appetite, increase blood pressure and heart rate, and cause sleeping problems. Mental health can be affected by ephedrine use. Patients may experience hallucinogens, anxiety, and chemical dependence.

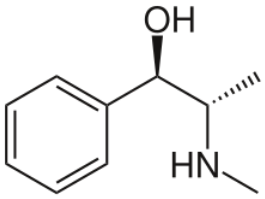


Figure 10.9.15: Chemical structure of Ephedrine, done using BKchem. (Copyright, https://commons.wikimedia.org/wiki/User:Bryan_Derksen)

Amphetamine is a potent central nervous system (CNS) stimulant of the phenethylamine class that is approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. Amphetamine is also used off-label as a performance and cognitive enhancer, and recreationally as an aphrodisiac and euphoriant. Although it is a prescription medication in many countries, unauthorized possession and distribution of amphetamine is often tightly controlled due to the significant health risks associated

with uncontrolled or heavy use. As a consequence, amphetamine is illegally manufactured in clandestine labs to be trafficked and sold to users. Based upon drug and drug precursor seizures worldwide, illicit amphetamine production and trafficking is much less prevalent than that of methamphetamine.

The first pharmaceutical amphetamine was Benzedrine, a brand of inhalers used to treat a variety of conditions. At therapeutic doses, this drug causes emotional and cognitive effects such as euphoria, change in libido, increased arousal, and improved cognitive control. Likewise, it induces physical effects such as decreased reaction time, fatigue resistance, and increased muscle strength. In contrast, supratherapeutic doses of amphetamine are likely to impair cognitive function and induce rapid muscle breakdown. Very high doses can result in psychosis (e.g., delusions and paranoia), which very rarely occurs at therapeutic doses even during long-term use. As recreational doses are generally much larger than prescribed therapeutic doses, recreational use carries a far greater risk of serious side effects, such as dependence, which only rarely arises with therapeutic amphetamine use.

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy, or molly) is a euphoriant, empathogen, and stimulant of the amphetamine class. Briefly used by some psychotherapists as an adjunct to therapy, the drug became popular recreationally and the DEA listed MDMA as a Schedule I controlled substance, prohibiting most medical studies and applications. MDMA is known for its entactogenic properties. The stimulant effects of MDMA include hypertension, anorexia (appetite loss), euphoria, social disinhibition, insomnia (enhanced wakefulness/inability to sleep), improved energy, increased arousal, and increased perspiration, among others. Relative to catecholaminergic transmission, MDMA enhances serotonergic transmission significantly more, when compared to classical stimulants like amphetamine. MDMA does not appear to be significantly addictive or dependence forming.

Methylenedioxypyrovalerone (MDPV) is a psychoactive drug with stimulant properties that acts as a norepinephrine-dopamine reuptake inhibitor (NDRI). It was first developed in the 1960s by a team at Boehringer Ingelheim. MDPV remained an obscure stimulant until around 2004, when it was reported to be sold as a designer drug. Products labeled as bath salts containing MDPV were previously sold as recreational drugs in gas stations and convenience stores in the United States, similar to the marketing for Spice and K2 as incense.

Incidents of psychological and physical harm have been attributed to MDPV use.

Mephedrone is a synthetic stimulant drug of the amphetamine and cathinone classes. Slang names include drone and MCAT. It is reported to be manufactured in China and is chemically similar to the cathinone compounds found in the khat plant of eastern Africa. It comes in the form of tablets or a powder, which users can swallow, snort, or inject, producing similar effects to MDMA, amphetamines, and cocaine.

Methamphetamine (contracted from *N*-**meth**yl-**a**lpha-**m**ethyl**ph**en**et**hyl**amine**) is a potent psychostimulant that is used to treat attention deficit hyperactivity disorder (ADHD) and obesity. Recreationally, methamphetamine is used to increase sexual desire, lift the mood, and increase energy, allowing some users to engage in sexual activity continuously for several days straight.

In low doses, methamphetamine can cause an elevated mood and increase alertness, concentration, and energy in fatigued individuals. At higher doses, it can induce psychosis, rhabdomyolysis, and cerebral hemorrhage. Methamphetamine is known to have a high potential for abuse and addiction. Recreational use of methamphetamine may result in psychosis or lead to post-withdrawal syndrome, a withdrawal syndrome that can persist for months beyond the typical withdrawal period. Unlike amphetamine and cocaine, methamphetamine is neurotoxic to humans, damaging both dopamine and serotonin neurons in the central nervous system (CNS). Entirely opposite to the long-term use of amphetamine, there is evidence that methamphetamine causes brain damage from long-term use in humans; this damage includes adverse changes in brain structure and function, such as reductions in gray matter volume in several brain regions and adverse changes in markers of metabolic integrity.

Methylphenidate is a stimulant drug that is often used in the treatment of ADHD and narcolepsy and occasionally to treat obesity in combination with diet restraints and exercise. Its effects at therapeutic doses include increased focus, increased alertness, decreased appetite, decreased need for sleep and decreased impulsivity. Methylphenidate is not usually used recreationally, but when it is used, its effects are very similar to those of amphetamines.

Methylphenidate is sold under a number of brand names including Ritalin. Other versions include the long lasting tablet Concerta and the long lasting transdermal patch Daytrana.

Phenylpropanolamine (PPA; Accutrim; β-hydroxyamphetamine), also known as norephedrine and norpseudoephedrine, is a psychoactive drug that is used as a stimulant, decongestant, and anorectic agent. It is commonly used in prescription and over-the-

counter cough and cold preparations. In veterinary medicine, it is used to control urinary incontinence in dogs under trade names Propalin and Proin.

In the United States, PPA is no longer sold without a prescription due to a proposed increased risk of stroke in younger women. In a few countries in Europe, however, it is still available either by prescription or sometimes over-the-counter.

Propylhexedrine (Hexahydromethamphetamine, Obesin) is a stimulant medication, sold over-the-counter in the United States as the cold medication Benzedrex. The drug has also been used as an appetite suppressant in Europe. Propylhexedrine is not an amphetamine, though it is structurally similar; it is instead a cycloalkylamine, and thus has stimulant effects that are less potent than similarly structured amphetamines, such as methamphetamine.

The abuse potential of propylhexedrine is fairly limited, due its limited routes of administration: in the United States, Benzedrex is only available as an inhalant, mixed with lavender oil and menthol. These ingredients cause unpleasant tastes, and abusers of the drug have reported unpleasant "menthol burps". Injection of the drug has been found to cause transient diplopia and brain stem dysfunction.

Pseudoephedrine is used as a nasal/sinus decongestant, as a stimulant, or as a wakefulness-promoting agent. The salts pseudoephedrine hydrochloride and pseudoephedrine sulfate are found in many over-the-counter preparations, either as a single ingredient or (more commonly) in combination with antihistamines, guaifenesin, dextromethorphan, and/or paracetamol (acetaminophen) or another NSAID (such as aspirin or ibuprofen). It is also used as a precursor chemical in the illegal production of methamphetamine.

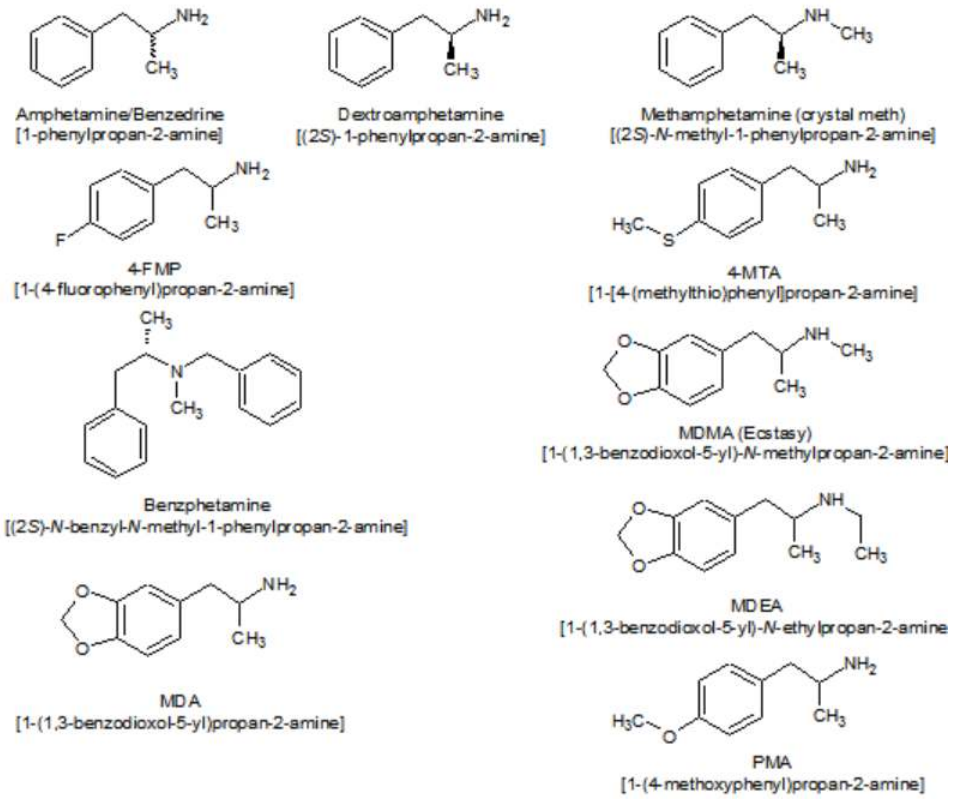


Figure 10.9.16 A chart comparing the chemical structures of different amphetamine derivatives. Source: Wikipedia

Cocaine, Caffeine, and Nicotine

Cocaine is a tropane alkaloid and stimulant drug obtained primarily from the leaves of two coca species, *Erythroxylum coca* and *Erythroxylum novogranatense*. It is most commonly used as a recreational drug and euphoriant. After extraction from coca leaves, cocaine may be snorted, heated until sublimated and then inhaled, or dissolved and injected into a vein. Mental effects may include an intense feeling of happiness, sexual arousal, loss of contact with reality, or agitation. Physical symptoms may include a fast heart rate, sweating, and dilated pupils. High doses can result in high blood pressure or body temperature. Effects begin within seconds to minutes of use and last between five and ninety minutes.

Cocaine is addictive due to its effect on the reward pathway in the brain. A single dose of cocaine induces tolerance to the drug's effects. After a short period of use, addiction is likely. Abstention from cocaine after chronic use results in drug withdrawal, with symptoms that may include depression, decreased ability to feel pleasure and subjective fatigue. Cocaine's use increases the overall risk of death and particularly the risk of trauma, and infectious diseases, such as blood infections and AIDS. It also increases risk of stroke, heart attack, cardiac arrhythmia, lung injury (when smoked), and sudden cardiac death. Illicitly-sold cocaine is commonly adulterated with local anesthetics, levamisole, cornstarch, quinine, or sugar, which can result in additional toxicity. The Global Burden of Disease study found that cocaine use caused the death of 7.3 people per 100,000 population world-wide.

Caffeine is a central nervous system (CNS) stimulant of the methylxanthine class. It is the world's most widely consumed psychoactive drug. Unlike many other psychoactive substances, it is legal and unregulated in nearly all parts of the world. There are several known mechanisms of action to explain the effects of caffeine. The most prominent is that it reversibly blocks the action of adenosine on its receptors and consequently prevents the onset of drowsiness induced by adenosine. Caffeine also stimulates certain portions of the autonomic nervous system.

Methyxanthines such as caffeine, theophylline and theobromine share in common several pharmacological actions of therapeutic interest. They stimulate the central nervous system, act on the kidney to produce diuresis, stimulate cardiac muscle, and relax smooth muscle, notably bronchial muscle. Because the various xanthines differ markedly in the intensity of their action on various structures, one particular xanthine has been used more than another for a particular therapeutic effect. Since theobromine displays low potency in these pharmacological actions, it has all but disappeared from the therapeutic scene.

Caffeine, theophyline, and theobromine occur naturally in plants widely distributed geographically. Caffeine is found in the coffee bean, tea leaves, guarana, and other plants. From the figure below, we can see that the methylxanthines have a structure which is very similar to adenine.

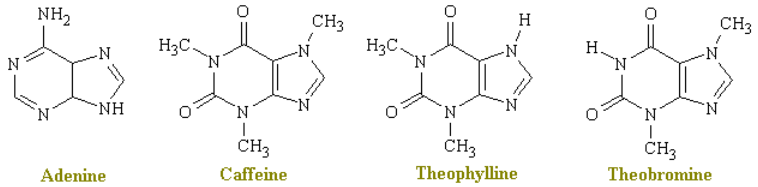


Figure 10.9.17 Adenine and other molecules with similar structures.

Table 10.9.1: Caffeine Content in Various Beverages and Foods

Beverage/Food	Milligrams
Starbuck's Grande Coffee (16 oz.)	380
Plain brewed coffee (8 oz.)	102–200
Espresso (1 oz.)	30–90
Plain, decaffeinated coffee (8 oz.)	3–12
Tea, brewed (8 oz.)	40–120
Green tea (8 oz.)	25–40
Coca-Cola Classic (12 oz.)	35
Dr. Pepper (12 oz.)	44
Jolt Cola (12 oz.)	72
Mountain Dew (12 oz.)	54
Mountain Dew, MDX (12 oz.)	71
Pepsi-Cola (12 oz.)	38
Red Bull (8.5 oz.)	80
Full Throttle (16 oz.)	144
Monster Energy (16 oz.)	160
Spike Shooter (8.4 oz.)	300

Source: MedicineNet.com. "Caffeine." Accessed October 2, 2011. http://www.medicinenet.com/caffeine/article.htm.

Health Benefits of Caffeine

The most renowned effects of caffeine on the body are increased alertness and delay of fatigue and sleep. How does caffeine stimulate the brain? Watch "Video 15.6.1" to see a graphic account of a brain on caffeine. Caffeine is chemically similar to a chemical in our brains (adenosine). Caffeine interacts with adenosine's specific protein receptor. It blocks the actions of the adenosine, and affects the levels of signaling molecules in the brain, leading to an increase in energy metabolism. At the molecular level, caffeine stimulates the brain, increasing alertness and causing a delay of fatigue and sleep. At high doses caffeine stimulates the motor cortex of the brain and interferes with the sleep-wake cycle, causing side effects such as shakiness, anxiety, and insomnia. People's sensitivity to the adverse effects of caffeine varies and some people develop side effects at much lower doses. The many effects caffeine has on the brain do not diminish with habitual drinking of caffeinated beverages.



Video 15.6.1: *A Brain on Caffeine. Watch this graphic account of the brain on caffeine.*

Scientific studies suggest caffeine can improve endurance capacity by increasing energy available during exercise. The effect may only work in non-caffeine drinkers and it only takes 1-3 days for the body to become "caffeine-naive."

Nicotine is the active chemical constituent in tobacco, which is available in many forms, including cigarettes, cigars, chewing tobacco, and smoking cessation aids such as nicotine patches, nicotine gum, and electronic cigarettes. Nicotine is used widely throughout the world for its stimulating and relaxing effects. Nicotine exerts its effects through the agonism of nicotinic acetylcholine receptor, resulting in multiple downstream effects such as increase in activity of dopaminergic neurons in the midbrain reward system, as well as the decreased expression of monoamine oxidase in the brain. Nicotine is addictive and dependence forming.

Note: Hallucinogens and Dissociative Drugs from NIH-National Institute on Drug Abuse

The information below is directly from the link below

https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/hallucinogensrrs4.pdf

Hallucinogens are a class of drugs that cause hallucinations—profound distortions in a person's perceptions of reality. Hallucinogens can be found in some plants and mushrooms (or their extracts) or can be man-made, and they are commonly divided into two broad categories: classic hallucinogens (such as LSD) and dissociative drugs (such as PCP). When under the influence of either type of drug, people often report rapid, intense emotional swings and seeing images, hearing sounds, and feeling sensations that seem real but are not. While the exact mechanisms by which hallucinogens and dissociative drugs cause their effects are not yet clearly understood, research suggests that they work at least partially by temporarily disrupting communication between neurotransmitter systems throughout the brain and spinal cord that regulate mood, sensory perception, sleep, hunger, body temperature, sexual behavior, and muscle control.



Figure 10.9.15 Psilocybin mushrooms, LSD, and Salvia divinorum are commonly used hallucinogenic and dissociative compounds.

Classic Hallucinogens

LSD (d-lysergic acid diethylamide)—also known as acid, blotter, doses, hits, microdots, sugar cubes, trips, tabs, or window panes—is one of the most potent moodand perception-altering hallucinogenic drugs. It is a clear or white, odorless, water-soluble material synthesized from lysergic acid, a compound derived from a rye fungus. LSD is initially produced in crystalline form, which can then be used to produce tablets known as "microdots" or thin squares of gelatin called "window panes." It can also be diluted with water or alcohol and sold in liquid form. The most common form, however, is LSD-soaked paper punched into small individual squares, known as "blotters."

Psilocybin (4-phosphoryloxyN, N-dimethyltryptamine)—also known as magic mushrooms, shrooms, boomers, or little smoke—is extracted from certain types of mushrooms found in tropical and subtropical regions of South America, Mexico, and the United States. In the past, psilocybin was ingested during religious ceremonies by indigenous cultures from Mexico and Central America. Psilocybin can either be dried or fresh and eaten raw, mixed with food, or brewed into a tea, and produces similar effects to LSD.

Peyote (Mescaline)— also known as buttons, cactus, and mesc— is a small, spineless cactus with mescaline as its main ingredient. It has been used by natives in northern Mexico and the southwestern United States as a part of religious ceremonies. The top, or "crown," of the peyote cactus has disc-shaped buttons that are cut out, dried, and usually chewed or soaked in water to produce an intoxicating liquid. Because the extract is so bitter, some users prepare a tea by boiling the plant for several hours. Mescaline can also be produced through chemical synthesis.

DMT (Dimethyltryptamine)—also known as Dimitri—is a powerful hallucinogenic chemical found naturally occurring in some Amazonian plant species (see "Ayahuasca") and also synthesized in the laboratory. Synthetic DMT usually takes the form of a white crystalline powder and is typically vaporized or smoked in a pipe. Ayahuasca—also known as hoasca, aya, and yagé—is a hallucinogenic brew made from one of several Amazonian plants containing DMT (the primary psychoactive ingredient) along with a vine containing a natural alkaloid that prevents the normal breakdown of DMT in the digestive tract. Ayahuasca tea has traditionally been used for healing and religious purposes in indigenous South American cultures, mainly in the Amazon region.

Dissociative Drugs

PCP (Phencyclidine)—also known as ozone, rocket fuel, love boat, hog, embalming fluid, or superweed—was originally developed in the 1950s as a general anesthetic for surgery. While it can be found in a variety of forms, including tablets or capsules, it is usually sold as a liquid or powder. PCP can be snorted, smoked, injected, or swallowed. It is sometimes smoked after being sprinkled on marijuana, tobacco, or parsley.

Ketamine—also known as K, Special K, or cat Valium—is a dissociative currently used as an anesthetic for humans as well as animals. Much of the ketamine sold on the street has been diverted from veterinary offices. Although it is manufactured as an injectable liquid, ketamine is generally evaporated to form a powder that is snorted or compressed into pills for illicit use. Because ketamine is odorless and tasteless and has amnesia-inducing properties, it is sometimes added to drinks to facilitate sexual assault. 2 NIDA Research Report Series Common Hallucinogens and Dissociative Drugs *In this report, the term "hallucinogen" will refer to the classic hallucinogenic drugs LSD and Psilocybin.

DXM (Dextromethorphan)— also known as robo—is a cough suppressant and expectorant ingredient in some over-the-counter (OTC) cold and cough medications that are often abused by adolescents and young adults. The most common sources of abused DXM are "extra-strength" cough syrup, which typically contains around 15 milligrams of DXM per teaspoon, and pills and gel capsules, which typically contain 15 milligrams of DXM per pill. OTC medications that contain DXM often also contain antihistamines and decongestants.

Salvia divinorum—also known as diviner's sage, Maria Pastora, Sally-D, or magic mint—is a psychoactive plant common to southern Mexico and Central and South America. Salvia is typically ingested by chewing fresh leaves or by drinking their extracted juices. The dried leaves of salvia can also be smoked or vaporized and inhaled.

Short-Term General Effects of Hallucinogens Sensory and Physical Effects

- Hallucinations, including seeing, hearing, touching, or smelling things in a distorted way or perceiving things that do not exist
- Intensified feelings and sensory experiences (brighter colors, sharper sounds)
- Mixed senses ("seeing" sounds or "hearing" colors)
- Changes in sense or perception of time (time goes by slowly) Physical Effects
- Increased energy and heart rate
- Nausea

Marijuana - NIH Medlineplus

Marijuana

The information below is directly from the link below

https://medlineplus.gov/marijuana.html

Marijuana is a green, brown, or gray mix of dried, crumbled parts from the marijuana plant. The plant contains chemicals which act on your brain and can change your mood or consciousness.

Marijuana can cause both short-term and long-term effects.

Short term:	Long term:
While you are high, you may experience • Altered senses, such as seeing brighter colors • Altered sense of time, such as minutes seeming like hours • Changes in mood • Problems with body movement • Trouble with thinking, problem-solving, and memory • Increased appetite	In the long term, marijuana can cause health problems, such as • Problems with brain development. People who started using marijuana as teenagers may have trouble with thinking, memory, and learning. • Coughing and breathing problems, if you smoke marijuana frequently • Problems with child development during and after pregnancy, if a woman smokes marijuana while pregnant.

Medical Marijuana

The marijuana plant has chemicals that can help with some health problems. More states are making it legal to use the plant as medicine for certain medical conditions. But there isn't enough research to show that the whole plant works to treat or cure these conditions. The U.S. Food and Drug Administration (FDA) has not approved the marijuana plant as a medicine. Marijuana is still illegal at the national level.

However, there have been scientific studies of cannabinoids, the chemicals in marijuana. The two main cannabinoids that are of medical interest are THC and CBD. The FDA has approved two drugs that contain THC. These drugs treat nausea caused by chemotherapy and increase appetite in patients who have severe weight loss from AIDS. There is also a liquid drug that contains CBD. It treats two forms of severe childhood epilepsy. Scientists are doing more research with marijuana and its ingredients to treat many diseases and conditions.

Summary

- Neurotransmitters are endogenous chemicals that enable neurotransmission. It is a type of chemical messenger which transmits signals across a chemical synapse, such as a neuromuscular junction, from one neuron (nerve cell) to another "target" neuron, muscle cell, or gland cell.
- Strong imbalances or disruptions to neurotransmitter systems have been associated with many diseases and mental disorders.
- Psychoactive drugs are substances that change the function of the brain and result in alterations of mood, thinking, perception, and/or behavior. They include prescription medications such as opioid painkillers, legal substances such as nicotine and alcohol, and illegal drugs such as LSD and heroin.
- Psychoactive drugs are divided into different classes according to their pharmacological effects. They include stimulants, depressants, anxiolytics, euphoriants, hallucinogens, and empathogens. Many psychoactive drugs have multiple effects so they may be placed in more than one class.
- Psychoactive drugs generally produce their effects by affecting brain chemistry. Generally, they act either as agonists, which enhance the activity of particular neurotransmitters; or as antagonists, which decrease the activity of particular neurotransmitters.
- Psychoactive drugs are used for various purposes, including medical, ritual, and recreational purposes.
- Misuse of psychoactive drugs may lead to addiction, which is compulsive use of a drug despite negative consequences such use may entail. Sustained use of an addictive drug may produce physical or psychological dependence on the drug. Rehabilitation typically involves psychotherapy and sometimes the temporary use of other psychoactive drugs.

Contributors

- Libretext: Human Biology (Wakim and Grewal)
- Edward B. Walker (Weber State University)
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- NIH National Institute of Mental Health
- NIH National Institute on Drug Abuse

- NIH-Medlineplus
- Psychology OPENSTAX
- Wikipedia
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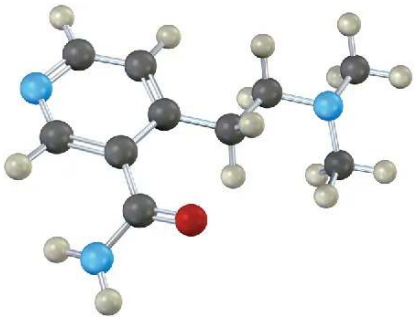
10.10: Additional Problems

Visualizing Chemistry

PROBLEM 10.26 Name the following amines, and identify each as primary, secondary, or tertiary:

(a)  (b)  (c) 

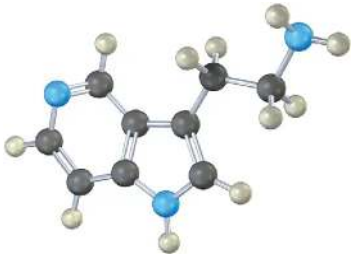
PROBLEM 10.27 The following compound contains three nitrogen atoms. Rank them in order of increasing basicity.



PROBLEM 10.28 Name the following amine, including *R*,*S* stereochemistry, and draw the product of its reaction with excess iodomethane followed by heating with Ag_2O (Hofmann elimination). Is the stereochemistry of the alkene product *Z* or *E*? Explain.

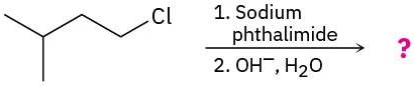


PROBLEM 10.29 Which nitrogen atom in the following compound is most basic? Explain.

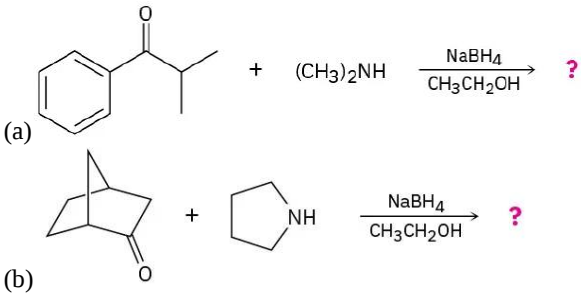


Mechanism Problems

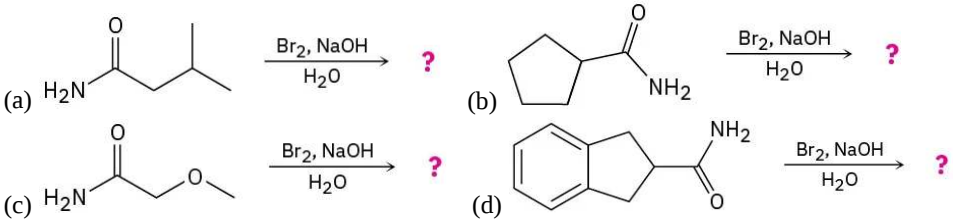
PROBLEM 10.30 Predict the product(s) and write the mechanism for each of the following reactions:

(a) (b) 

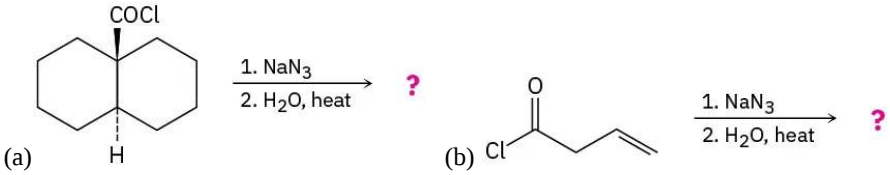
Problem 10-31 Predict the product(s) and write the mechanism for each of the following reactions:



Problem 10-32 Predict the product(s) and write the mechanism for each of the following reactions:

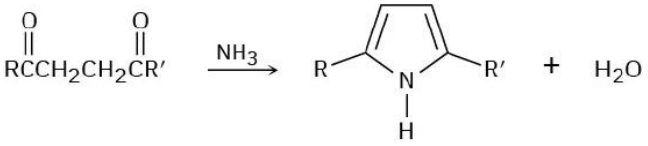


Problem 10-33 Predict the product(s) and write the mechanism for each of the following reactions:

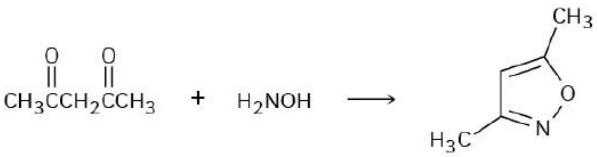


Problem 10-34 The diazotization of aniline first involves the formation of NO^+ (nitrosonium ion) by the dehydration of nitrous acid with sulfuric acid. The aniline nitrogen then acts as a nucleophile and eventually loses water. Propose a mechanism for the formation of the dizaonium salt of aniline using curved arrows to show all electron movement.

Problem 10-35 Substituted pyrroles are often prepared by treatment of a 1,4-diketone with ammonia. Propose a mechanism.



Problem 10-36 3,5-Dimethylisoxazole is prepared by reaction of 2,4-pentanedione with hydroxylamine. Propose a mechanism.

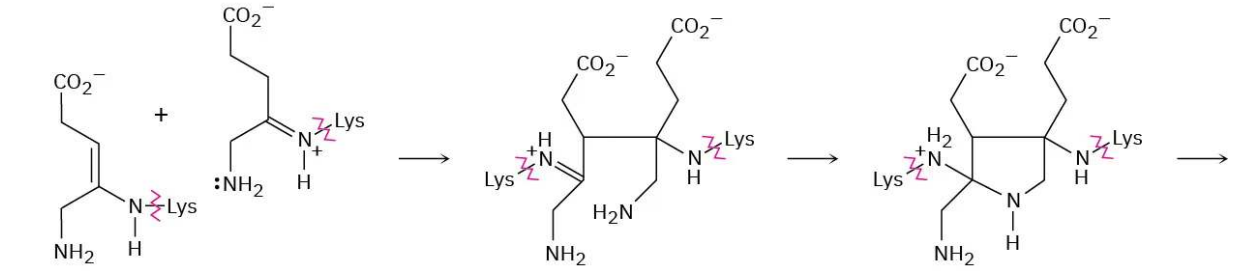


3,5-Dimethylisoxazole

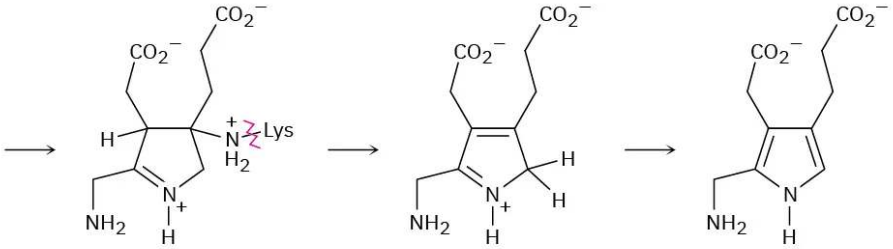
Problem 10-37 One problem with reductive amination as a method of amine synthesis is that by-products are sometimes obtained. For example, reductive amination of benzaldehyde with methylamine leads to a mixture of *N*-methylbenzylamine and *N*-methyldibenzylamine. How do you suppose the tertiary amine by-product is formed? Propose a mechanism.

Problem 10-38 Chlorophyll, heme, vitamin B_{12}, and a host of other substances are biosynthesized from porphobilinogen (PBG), which is itself formed from condensation of two molecules of 5-aminolevulinate. The two 5-aminolevulinates are bound to lysine (Lys) amino acids in the enzyme, one in the enamine form and one in the imine form, and their condensation is thought to occur by the following steps. Use curved arrows to show the mechanism of each step.

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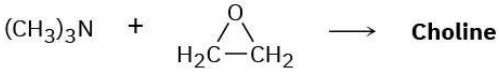


Enzyme-bound 5-aminolevulinate



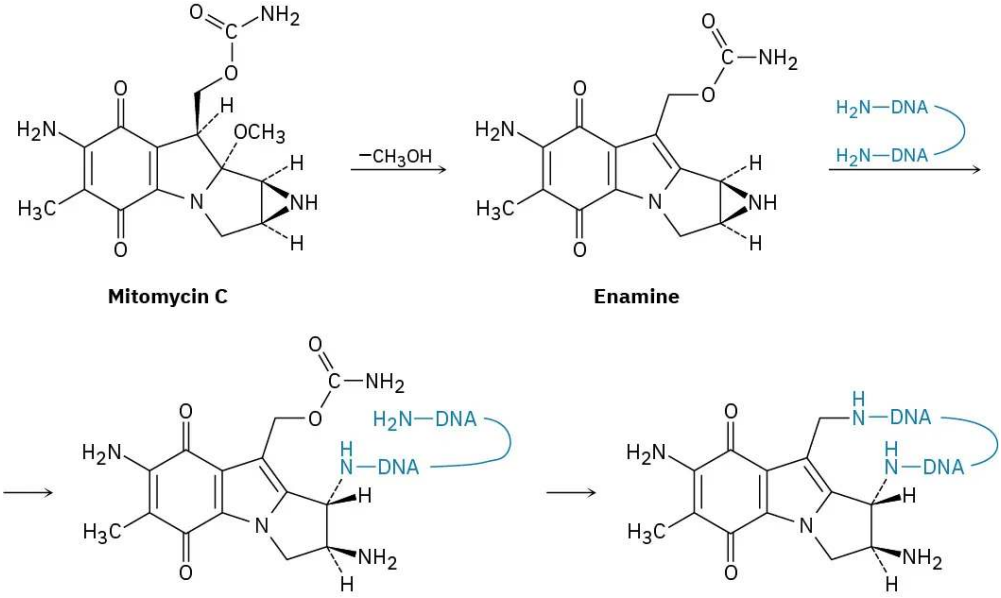
Porphobilinogen (PBG)

Problem 10-39 Choline, a component of the phospholipids in cell membranes, can be prepared by S_N2 reaction of trimethylamine with ethylene oxide. Show the structure of choline, and propose a mechanism for the reaction.



Choline

Problem 10-40 The antitumor antibiotic mitomycin C functions by forming cross-links in DNA chains.



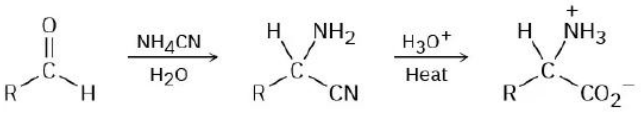
Mitomycin C **Enamine**

(a)The first step is loss of methoxide and formation of an iminium ion intermediate that is deprotonated to give an enamine. Show the mechanism.

(b) The second step is the reaction of the enamine with DNA to open the three-membered, nitrogen-containing (aziridine) ring. Show the mechanism.

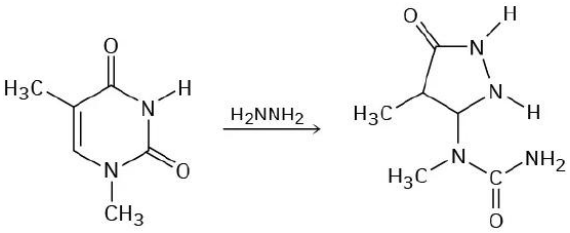
(c) The third step is loss of carbamate ($NH_2CO_2^-$) and formation of an unsaturated iminium ion, followed by a conjugate addition of another part of the DNA chain. Show the mechanism.

Problem 10-41 α-Amino acids can be prepared by the Strecker synthesis, a two-step process in which an aldehyde is treated with ammonium cyanide followed by hydrolysis of the amino nitrile intermediate with aqueous acid. Propose a mechanism for the reaction.

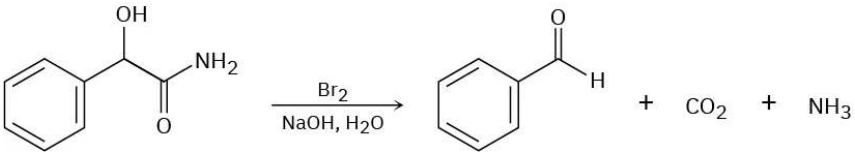


An α-amino acid

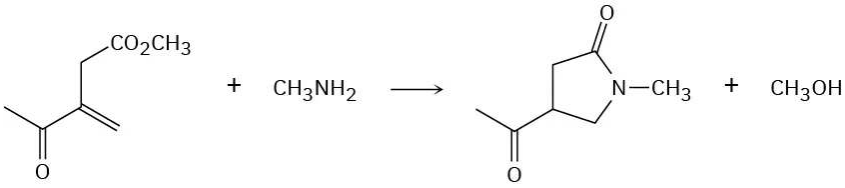
Problem 10-42 One of the reactions used in determining the sequence of nucleotides in a strand of DNA is the reaction with hydrazine. Propose a mechanism for the following reaction, which occurs by an initial conjugate addition followed by internal amide formation.



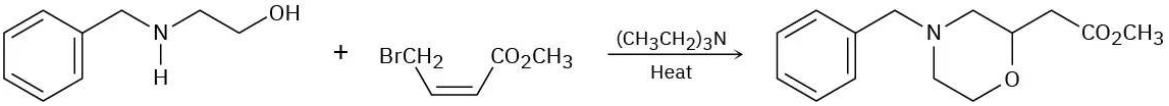
Problem 10-43 When an α-hydroxy amide is treated with Br_2 in aqueous NaOH under Hofmann rearrangement conditions, loss of CO_2 occurs and a chain-shortened aldehyde is formed. Propose a mechanism.



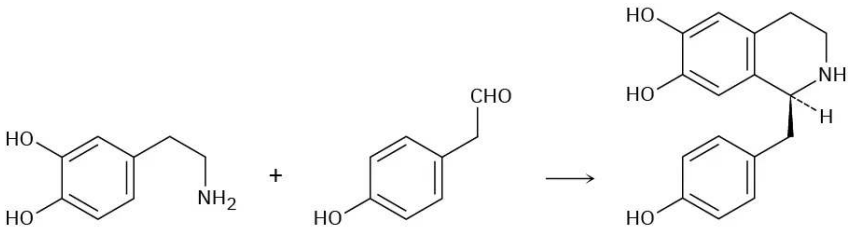
Problem 10-44 The following transformation involves a conjugate nucleophilic addition reaction (**Section 5.13**) followed by an intramolecular nucleophilic acyl substitution reaction (**Section 7.2**). Show the mechanism.



Problem 10-45 Propose a mechanism for the following reaction:



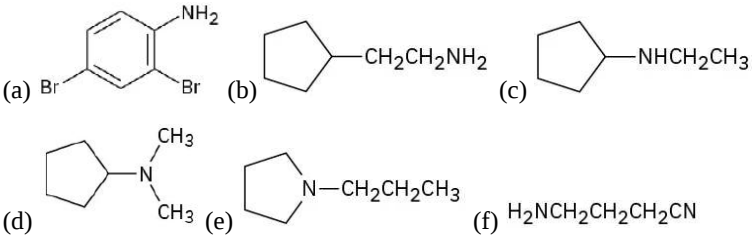
Problem 10-46 One step in the biosynthesis of morphine is the reaction of dopamine with *p*-hydroxyphenylacetaldehyde to give (*S*)-norcoclaurine. Assuming that the reaction is acid-catalyzed, propose a mechanism.



Dopamine **p-Hydroxyphenyl-acetaldehyde** **(S)-Norcoclaurine**

Naming Amines

Problem 10-47 Name the following compounds:

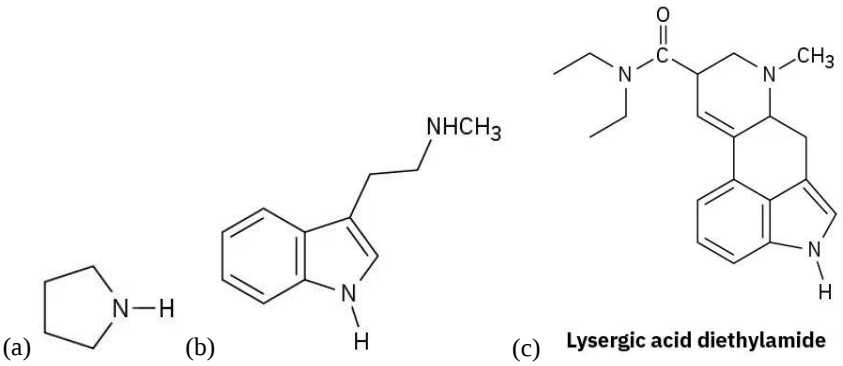


Problem 10-48 Draw structures corresponding to the following IUPAC names:

(a) *N*,*N*-Dimethylaniline **(b)** (Cyclohexylmethyl)amine **(c)** *N*-Methylcyclohexylamine

(d) (2-Methylcyclohexyl)amine **(e)** 3-(*N*,*N*-Dimethylamino)propanoic acid

Problem 10-49 Classify each of the amine nitrogen atoms in the following substances as primary, secondary, or tertiary:

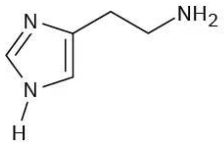


Lysergic acid diethylamide

Amine Basicity

Problem 10-50 Although pyrrole is a much weaker base than most other amines, it is a much stronger acid ($pK_a \approx 15$ for the pyrrole versus 35 for diethylamine). The N–H hydrogen is readily abstracted by base to yield the pyrrole anion, $C_4H_4N^-$. Explain.

Problem 10-51 Histamine, whose release in the body triggers nasal secretions and constricted airways, has three nitrogen atoms. List them in order of increasing basicity and explain your ordering.



Histamine

Problem 10-52 Account for the fact that *p*-nitroaniline ($pK_a = 1.0$) is less basic than *m*-nitroaniline ($pK_a = 2.5$) by a factor of 30. Draw resonance structures to support your argument. (The pK_a values refer to the corresponding ammonium ions.)

Synthesis of Amines

Problem 10-53 How would you prepare the following substances from 1-butanol?

(a) Butylamine (b) Dibutylamine (c) Propylamine (d) Pentylamine (e) *N*,*N*-Dimethylbutylamine (f) Propene

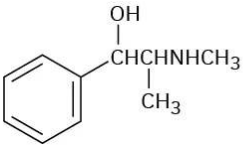
Problem 10-54 How would you prepare the following substances from pentanoic acid?

(a) Pentanamide (b) Butylamine (c) Pentylamine (d) 2-Bromopentanoic acid (e) Hexanenitrile (f) Hexylamine

Problem 10-57 How might you prepare pentylamine from the following starting materials?

(a) Pentanamide (b) Pentanenitrile (c) 1-Butene (d) Hexanamide (e) 1-Butanol (f) 5-Decene (g) Pentanoic acid

Problem 10-58 How might a reductive amination be used to synthesize ephedrine, an amino alcohol that was widely used for the treatment of bronchial asthma?



Ephedrine

Reactions of Amines

Problem 10-59 How would you convert aniline into each of the following products?

(a) Benzene (b) Benzamide (c) Toluene

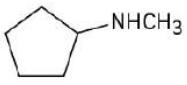
Problem 10-60 Write the structures of the major organic products you would expect from reaction of <i">m-toluidine (*m*-methylaniline) with the following reagents:

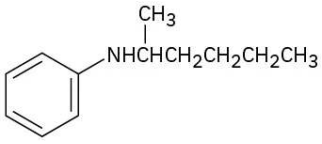
(a) Br_2 (1 equivalent) (b) CH_3I (excess) (c) CH_3COCl in pyridine (d) The product of (c), then HSO_3Cl

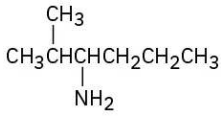
Problem 10-61 Show the products from the reaction of *p*-bromoaniline with the following reagents:

(a) CH_3I (excess) (b) HCl (c) HNO_2, H_2SO_4 (d) CH_3COCl (e) CH_3MgBr (f) CH_3CH_2Cl, $AlCl_3$ (g) Product of (c) with CuCl, HCl (h) Product of (d) with CH_3CH_2Cl, $AlCl_3$

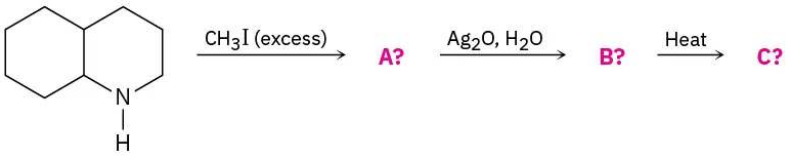
Problem 10-62 What are the major products you would expect from Hofmann elimination of the following amines?

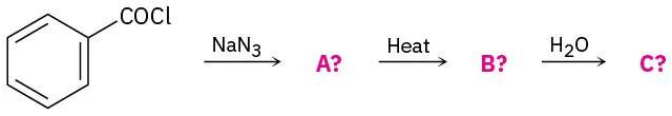
(a)


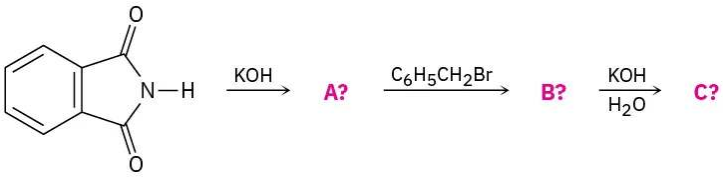
(b)


(c)


Problem 10-64 Predict the product(s) of the following reactions. If more than one product is formed, tell which is major.

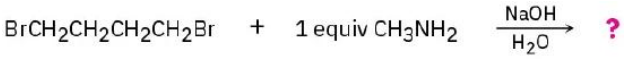
(a)


(b)


(c)


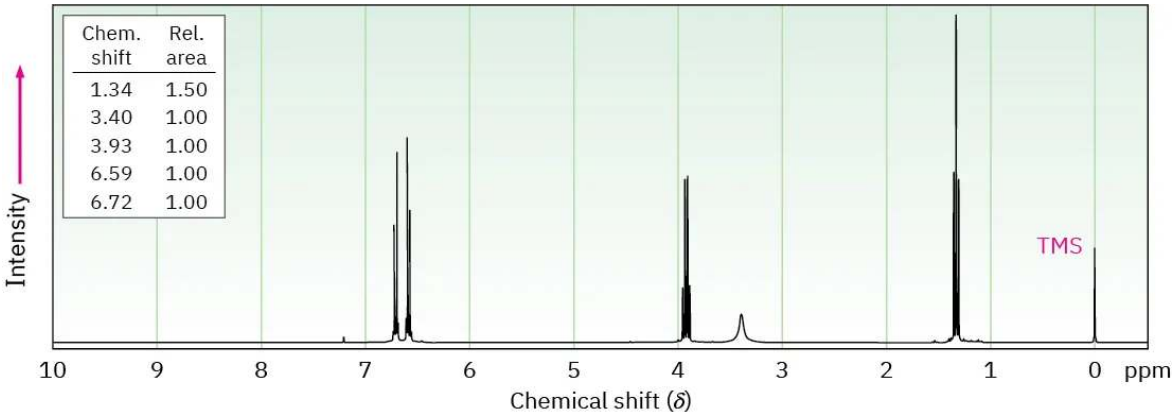
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(d)



Spectroscopy

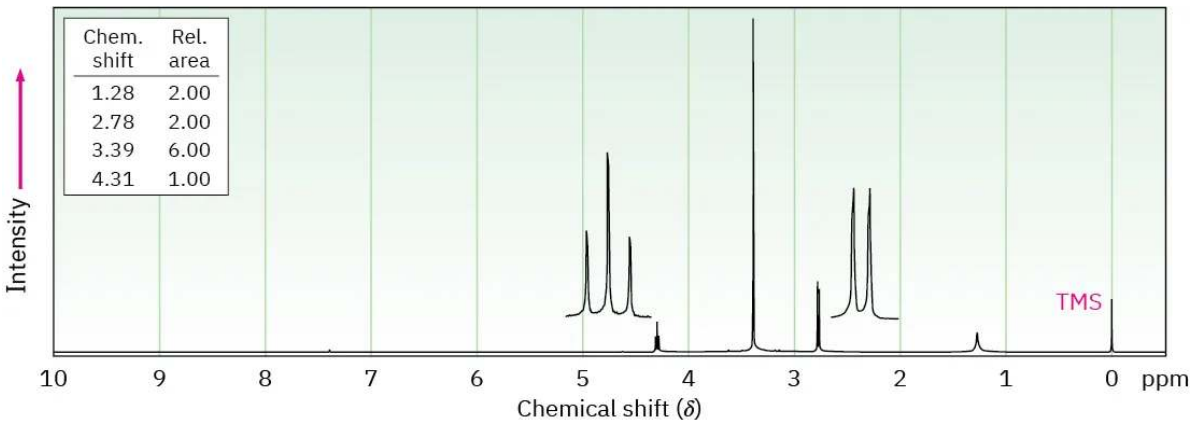
Problem 10-65 Phenacetin, a substance formerly used in over-the-counter headache remedies, has the formula $C_{10}H_{13}NO_2$. Phenacetin is neutral and does not dissolve in either acid or base. When warmed with aqueous NaOH, phenacetin yields an amine, $C_8H_{11}NO$, whose ^1H NMR spectrum is shown. When heated with HI, the amine is cleaved to an aminophenol, C_6H_7NO. What is the structure of phenacetin, and what are the structures of the amine and the aminophenol?



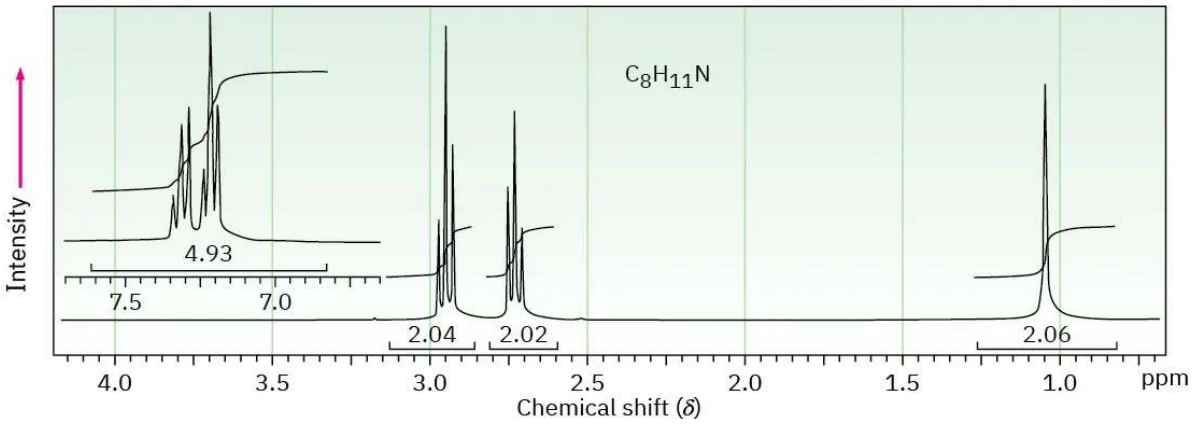
Problem 10-66 Propose structures for amines with the following 1H NMR spectra:

(a) C_3H_9NO

(b) $C_4H_{11}NO_2$



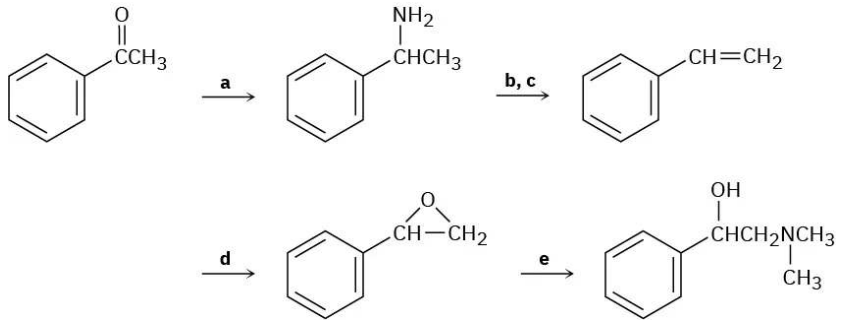
(c) $C_8H_{11}N$



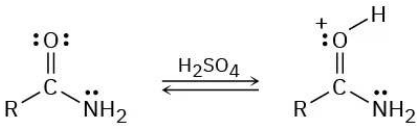
Problem 10-67 Draw the structure of the amine that produced the ^{1}H NMR spectrum shown in Problem 10-66(c). This compound has a single strong peak in its IR spectrum at 3280 cm^{-1}.

General Problems

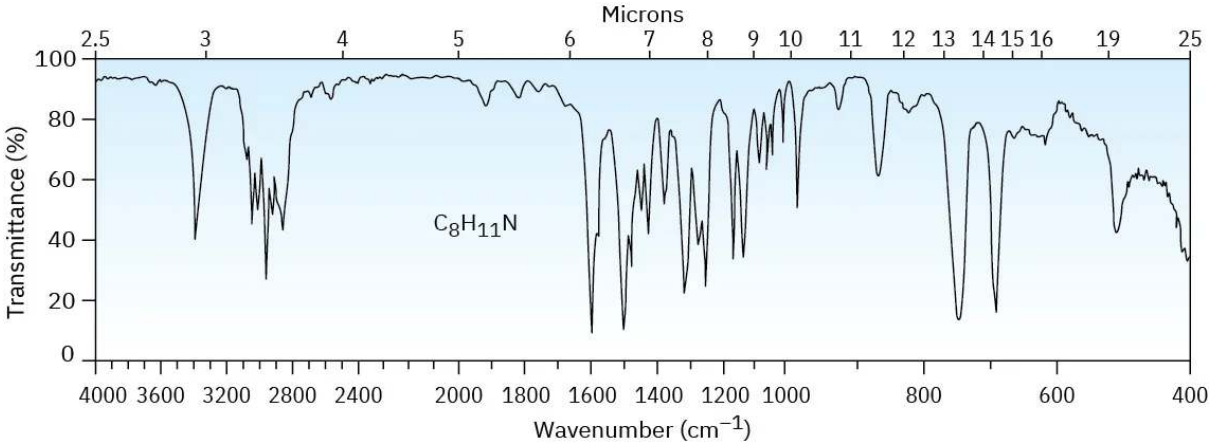
Problem 10-68 Fill in the missing reagents **a**–**e** in the following scheme:



Problem 10-70 Protonation of an amide using strong acid occurs on oxygen rather than on nitrogen. Suggest a reason for this behavior, taking resonance into account.

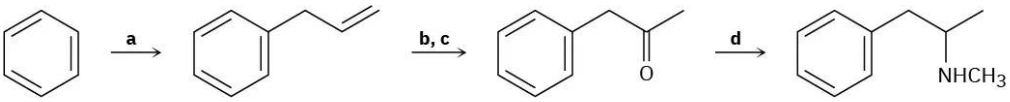


Problem 10-71 What is the structure of the compound with formula $C_8H_{11}N$ that produced the following IR spectrum?



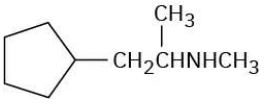
Problem 10-72 Fill in the missing reagents a–d in the following synthesis of racemic methamphetamine from benzene.

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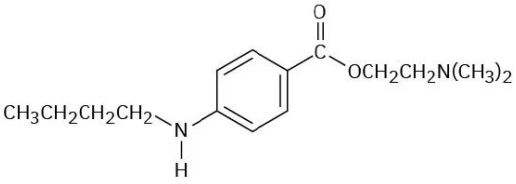
(*R*,*S*)-Methamphetamine

Problem 10-73 Cyclopentamine is an amphetamine-like central nervous system stimulant. Propose a synthesis of cyclopentamine from materials of five carbons or less.



Cyclopentamine

Problem 10-74 Tetracaine is a substance used as a spinal anesthetic.



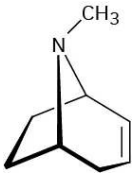
Tetracaine

(a) How would you prepare tetracaine from the corresponding aniline derivative, $ArNH_2$?

(b) How would you prepare tetracaine from *p*-nitrobenzoic acid?

(c) How would you prepare tetracaine from benzene?

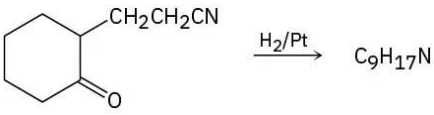
Problem 10-75 Atropine, $C_{17}H_{23}NO_3$, is a poisonous alkaloid isolated from the leaves and roots of *Atropa belladonna*, the deadly nightshade. In small doses, atropine acts as a muscle relaxant; 0.5 ng (nanogram, 10^{-9} g) is sufficient to cause pupil dilation. On basic hydrolysis, atropine yields tropic acid, $C_6H_5CH(CH_2OH)CO_2H$, and tropine, $C_8H_{15}NO$. Tropine is an optically inactive alcohol that yields tropidene on dehydration with H_2SO_4. Propose a structure for atropine.



Tropidene

Problem 10-76 Tropidene (Problem 10-75) can be converted by a series of steps into tropilidene (1,3,5-cycloheptatriene). How would you accomplish this conversion?

Problem 10-77 Propose a structure for the product with formula $C_9H_{17}N$ that results when 2-(2-cyanoethyl)cyclohexanone is reduced catalytically.

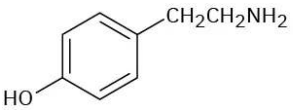


Problem 10-78 Coniine, $C_8H_{17}N$, is the toxic principle of the poison hemlock drunk by Socrates. When subjected to Hofmann elimination, coniine yields 5-(*N*,*N*-dimethylamino)-1-octene. If coniine is a secondary amine, what is its structure?

Problem 10-79 How would you synthesize coniine (Problem 10-78) from acrylonitrile ($H_2C{=}CHCN$) and ethyl 3-oxohexanoate ($CH_3CH_2CH_2COCH_2CO_2Et$)? (See Problem 10-77.)

Problem 10-80 Tyramine is an alkaloid found, among other places, in mistletoe and ripe cheese. How would you synthesize tyramine from benzene? From toluene?

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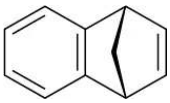


Tyramine

Problem 10-81 Reaction of anthranilic acid (*o*-aminobenzoic acid) with HNO_2 and H_2SO_4 yields a diazonium salt that can be treated with base to yield a neutral diazonium carboxylate.

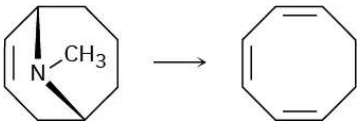
(a) What is the structure of the neutral diazonium carboxylate?

(b) Heating the diazonium carboxylate results in the formation of CO_2, N_2, and an intermediate that reacts with 1,3-cyclopentadiene to yield the following product:



What is the structure of the intermediate, and what kind of reaction does it undergo with cyclopentadiene?

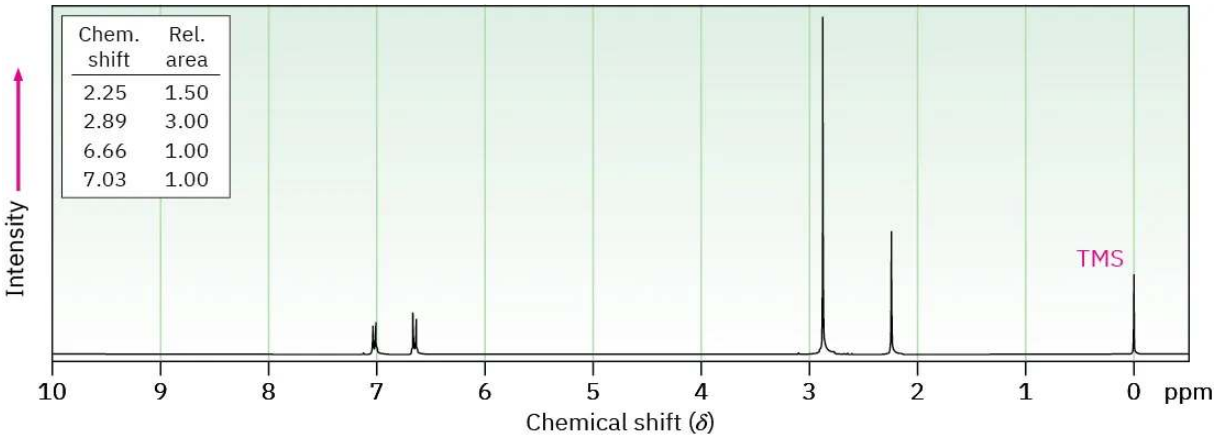
Problem 10-82 Cyclooctatetraene was first synthesized in 1911 by a route that involved the following transformation:



How might you use the Hofmann elimination to accomplish this reaction? How would you finish the synthesis by converting cyclooctatriene into cyclooctatetraene?

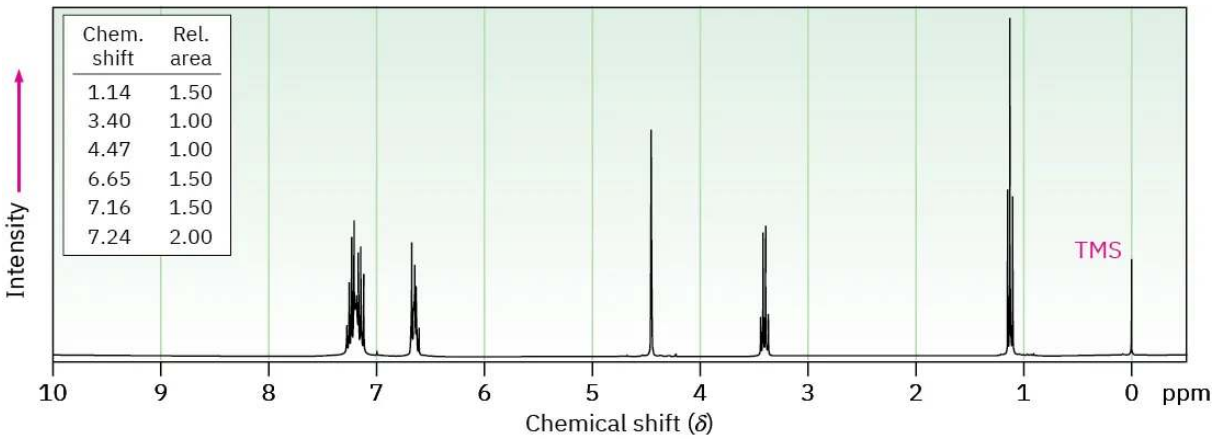
Problem 10-83 Propose structures for compounds that show the following ^1H NMR spectra.

(a) $C_9H_{13}N$

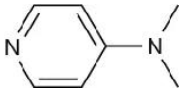


(b) $C_{15}H_{17}N$

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Problem 10-84 4-Dimethylaminopyridine (DMAP) acts as a catalyst in acyl transfer reactions. DMAP's catalytic activity stems from its nucleophilic character at the pyridine nitrogen, not the dimethylamino group. Explain this behavior, taking resonance into account.



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10.S: Amines and Heterocycles (Summary)

Concepts & Vocabulary

- Design a multi-step synthesis that involves the use of any of the reactions described in this unit.
- Solve road-map problems that require a knowledge of amine chemistry.
- Define, and use in context, the key terms introduced.

10.1 Naming Amines

- Amines are derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group.
- Several different nomenclature systems exist for naming amines, which is complicates this topic since there is no preferred option.
- The terms primary (1°), secondary (2°) & tertiary (3°) are used to classify amines by referring to the number of alkyl (or aryl) substituents bonded to the nitrogen atom.
- A nitrogen bonded to four alkyl groups will necessarily be positively charged, and is called a quaternary (4°)-ammonium cation.
- Amines are named following the IUPAC rules with -amino being added as a substitutent.
- Amines are named following the Chemical Abstract Service which the suffix -amine is attached to the root alkyl name.
- Amines are named with a common system where each alkyl substituent on nitrogen in alphabetical order, followed by the suffix -amine.

10.2 Structure and Properties of Amines

- Neutral amines have three bonds and one lone pair.
- The central nitrogen has sp^3 hybridization, which leads to trigonal pyramidal geometry with bond angles of 109.5°.
- Nitrogen does not lend to isolable stereisomers since it rapidly inverts its configuration (equilibrium arrows) by passing through a planar, sp^2-hybridized transition state, leading to a mixture of interconverting *R* and *S* configurations.
- Hydrogen bonding is the dominant factor for amines.
- Branching of amines (less bonds to Hydrogen) lowers the boiling point of amines.

10.3 Basicity of Amines

- When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic) is the lone pair on the nitrogen?
- For amines, the more alkyl groups attached, the more basic the amine is due to the electron-donating effect of the alkyl group.
- The lone pair on the nitrogen atom in an amide is in resonance with the double bond making it a more stabilized lone pair and less basic.
- In extraction, one can take advantage of amines and their basicity by forming the protonated salt ($RNH_2^+Cl^-$), which is soluble in water, in order to separate them.
- Amines are also acidic, and the same factors that decreased the basicity of amines increase their acidity.
- Amines are often utilized as bases in reactions.

10.5 Biological Amines and the Henderson-Hasselbalch Equation

- The chemistry of life occurs in a buffer that consists of a mixture of various phosphate and ammonium compounds.
- In an aqueous solution buffered at pH 7, carboxylic acid groups can be expected to be essentially 100% deprotonated and negatively charged (ie. in the carboxylate form), and amine groups essentially 100% protonated and positively charged (i.e., in the ammonium form).
- The imidizole group on the histidine side chain has a pK_a near 7, and thus exists in physiological solutions as mixture of both protonated and deprotonated forms.

10.6 Synthesis of Amines

- Secondary amines and their salts can be synthesized from primary amines and an alkyl halide.
- Tertiary amines and their salts can be synthesized from primary amines and an alkyl halide.
- Quaternary ammonium salts can be synthesized from primary amines and an alkyl halide.
- While a primary amine can by synthesized from ammonia and an alkyl halide, there are other better options.

- The reactions that provide a good route to primary amines in high yield occur in two steps.
  - First, form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile.
  - Second, any extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.
- Another option to synthesize amines is to reduce nitro groups, which include catalytic hydrogenation, zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution.
- Reacting a nitrile with lithium aluminum hydride will yield a primary amine.
- Amides can be reduced to primary, secondary or tertiary amines using lithium aluminum hydride.
- Aldehydes and ketones can be converted to primary, secondary, or tertiary amines using reductive amination.
- Hofmann rearrangement is the reaction of a primary amide with a halogen in strongly basic conditions to give a primary amine as a product.
- The Curtius rearrangement converts an acid chloride to an amine by the migration of an -R group form the carbonyl carbon to the the neighboring nitrogen in the acyl azide intermediate.

10.7 Reactions of Amines

- The direct alkylation of 1º or 2º-amines gives a more substituted product does not proceed cleanly.
- Acid chlorides can react with amines to form amides.
- Elimination reactions of 4º-ammonium salts are termed Hofmann eliminations, where the products are a tertiary amine and a alkene.
- The double bond Hofmann eliminations tends to give the less-substituted double bond isomer due to the Hofmann Rule.

10.8 Reactions of Arylamines

- Arylamines are very reactive towards electrophilic aromatic substitution substitutions.
- Aniline is a strong activating group and can overreact in electrophilic aromatic substitutions.
- Changing the functional group from an amine to an amide on an aromatic ring alters the reactivity in electrophilic aromatic substitutions for more control in the reaction.
- Sulfa drugs are an important group of synthetic antimicrobial agents (pharmaceuticals) that contain the sulfonamide group.
- The synthesis of sulfanilamide (a sulfa drug) illustrates how the reactivity of aniline can be modified to make possible an electrophilic aromatic substitution.
- Aryl diazonium salts are important intermediates, since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored.
- Diazonium ions show that the positive charge is delocalized over the two nitrogen atoms while it is not possible for nucleophiles to bond to the inner nitrogen, negative nucleophiles can bond to the terminal nitrogen gives neutral azo compounds.
- The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles.
- The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes.

10.9 Heterocyclic Amines

- Heterocyclic structures are found in many natural products an example of some nitrogen compounds, known as alkaloids because of their basic properties.
- Pyrrole is obtained commercially by the reaction of furan with ammonia.
- In a pyrrole ring, the nitrogen lone pair is part of the aromatic sextet, thus not very basic.
- Substitution preference is on the 2-position of pyrrole.
- Imidazole is another five-membered heterocyclic amine, which is part of the amino acid histidine.
- Thiazole is a five-membered ring system which is found in biological systems.
- When a nitrogen atom is incorporated directly into an aromatic ring, its basicity depends on the bonding context.
- In pyridine, the nitrogen lone pair occupies an sp^2-hybrid orbital, and is not part of the aromatic sextet, therefore, its electron pair is available for forming a bond to a proton, and thus the pyridine nitrogen atom is somewhat basic.
- The aromatic stabilization energy of pyridine is 21 kcal/mole based on heat of combustion measurements.
- Polycyclic heterocyclic structures are found in many natural products like caffeine.

- Derivatives of the simple fused ring heterocycle purine constitute an especially important and abundant family of natural products.
- The amino compounds adenine and guanine are two of the complementary bases that are essential components of DNA.

10.10 Spectroscopy of Amines

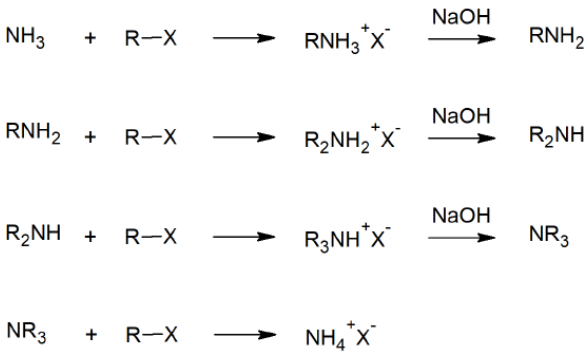
- The hydrogens attached to an amine show up ~ 0.5-5.0 ppm in ^{1}H NMR.
- The broad range is due to the fact that the location is dependent on the amount of hydrogen bonding and the sample's concentration.
- The hydrogens on carbons directly bonded to an amine typically appear ~2.3-3.0 ppm in ^{1}H NMR.
- IR for primary amines a free N-H absorption is observed in the 3400 to 3500 cm^{-1} region as two well-defined peaks.
- IR for amines the C-N stretching absorptions are found at 1200 to 1350 cm^{-1} for aromatic amines, and at 1000 to 1250 cm^{-1} for aliphatic amines.
- Secondary amines exhibit only one absorption near 3420 cm^{-1} in IR.
- For tertiary amines, there is not N-H stretch.

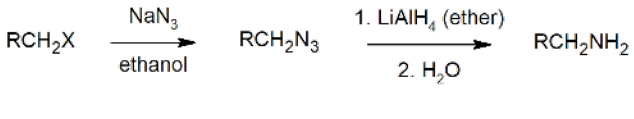
Skills to Master

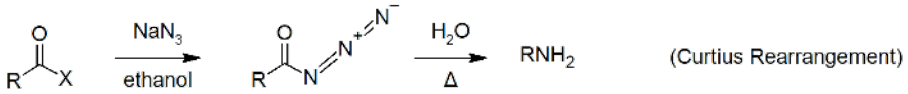
- Skill 1 Name amines using IUPAC rules.
- Skill 2 Draw the structure of amines from the IUPAC name.
- Skill 3 Describe the geometries and approximate bond angles of amines.
- Skill 4 Explain physical properties of amines.
- Skill 5 Explain why one amine is more basic than another.
- Skill 6 Explain how the basicity of an amine when the Nitrogen atom is incorporated in a ring depends on the bonding context.
- Skill 7 Describe how an amine can be extracted from a mixture that also contains neutral compounds illustrating the reactions which take place with appropriate equations.
- Skill 8 Explain why primary and secondary (but not tertiary) amines may be regarded as very weak acids.
- Skill 9 Use the concept of resonance to explain why arylamines are less basic than their aliphatic counterparts.
- Skill 10 Arrange a given series of arylamines in order of increasing or decreasing basicity.
- Skill 11 Explain using inductive and resonance effects arguments as to why a given arylamine is more or less basic than aniline.
- Skill 12 Identify the form that amine bases take within living cells.
- Skill 13 Use the Henderson-Hasselbalch equation to calculate the percentage of a base that is protonated in a solution, given the pK_a value of the associated ion and the pH of the solution.
- Skill 14 List general ways to synthesize amines.
- Skill 15 Draw mechanisms for preparing amines, including:
  - reduction of nitriles, amides, and nitro compounds.
  - Reactions involving alkyl groups:
    1. S_N2 reactions of alkyl halides, ammonia, and other amines.
    2. nucleophilic attack by an azide ion on an alkyl halide, followed by reduction of the azide so formed.
    3. alkylation of potassium phthalimide, followed by hydrolysis of the *N*-alkyl phthalimide so formed (i.e., the Gabriel synthesis).
  - reductive amination of aldehydes or ketones.
  - Hofmann or Curtius rearrangements.
- Skill 16 Write an equation to represent the reaction that takes place between ammonia, a primary or secondary amine, and an acid chloride.
- Skill 17 Identify the product formed when a given amine reacts with a given acid chloride.
- Skill 18 Draw the product for a Hoffman elimination.
- Skill 19 Use IR, NMR and MS in combination with the nitrogen rule to identify amines.

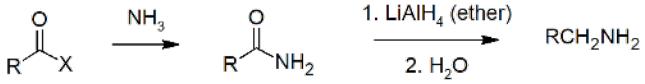
Summary of Reactions

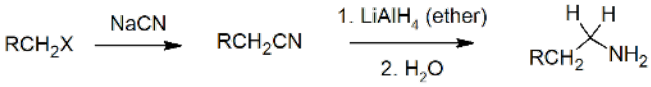
Amine Preparation

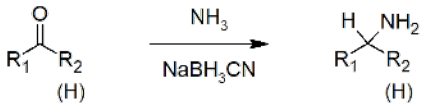


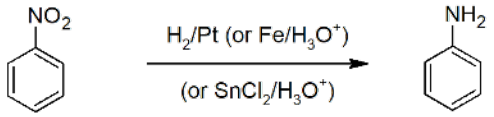


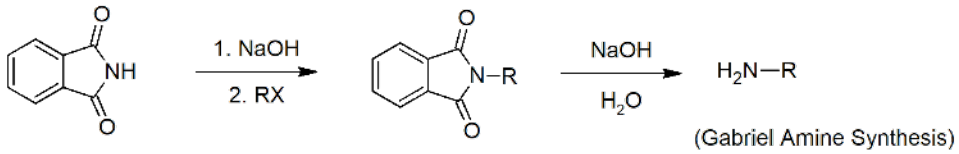






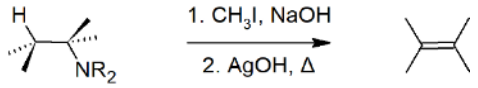


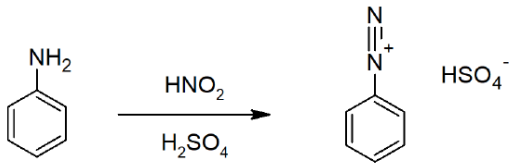


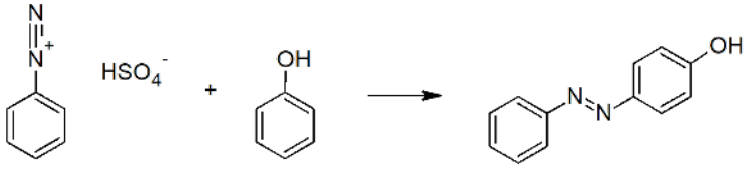


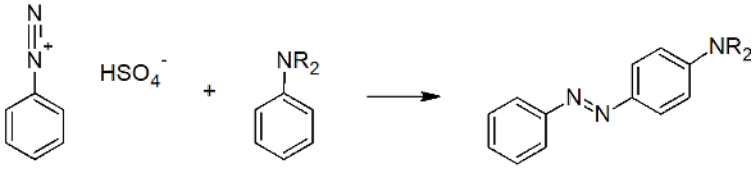


Amine Reactions

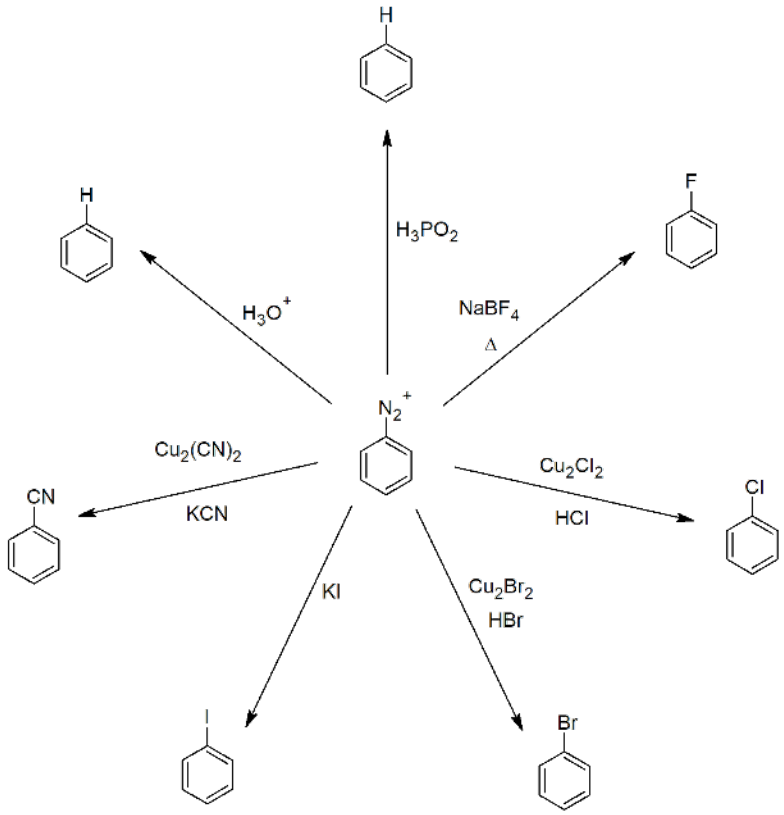








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CHAPTER OVERVIEW

11: Biomolecules - Carbohydrates

The chapter begins with an explanation of the classification schemes used to simplify the study of carbohydrates. We make extensive use of Fischer projection formulas throughout the chapter. We place considerable emphasis on gaining an appreciation of the configurations of carbohydrates, particularly of the aldoses. We describe the disadvantages of representing monosaccharides by open-chain structures, and at this point, introduce you to cyclic representations—called Haworth projections—of these substances. We describe the mutarotation of glucose, explaining it in terms of the existence of anomers. We then examine some reactions of monosaccharides, including the formation of ethers and esters, the formation of glycosides, and reduction and oxidation. We discuss the structures of some common disaccharides and polysaccharides, and conclude the chapter with a brief explanation of the role played by carbohydrates in cell recognition.

11.0: Introduction
11.1: Classification of Carbohydrates
11.2: Depicting Carbohydrate Stereochemistry - Fischer Projections
11.3: D, L Sugars
11.4: Configurations of Aldoses
11.5: Cyclic Structures of Monosaccharides - Anomers
11.6: Reactions of Monosaccharides
11.7: The Eight Essential Monosaccharides + Fructose
11.8: Disaccharides
11.9: Polysaccharides and Their Synthesis
11.10: Other Important Carbohydrates
11.11: Cell-Surface Carbohydrates and Influenza Viruses
11.12: Additional Problems
11.S: Biomolecules- Carbohydrates (Summary)

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11.0: Introduction

Objectives

After completing this section, you should be able to

1. identify carbohydrates (sugars) as being polyhydroxylated aldehydes and ketones.
2. describe, briefly, the process of photosynthesis, and identify the role played by carbohydrates as an energy source for living organisms.

Key Terms

Make certain that you can define, and use in context, the key term below.

- carbohydrate

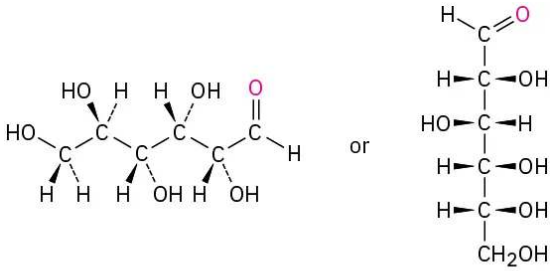
We've now seen all the common functional groups and reaction types that occur in organic and biological chemistry. In this and the next four chapters, we'll focus on the major classes of biological molecules, beginning with a look at the structures and primary biological functions of carbohydrates.



Figure 11.0.1: Produced by honeybees from the nectar of flowers, honey is primarily a mixture of the two simple sugars fructose and glucose. (credit: modification of work "Apis mellifera" by Thomas Bresson/Flickr, CC BY 2.0)

Carbohydrates occur in every living organism. The sugar and starch in food, and the cellulose in wood, paper, and cotton are nearly pure carbohydrates. Modified carbohydrates form part of the coating around living cells, other carbohydrates are part of the nucleic acids that carry our genetic information, and still others are used as medicines.

The word carbohydrate derives historically from the fact that glucose, the first simple carbohydrate to be obtained in pure form, has the molecular formula $C_6H_{12}O_6$ and was originally thought to be a "hydrate of carbon, $C_6(H_2O)_6$." This view was soon abandoned, but the name persisted. Today, the term *carbohydrate* is used to refer loosely to the broad class of polyhydroxylated aldehydes and ketones commonly called sugars. Glucose, also known as dextrose in medical work, is the most familiar example.



Glucose (dextrose), a pentahydroxyhexanal

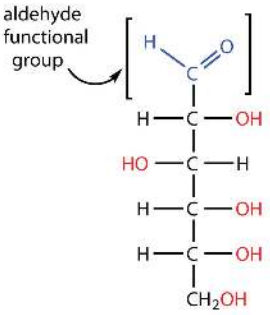
Carbohydrates are synthesized by green plants during photosynthesis, a complex process in which sunlight provides the energy to convert CO_2 and H_2O into glucose plus oxygen. Many molecules of glucose are then chemically linked for storage by the plant in the form of either cellulose or starch. It has been estimated that more than 50% of the dry weight of the earth's biomass—all plants and animals—consists of glucose polymers. When eaten and metabolized, carbohydrates then provide animals with a source of readily available energy. Thus, carbohydrates act as the chemical intermediaries by which solar energy is stored and used to support life.

$$6\,CO_2 + 6\,H_2O \xrightarrow{\text{Sunlight}} 6\,O_2 + \underbrace{C_6H_{12}O_6}_{\textbf{Glucose}} \longrightarrow \text{Cellulose, starch}$$

Because humans and most other mammals lack the enzymes needed for the digestion of cellulose, they require starch as their dietary source of carbohydrates. Grazing animals such as cows, however, have microorganisms in their first stomach that are able to digest cellulose. The energy stored in cellulose is thus moved up the biological food chain when these ruminant animals eat grass and are themselves used for food.

Introduction

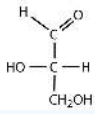
All carbohydrates consist of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes or ketones or are compounds that can be broken down to form such compounds. Examples of carbohydrates include starch, fiber, the sweet-tasting compounds called sugars, and structural materials such as cellulose. The term *carbohydrate* had its origin in a misinterpretation of the molecular formulas of many of these substances. For example, because its formula is $C_6H_{12}O_6$, glucose was once thought to be a "carbon hydrate" with the structure $C_6{\cdot}6H_2O$.



Because glucose has an aldehyde functional group and several –OH (hydroxyl) groups, it is described as a polyhydroxy aldehyde.

Example 1

Which compounds would be classified as carbohydrates?

a. 

b. 

c. 

d. 

Solution

a. This is a carbohydrate because the molecule contains an aldehyde functional group with OH groups on the other two carbon atoms.

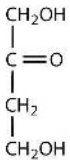
b. This is not a carbohydrate because the molecule does not contain an aldehyde or a ketone functional group.

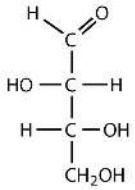
c. This is a carbohydrate because the molecule contains a ketone functional group with OH groups on the other two carbon atoms.

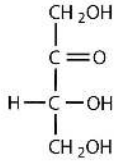
d. This is not a carbohydrate; although it has a ketone functional group, one of the other carbons atoms does not have an OH group attached.

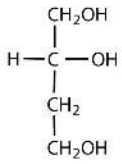
Exercise 1

Which compounds would be classified as carbohydrates?

a. 

b. 

c. 

d. 

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11.1: Classification of Carbohydrates

Objectives

After completing this section, you should be able to

1. classify a specific carbohydrate as being a monosaccharide, disaccharide, trisaccharide, etc., given the structure of the carbohydrate or sufficient information about its structure.
2. classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.

Key Terms

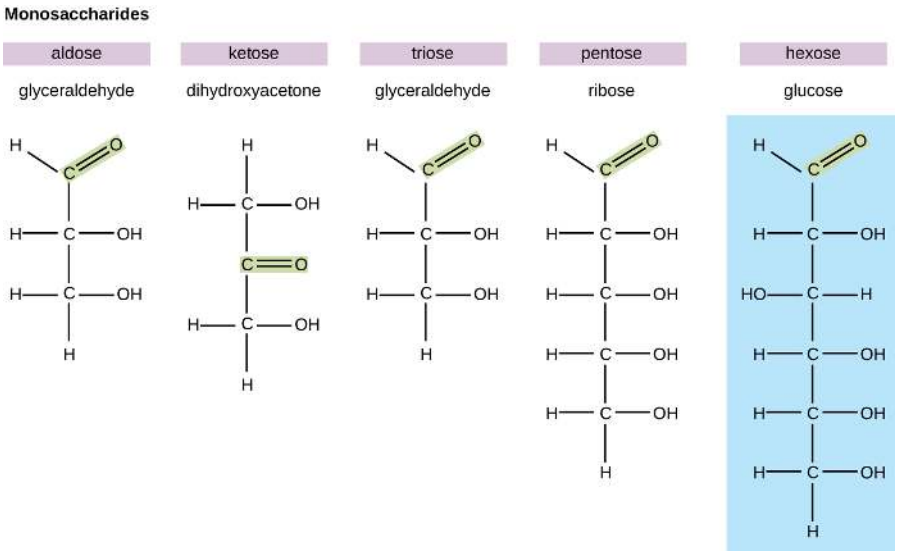
Make certain that you can define, and use in context, the following key terms: aldose; disaccharide; ketose; monosaccharide (simple sugar); and polysaccharide.

What Are Carbohydrates?

The most abundant biomolecules on earth are carbohydrates. From a chemical viewpoint, carbohydrates are primarily a combination of carbon and water, and many of them have the empirical formula $(CH_2O)_n$, where *n* is the number of repeated units. This view represents these molecules simply as “hydrated” carbon atom chains in which water molecules attach to each carbon atom, leading to the term “carbohydrates.” Although all carbohydrates contain carbon, hydrogen, and oxygen, there are some that also contain nitrogen, phosphorus, and/or sulfur. Carbohydrates have myriad different functions. They are abundant in terrestrial ecosystems, many forms of which we use as food sources. These molecules are also vital parts of macromolecular structures that store and transmit genetic information (i.e., DNA and RNA). They are the basis of biological polymers that impart strength to various structural components of organisms (e.g., cellulose and chitin), and they are the primary source of energy storage in the form of starch and glycogen.

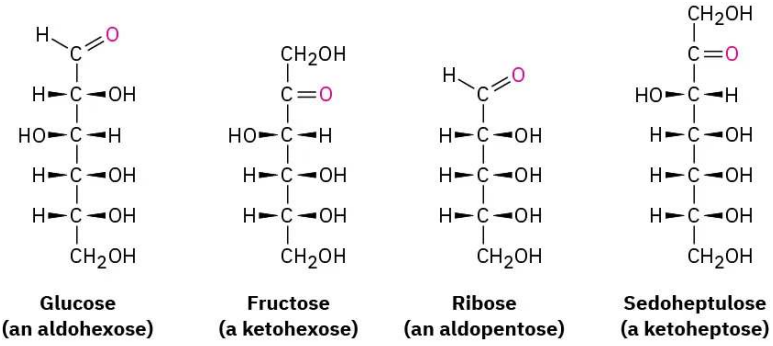
Monosaccharides

In biochemistry, carbohydrates are often called saccharides, from the Greek *sakcharon*, meaning sugar, although not all the saccharides are sweet. The simplest carbohydrates are called monosaccharides, or simple sugars. They are the building blocks (monomers) for the synthesis of polymers or complex carbohydrates, as will be discussed further in this section. Monosaccharides are classified based on the number of carbons in the molecule. General categories are identified using a prefix that indicates the number of carbons and the suffix *–ose*, which indicates a saccharide; for example, triose (three carbons), tetrose (four carbons), pentose (five carbons), and hexose (six carbons). The hexose D-glucose is the most abundant monosaccharide in nature. Other very common and abundant hexose monosaccharides are galactose, used to make the disaccharide milk sugar lactose, and the fruit sugar fructose.



A second comparison can be made when looking at glucose, galactose, and **fructose**. All three are hexoses; however, there is a major structural difference between glucose and galactose versus fructose: the carbon that contains the **carbonyl** (C=O). In glucose and galactose, the carbonyl group is on the C_1 carbon, forming an **aldehyde** group. In fructose, the carbonyl group is on the C_2 carbon, forming a **ketone** group. The former sugars are called **aldoses** based on the aldehyde group that is formed; the latter is designated as a **ketose** based on the ketone group. Again, this difference gives fructose different chemical and structural properties from those of the related aldoses, glucose, and galactose, even though fructose, glucose, and galactose all have the same chemical composition: $C_6H_{12}O_6$.

Putting it all together, glucose is an aldohexose, a six-carbon aldehyde sugar; fructose is a ketohexose, a six-carbon keto sugar; ribose is an aldopentose, a five-carbon aldehyde sugar; and sedoheptulose is a ketoheptose, a seven-carbon keto sugar. Most of the common simple sugars are either pentoses or hexoses.



Complex Carbohydrates

The simple sugars form the foundation of more complex carbohydrates. The cyclic forms of two sugars can be linked together by means of a condensation reaction to form a disaccharide. Multiple sugars can be linked to form polysaccharides.

Disaccharides

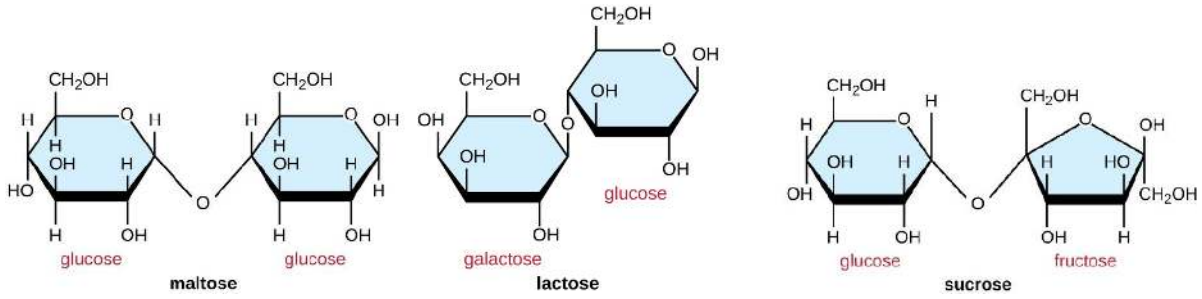
Two monosaccharide molecules may chemically bond to form a disaccharide. The name given to the covalent bond between the two monosaccharides is a glycosidic bond. **Glycosidic bonds** form between hydroxyl groups of the two saccharide molecules, an example of the dehydration synthesis described later in this chapter.

(7.2.1)monosaccharide—OH+HO—monosaccharide⟶monosaccharide—O—monosaccharide_disaccharide" id="MathJax-Element-6-Frame" role="presentation" style="position:relative;" tabindex="0">

$$\text{monosaccharide—OH} + \text{HO—monosaccharide} \longrightarrow \underbrace{\text{monosaccharide—O—monosaccharide}}_{\text{disaccharide}}$$

https://chem.libretexts.org/@go/page/500484

Common disaccharides are the grain sugar maltose, made of two glucose molecules; the milk sugar lactose, made of one galactose and one glucose molecule; and the table sugar sucrose, made of one glucose and one fructose molecule.

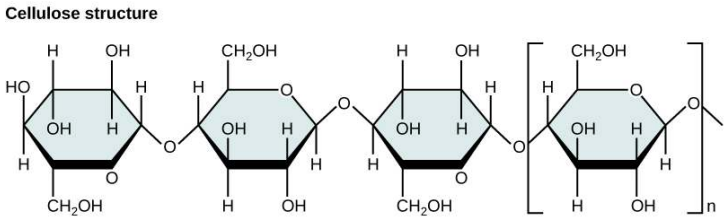


(7.2.1)monosaccharide—OH+HO—monosaccharide⟶monosaccharide—O—monosaccharide␣disaccharide" role="presentation" style="position:relative;" tabindex="0">

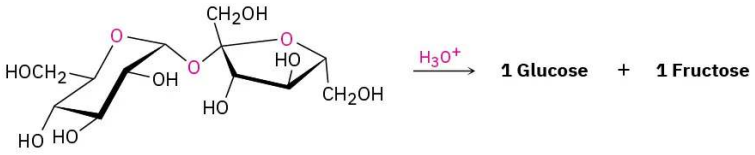
Polysaccharides

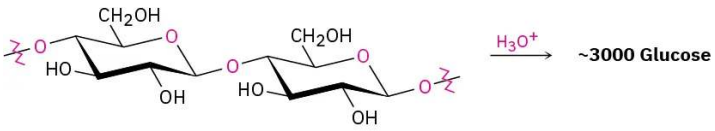
Polysaccharides, also called glycans, are large polymers composed of hundreds of monosaccharide monomers. Unlike mono- and disaccharides, polysaccharides are not sweet and, in general, they are not soluble in water. Like disaccharides, the monomeric units of polysaccharides are linked together by glycosidic bonds.

Polysaccharides are very diverse in their structure. Three of the most biologically important polysaccharides—starch, glycogen, and cellulose—are all composed of repetitive glucose units, although they differ in their structure. **Cellulose** consists of a linear chain of glucose molecules and is a common structural component of cell walls in plants and other organisms. **Glycogen** and **starch** are branched polymers; glycogen is the primary energy-storage molecule in animals and bacteria, whereas plants primarily store energy in starch. The orientation of the glycosidic linkages in these three polymers is different as well and, as a consequence, linear and branched macromolecules have different properties.



Enzyme-catalyzed hydrolysis of a complex carbohydrate breaks it down into its constituent monosaccharides.





Summary

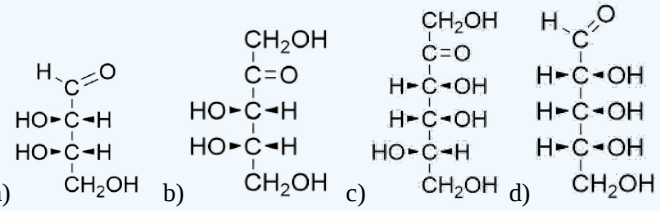
Complexity	**Simple Carbohydrates** monosaccharides	**Complex Carbohydrates** disaccharides, oligosaccharides & polysaccharides

Size	**Tetrose** C_4 sugars	**Pentose** C_5 sugars	**Hexose** C_6 sugars	**Heptose** C_7 sugars	etc.

C=O Function	**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.

? Exercise 11.1.1

1) Classify each of the following sugars.



Answer

a. Aldotetrose
b. Ketopentose
c. Ketohexose
d. Aldopentose

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11.2: Depicting Carbohydrate Stereochemistry - Fischer Projections

Objectives

After completing this section, you should be able to

1. draw the Fischer projection of a monosaccharide, given its wedge and dash structure or a molecular model.
2. draw the wedge and dash structure of a monosaccharide, given its Fischer projection or a molecular model.
3. construct a molecular model of a monosaccharide, given its Fischer projection or wedge and dash structure.

Key Terms

Make certain that you can define, and use in context, the key term below.

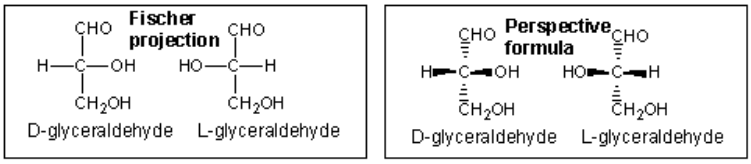
- Fischer projection

Study Notes

When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often the simplest way to check is to construct a molecular model corresponding to each projection formula, and then compare the two models.

Drawing Representations of 3D Structures

The problem of drawing three-dimensional configurations on a two-dimensional surface, such as a piece of paper, has been a long-standing concern of chemists. The wedge and dash notations we have been using are effective, but can be troublesome when applied to compounds having many chiral centers. As part of his Nobel Prize-winning research on carbohydrates, the great German chemist Emil Fischer, devised a simple notation that is still widely used. Fischer Projections allow us to represent 3D molecular structures in a 2D environment without changing their properties and/or structural integrity.



Below in Figure 11.2.1 are different representations of (R)-glyceraldehyde, the smallest sugar molecule (also called D-glyceraldehyde in the stereochemical nomenclature used for sugars):

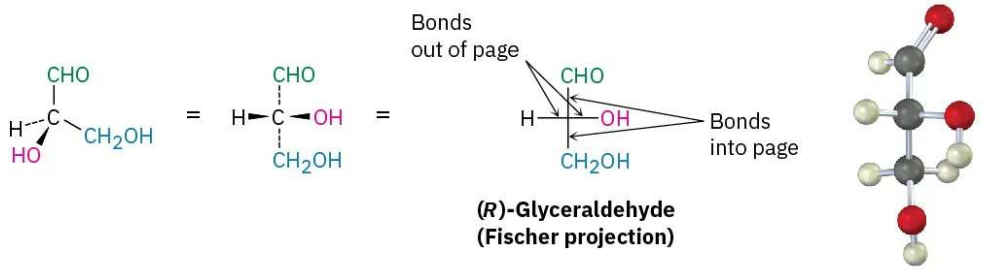
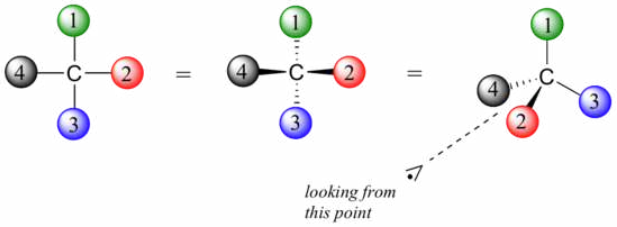
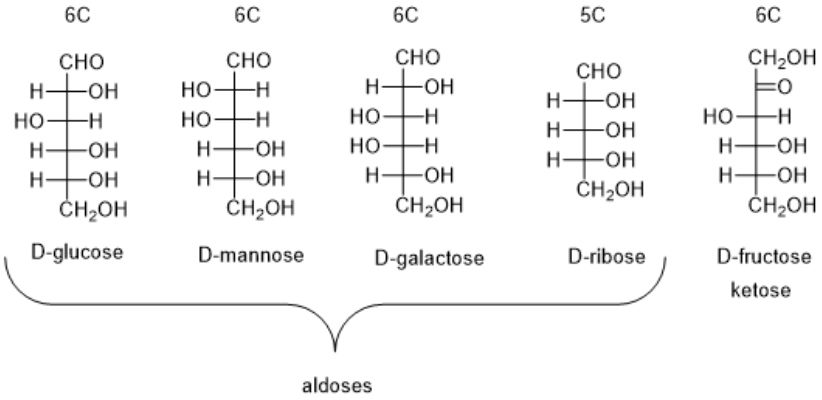


Figure 11.2.1: A Fischer projection of (*R*)-glyceraldehyde (D-glyceraldehyde).

Fischer projections show sugars in their open-chain form. In a Fischer projection, the carbon atoms of a sugar molecule are connected vertically by solid lines, while carbon-oxygen and carbon-hydrogen bonds are shown horizontally. Stereochemical information is conveyed by a simple rule: vertical bonds point into the plane of the page, while horizontal bonds point out of the page.



The Fisher structures of the most common monosaccharides (other than glyceraldehyde and dihydroxyacetone), which you will encounter most frequently, are shown below.

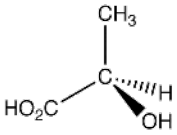


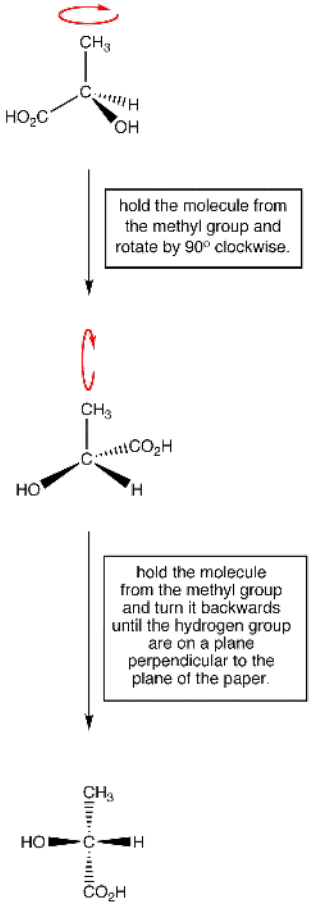
How to Draw Fischer Projections

A Fischer projection or Fischer projection formula is a convention used to depict a stereoformula in two dimension without destroying the stereochemical information, i.e., absolute configuration, at chiral centers. To make a Fischer Projection, it is easier to show through examples than through words. Let's start with the first example, turning a 3D structure of (*R*)-Lactic acid into a 2D Fischer Projection.

To convert this stereoformula into a Fischer projection use the following procedure:

(*R*)-Lactic acid:





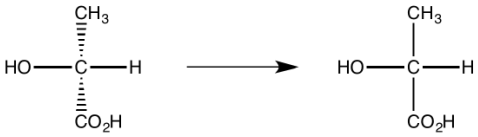
Step 1: Hold the molecule so that

1. the chiral center and the methyl group are vertically aligned and on the plane of the paper,
2. Rotate the molecule, keeping the methyl group up and in the plane of the paper, until the two groups that are not part of the main chain are horizontal and coming out of the plane of the paper.
3. Keeping th emethyl group up, the two remaining bonds are going into the plane of the paper and are on a vertical plane

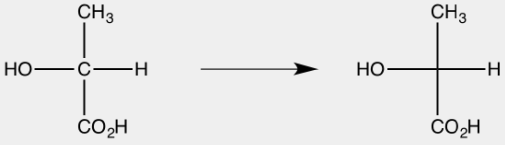
Step 2: Push the two bonds coming out of the plane of the paper onto the plane of the paper.



Step 3: Pull the two bonds going into the plane of the paper onto the plane of the paper.



Step 4: Omit the chiral atom symbol for convenience.



How to Draw Wedge and Dash Structures from Fischer Projections

Sugars can be drawn in the straight chain form as either Fisher projections or perspective structural formulas. Below in Figure 11.2.2 are Fisher projections and perspective structural representation of (R)-glyceraldehyde (D-glyceraldehyde):

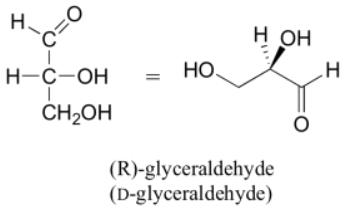
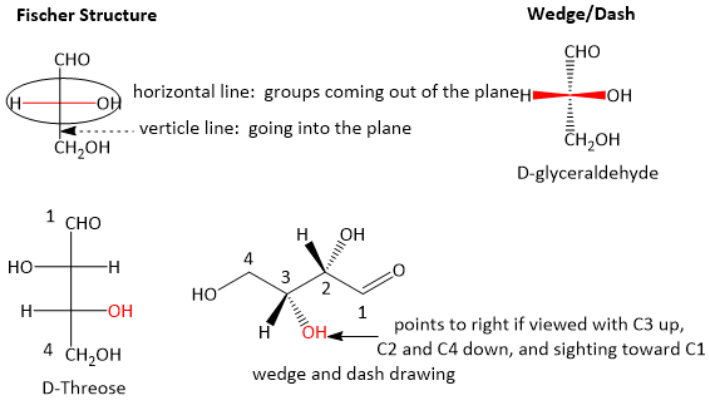


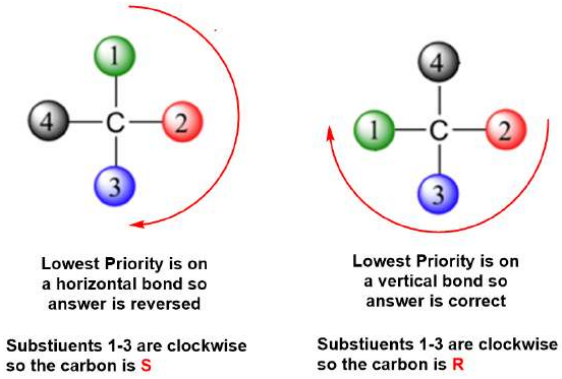
Figure 11.2.2: A Fischer projection and perspective structural representation of (*R*)-glyceraldehyde (D-glyceraldehyde).

In the Fisher projection, the vertical bonds point down into the plane of the paper. That's easy to visualize for 3C molecules. but more complicated for bigger molecules. For those draw a wedge and dash line drawing of the molecule. When determining the orientation of the hydroxides on each C, orient the wedge and dash drawing in your mind so that the C atoms adjacent to the one of interest are pointing down. Sighting towards the carbonyl C, if the OH is pointing to the right in the Fisher project, it should be pointing to the right in the wedge and dash drawing, as shown below for D-erthyrose.



Determining R and S in Fischer Projections

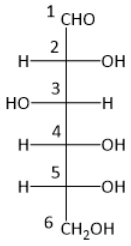
Determining whether a chiral carbon is R or S may seem difficult when using Fischer projections, but it is actually quite simple. If the lowest priority group (often a hydrogen) is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents. If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer (you are in looking at the configuration from the wrong side), so you simply reverse it.



Worked Example 11.2.1

Determine if carbon #2 in D-glucose is R or S.

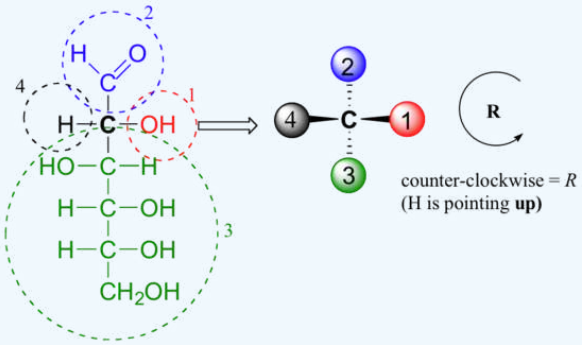
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D-Glucose

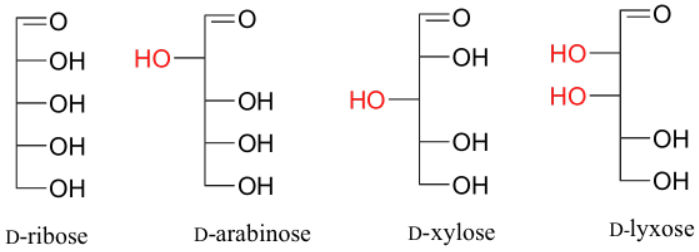
Answer

When deciding whether a stereocenter in a Fischer projection is *R* or *S*, realize that the hydrogen, in a horizontal bond. Therefore, the orientation of the three remaining substituents is reversed to create the correct answer or a counterclockwise circle means *R*, and a clockwise circle means *S*. For carbon #2 in D-Glucose substituent 1, 2, and 3 form a counterclockwise circle so the carbon is R.



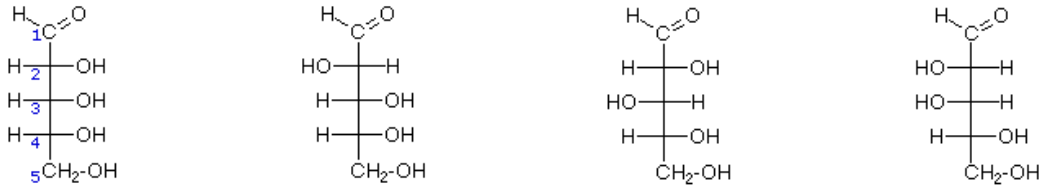
Determining Isomeric Relationships in Fischer Projections

Fischer projections are useful when looking at many different diastereomeric sugar structures, because the eye can quickly pick out stereochemical differences according to whether a hydroxyl group is on the left or right side of the structure.



The usefulness of this notation to Fischer, in his carbohydrate studies, is evident in the following diagram. There are eight stereoisomers of 2,3,4,5-tetrahydroxypentanal, a group of compounds referred to as the aldopentoses (aldo- since the oxidized carbon is an aldehyde and -pentose since the molecules contain 5 carbons). Since there are three chiral centers in this constitution, we should expect a maximum of 2^3 stereoisomers. These eight stereoisomers consist of four sets of enantiomers. If the configuration at C-4 is kept constant (*R* in the examples shown here), the four stereoisomers that result will be **diastereomers**.

Four Diastereomeric $C_5H_{10}O_5$ Aldopentoses

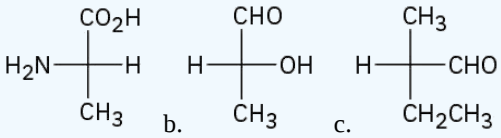


D-(-)-ribose (2*R*, 3*R*, 4*R*) | D-(-)-arabinose (2*S*, 3*R*, 4*R*) | D-(+)-xylose (2*R*, 3*S*, 4*R*) | D-(-)-lyxose (2*S*, 3*S*, 4*R*)

The aldopentose structures drawn above are all diastereomers. A more selective term, **epimer**, is used to designate diastereomers that differ in configuration at only one chiral center. Thus, ribose and arabinose are epimers at C-2, and arabinose and lyxose are epimers at C-3. However, arabinose and xylose are not epimers, since their configurations differ at both C-2 and C-3.

Exercise 11.2.1

Convert each of the following Fischer projections into a tetrahedral representation and assign *R* or *S* stereochemistry:



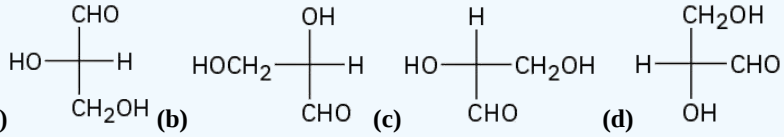
a. b. c.

Answer

a. S b. R c. S

Exercise 11.2.2

Which of the following Fischer projections of glyceraldehyde represent the same enantiomer?



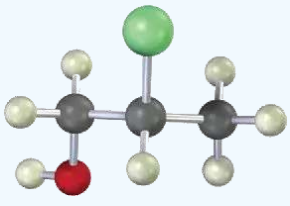
(a) **(b)** **(c)** **(d)**

Answer

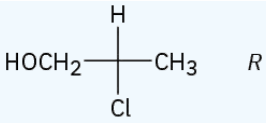
A, B, and C are the same.

Exercise 11.2.3

Redraw the following molecule as a Fischer projection, and assign *R* or *S* configuration to the chirality center (green = Cl):

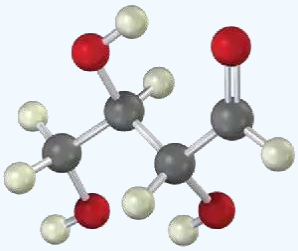


Answer

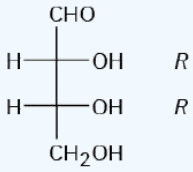


Exercise 11.2.4

Redraw the following aldotetrose as a Fischer projection, and assign *R* or *S* configuration to each chirality center:



Answer

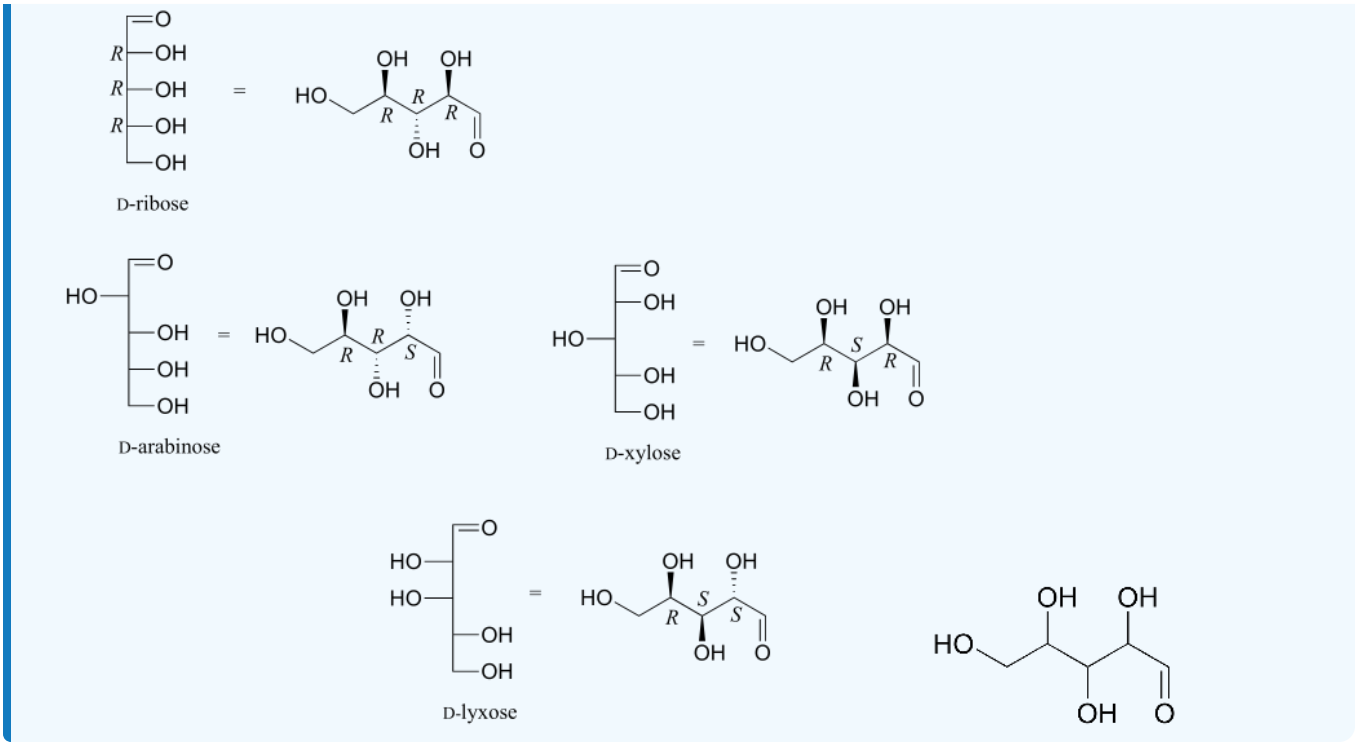


Exercise 11.2.5

Draw 'zigzag' structures (using the solid/dash wedge convention to show stereochemistry) for the following sugars. Label all stereocenters *R* or *S*.

a) D-ribose, b) D-arabinose, c) D-xylose, d) D-lyxose.

Answer



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11.3: D, L Sugars

Objectives

After completing this section, you should be able to

1. identify a specific enantiomer of a monosaccharide as being D or L, given its Fischer projection.
2. identify the limitations of the D, L system of nomenclature for carbohydrates.
3. assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
4. draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
5. construct a molecular model of a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.

Key Terms

Make certain that you can define, and use in context, the key terms below.

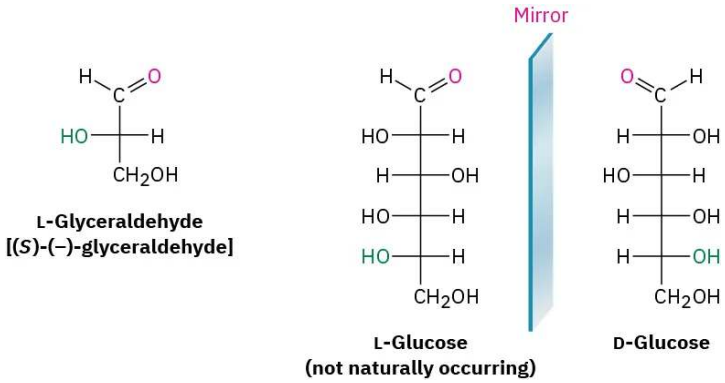
- D sugar
- L sugar

D and L Labeling of Monosaccharide Stereochemistry

Glyceraldehyde, the simplest possible aldose, is made up of three carbons, and only one these is chiral. Glyceraldehyde has two stereoisomers, an R/S pair of enantiomers. Before the R,S system for designating chiral configuration was adopted by organic chemists (R)-glyceraldehyde was called D-glyceraldehyde (Latin for right: dexter), and (S)-glyceraldehdye was called L-glyceraldehyde (Latin for left:laevus).

D- and L-glyceraldehyde were then used to provide reference points for designating and drawing all other monosaccharides. Sugars whose Fischer projections have the same configuration at the chiral carbon furthest from the carbonyl group as D-glyceraldehyde are designated as **D sugars**; those with the same configuration as L-glyceraldehyde are designated as **L sugars**. D and L designations of sugars are based on the position of the hydroxyl on the chiral carbon farthest from the carbonyl group in the Fischer projection of the molecule. All D-sugars have the –OH on the right side, and L-sugars have the –OH on the left side.

In contrast with D sugars, L sugars have an *S* configuration at the lowest chirality center, with the bottom –OH group pointing to the left in Fischer projections. Thus, an L sugar is the mirror image (enantiomer) of the corresponding D sugar and has the opposite configuration from the D sugar at all chirality centers.



Because of the way that monosaccharides are biosynthesized in nature, glucose, fructose, and most other naturally occurring monosaccharides all have the same *R* stereochemical configuration as D-glyceraldehyde at the chirality center farthest from the carbonyl group. In Fischer projections, therefore, most naturally occurring sugars have the hydroxyl group at the bottom chirality center pointing to the right (Figure 11.3.1). Such compounds are referred to as D sugars.

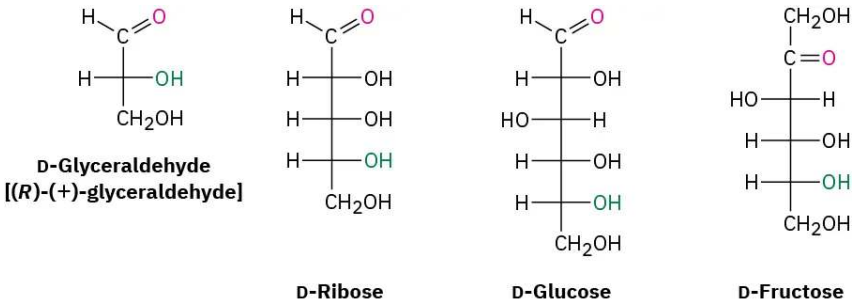


Figure 11.3.1: Some naturally occurring D sugars. The –OH group at the chirality center farthest from the carbonyl group has the same configuration as (*R*)-(+)-glyceraldehyde and points toward the right in Fischer projections.

D-sugars predominate in nature, though L-forms of some sugars, such as fucose, do exist. The D and L designation is a bit more complicated than it would appear on the surface. The confusion about D and L arises because the L sugars of a given name (glucose, for example) are mirror images of the D sugars of the same name. This concept is most easily seen with glyceraldehyde. In the same way D- and L- glyceraldehyde represent two enantiomers, the D- and L- forms larger monosaccharides are enantiomers of one another. The figure below shows the structure of D- and L- glucose. Notice that D-glucose is not converted into L-glucose simply by flipping the configuration of the fifth carbon in the molecule. Rather, all of the arrangements around all of the chiral centers (horizontal lines) in the Fischer project of D-glucose need to be opposite to make L-glucose.

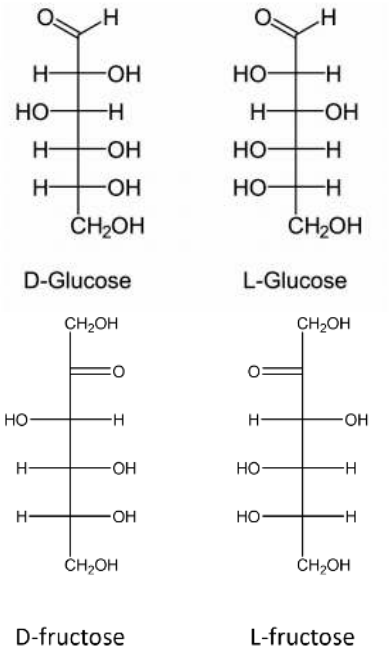
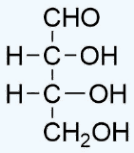


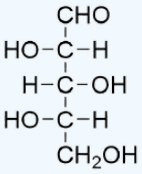
Figure 11.3.2: Fischer projections of enantiomers of glucose (left) and fructose (right).

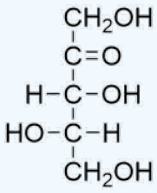
It is important to recognize that the sign of a compound's specific rotation of plane polarized light (+)/(−) does not correlate with its configuration (D or L). The D/L labeling does not indicate which enantiomer is (+)/(−). Rather, it says that the compound's stereochemistry is related to that of the D or L enantiomer of glyceraldehyde. It is a simple matter to measure an optical rotation with a polarimeter. Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

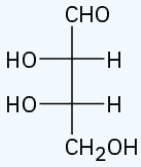
? Exercise 11.3.1

In the following Fischer projections, assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

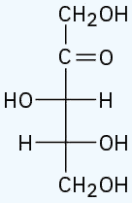

a)


b)


c)


d)

e)


f)

Answer

a) From top to bottom, 2R, 3R, and it is a D sugar.

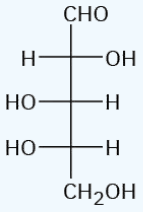
b) 2S, 3R, 4S, and it is an L sugar. c) 3R, 4S, and it is an L sugar.

d) L-Erythrose; 2*S*,3*S* e) D-Xylose; 2*R*,3*S*,4*R* f) D-Xylulose; 3*S*,4*R*

Exercise 11.3.2

(+)-Arabinose, an aldopentose that is widely distributed in plants, is systematically named (2*R*,3*S*,4*S*)-2,3,4,5-tetrahydroxypentanal. Draw a Fischer projection of (+)-arabinose, and identify it as a D sugar or an L sugar.

Answer

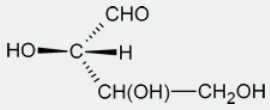

L-(+)-Arabinose

Study Notes

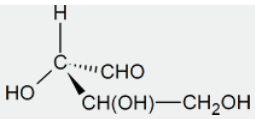
If you find that you have forgotten the meanings of terms such as dextrorotatory and polarimeter, refer back to Section 5.3 in which the fundamentals of optical activity were introduced.

How would you set about the task of deciding whether each chiral carbon has an *R* or an *S* configuration? True, you could use molecular models, but suppose that a model set had not been available—what would you have done then?

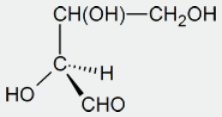
One approach is to focus on the carbon atom of interest and sketch a three-dimensional representation of the configuration around that atom, remembering the convention used in Fischer projections: vertical lines represent bonds going into the page, and horizontal lines represent bonds coming out of the page. Thus, the configuration around carbon atom 2 in structure a can be represented as follows:



In your mind, you should be able to imagine how this molecule would look if it was rotated so that the bonds that are shown as coming out of the page are now in the plane of the page. [One possible way of doing this is to try and imagine how the molecule would look if it was viewed from a point at the bottom of the page.] What you should see in your mind is a representation similar to the one drawn below.



To determine whether the configuration about the central carbon atom is *R* or *S*, we must rotate the molecule so that the group with the lowest priority (H), is directed away from the viewer. This effect can be achieved by keeping the hydroxyl group in its present position and moving each of the other three groups one position clockwise.



The Cahn-Ingold-Prelog order of priority for the three remaining groups is OH > CHO > $CH(OH)CH_2OH$; thus, we see that we could trace out a counterclockwise path going from the highest-priority group to the second- and third-highest, and we conclude that the central carbon atom has an *S* configuration.

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11.4: Configurations of Aldoses

Objectives

After completing this section, you should be able to

1. Draw the structures of all possible aldotetroses, aldopentoses, and aldohexoses, without necessarily being able to assign names to the individual compounds.
2. Draw the Fischer projection of D-glyceraldehyde, D-ribose, and D-glucose from memory.

Below are the Fischer projects 3-6 carbon aldoses. Starting with the three-carbon aldose D-glyceraldehyde, each additional carbon adds a new chiral center and doubles the number of possible stereoisomers of the D-aldoses. Notice that only D-aldoses are represented below. Each D-aldose has an L-aldose enantiomer, which is not shown. As discussed in the previous section, the L-aldose versions can be drawn by inverting all of the chiral centers in the D-aldose's Fischer projection.

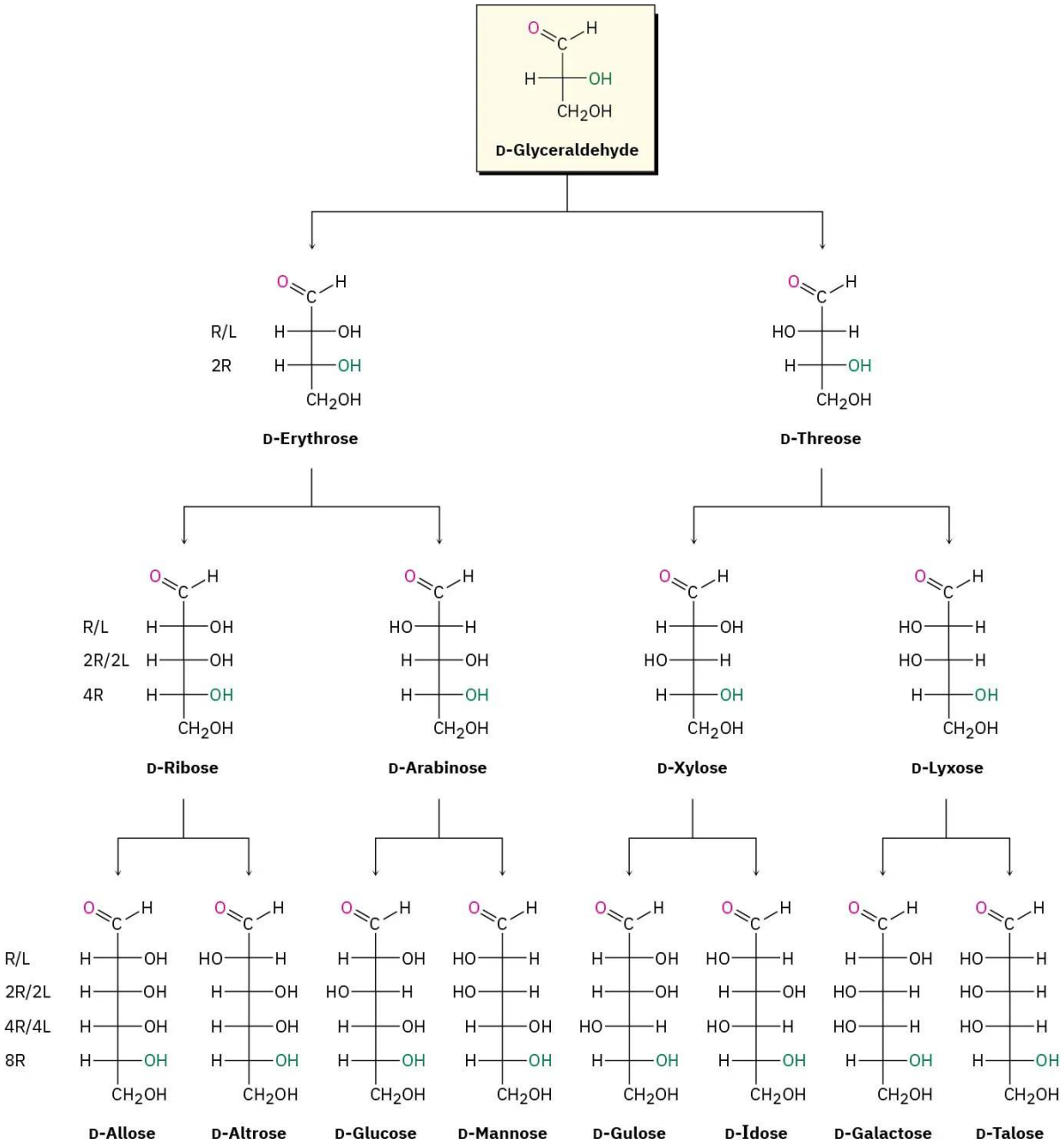


Figure 11.4.1: Configurations of D aldoses. The structures are arranged from left to right so that the –OH groups on C2 alternate right/left (R/L) across each series. Similarly, the –OH groups at C3 alternate two right/two left (2R/2L), the –OH groups at C4 alternate 4R/4L, and the –OH groups at C5 are to the right in all eight (8R). Each D aldose has a corresponding L enantiomer that is not shown.

The four chiral centers in glucose indicate there may be as many as sixteen (2^4) stereoisomers having this constitution. These would exist as eight diastereomeric pairs of enantiomers, and the initial challenge was to determine which of the eight corresponded to glucose. This challenge was accepted and met in 1891 by the German chemist Emil Fischer. His successful negotiation of the stereochemical maze presented by the aldohexoses was a logical tour de force, and it is fitting that he received the 1902 Nobel Prize for chemistry for this accomplishment. At the time Fischer undertook the glucose project it was not possible to establish the **absolute configuration** of an enantiomer. Consequently, Fischer made an arbitrary choice for (D)-glucose and established a network of related aldose configurations that he called the **D**-family. The mirror images of these configurations were then designated the **L**-family of aldoses. To illustrate using present day knowledge, Fischer projection formulas and names for the D-aldose family (three to six-carbon atoms) are shown below, with the asymmetric carbon atoms (chiral centers) colored red.

Aldotrioses: 3 carbon sugars with one chiral center. Aldotrioses have two (2^1) possible stereoisomers. A pair of enantiomers called D-gylceraldehyde and L-glyceraldehyde.

Aldotetroses: 4 carbon sugars with two chiral centers. Aldotetroses have four (2^2) possible stereoisomers. Two pairs of D/L enantiomers called erythrose and threose.

Aldopentoses: 5 carbon sugars with three chiral centers. Aldopentoses have eight (2^3) possible stereoisomers. Four pairs of D/L enantiomers called ribose, arabinose, xylose, and lyxose.

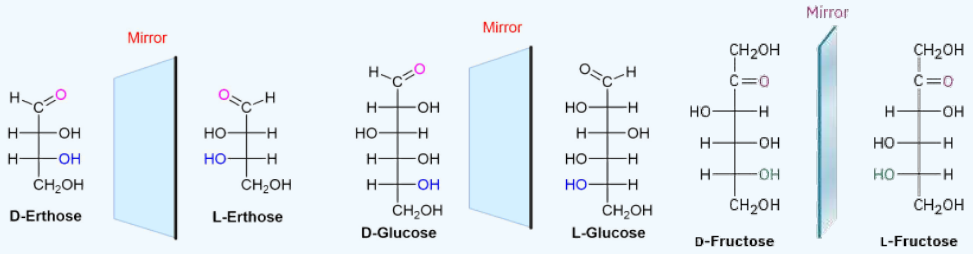
Aldohexoses: 6 carbon sugars with four chiral centers. Aldohexoses have sixteen (2^4) possible stereoisomers. five pairs of D/L enantiomers called allose, altrose, glucose, mannose, gulose, idose, galactose, and talose.

Worked Example 11.4.1

Draw the Fisher projection of L-erythrose, L-Glucose, and L-fructose.

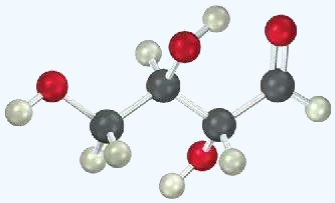
Solution

Use the Fischer projection provided above and reverse all of the chiral centers to provide the L-sugar. Note that in both cases the D sugars have the OH going to the right on the chiral center furthest away from the carbonyl. The L-sugars have the OH going to the left.



Worked Example 11.4.2: Drawing a Fischer Projection of a Molecular Model

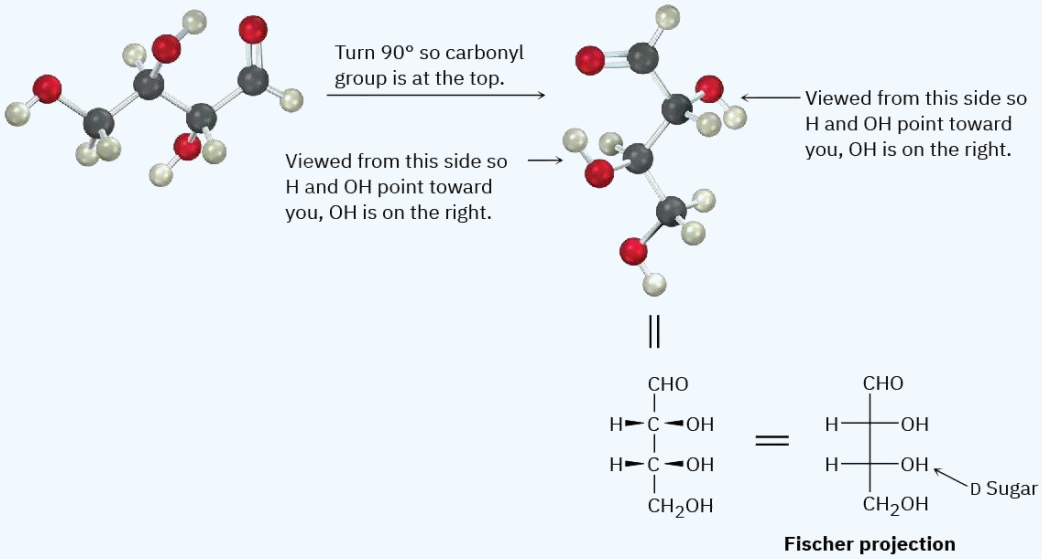
Draw the following aldotetrose as a Fischer projection and identify it as a D sugar or an L sugar:



Strategy

The Fischer projection of a monosaccharide is drawn vertically, with the carbonyl group at or near the top and the –CH_2OH group at the bottom. The interior –H and –OH are drawn to the sides, pointing out of the page toward the viewer.

Solution



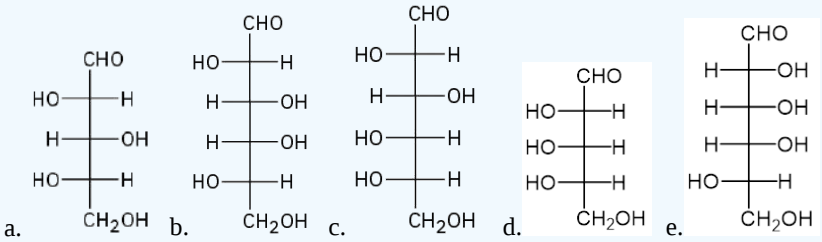
Fischer projection

Exercise 11.4.1

Only the D sugars are shown in Figure 11.5.1. Draw Fischer projections for the following L-sugars:

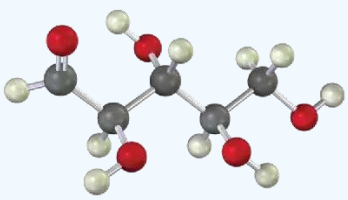
a. L-Xylose
b. L-Galactose
c. L-Allose
d. L-Ribose
e. L-Talose

Answer



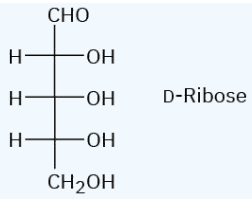
Exercise 11.4.2

The following model represents an aldopentose. Draw a Fischer projection of the sugar, name it, and identify it as a D or L sugar.



Answer

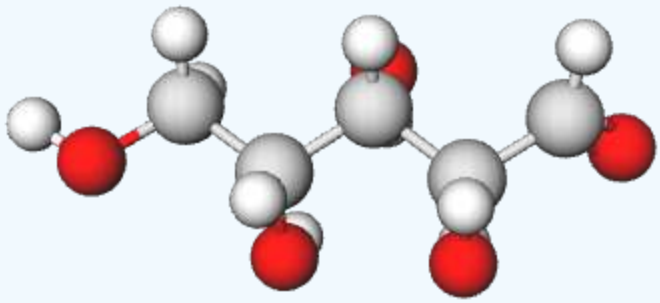
https://chem.libretexts.org/@go/page/500487



D-Ribose

Exercise 11.4.3

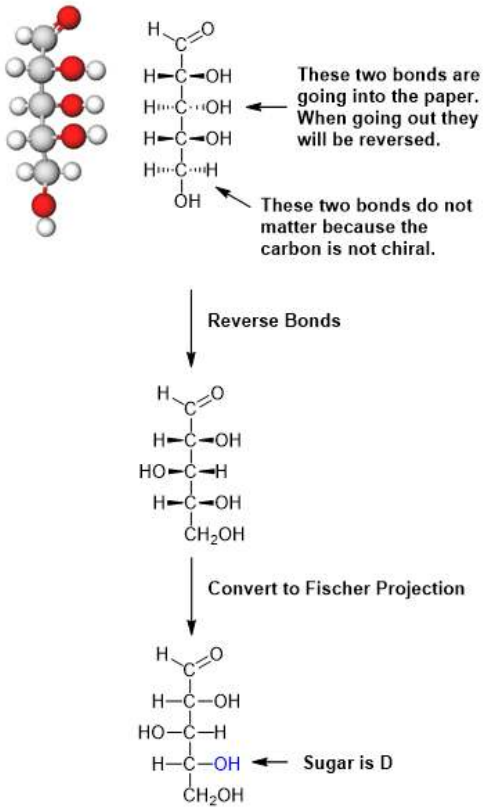
Please draw the Fischer projection for the following aldopentose and determine whether the sugar is D- or L-configuration.



GLmol

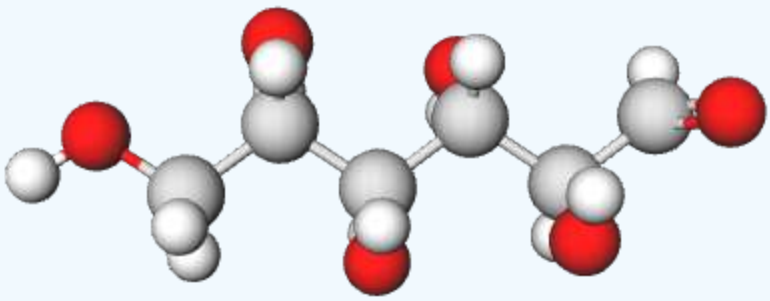
Answer

First, rotate the model so that the carbonyl is at the top. This is requirement of a Fischer projection. Next rotate the model so that the H and OH of the chiral carbon just below the carbonyl are facing towards you. In this orientation, a dash/wedge model will have every other set of bonds going into the plane of the page. This is not the correct orientation of a Fischer project so they must be modified. The H and OH bonds need to be coming out of the plane of the page in a Fisher projects. When converting bonds from going into the page to going out of the page the orientation of the H and OH are reversed. Remember that the last -CH_2OH of a sugar is achiral so the orientation does not need to be shown. Once the bonds are oriented correctly the wedge bonds can be converted to those of a Fischer projection.

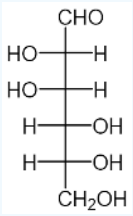


Exercise 11.4.4

For the following model of a sugar, please draw its Fischer projection and name it.



Answer

D-Mannose 

? Exercise 11.4.5

How many heptose stereoisomers would there expected to be? How many would be D-Sugars?

Answer

There would be 2^5 = 32 heptose stereoisomers. Half of these would be D-sugars or 16

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11.5: Cyclic Structures of Monosaccharides - Anomers

Objectives

After completing this section, you should be able to

1. determine whether a given monosaccharide will exist as a pyranose or furanose.
2. draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
3. draw the Fischer projection of a monosaccharide, given its cyclic pyranose form.
4. draw, from memory, the cyclic pyranose form of D-glucose.
5. determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
6. describe the phenomenon known as mutarotation.
7. explain, through the use of chemical equations, exactly what happens at the molecular level during the mutarotation process.

Key Terms

Make certain that you can define, and use in context, the key terms below.

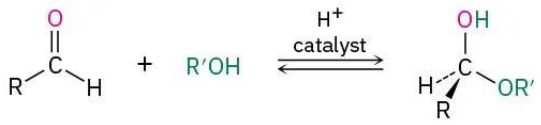
anomer, anomeric centre, alpha anomer, beta anomer, furanose, mutarotation, pyranose

Study Notes

If necessary, before you attempt to study this section, review the formation of hemiacetals discussed in Section 5.10.

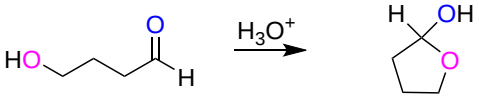
Cyclic Monosaccharides

In Section 5-10 it was discussed that the reaction of one equivalent of an alcohol, in the presence of an acid catalyst, adds reversibly to aldehydes and ketones to form a hydroxy ether called a **hemiacetal** (R_2COHOR') (h*emi*, Greek, half).



An aldehyde **A hemiacetal**

Molecules which have both an alcohol and a carbonyl can undergo an intramolecular version of the same reaction forming a cyclic hemiacetal.



Cyclic Hemiacetal

Because sugars often contain alcohol and carbonyl functional groups, intramolecular hemiacetal formation is common in carbohydrate chemistry. Five and six-membered rings are favored over other ring sizes because of their low angle and eclipsing strain. Cyclic structures of this kind are termed furanose (five-membered) or pyranose (six-membered), reflecting the ring size relationship to the common heterocyclic compounds furan and pyran shown below.



Figure 11.5.1: Furan (5-membered ring) and pyran (6-membered ring) structures

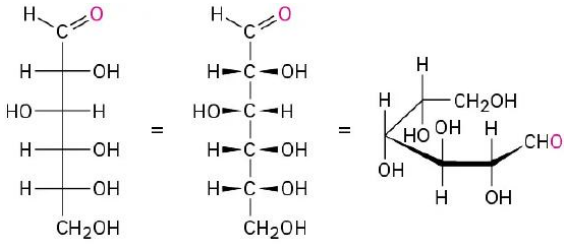
Unlike most of the biochemical reactions you will see in this text, sugar cyclization reactions are not catalyzed by enzymes: they occur spontaneously and reversibly in aqueous solution. Sugars are often shown in their open-chain form, however, in aqueous solution, glucose, fructose, and other sugars of five or six carbons rapidly interconvert between straight-chain and cyclic forms. For most five- and six-carbon sugars, the cyclic forms predominate in equilibrium since they are more stable. The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features.

Aldohexoses usually form pyranose rings, and their pentose homologs tend to prefer the furanose form, but there are many counterexamples.

Pyranose Rings

At equilibrium in aqueous solution, less than 1% of glucose is in an open chain form, with the rest being almost exclusively in its cyclic pyranose form. The 6-member cyclic form of glucose is called **glucopyranose**.

The best way to understand the the final position of the substituents after the nucleophilic attack, is to change the representations of the conventional Fischer projection, to a wedge/dash version of the Fischer projection, and finally, place the main chain horizontally keeping in mind that on each chiral center, the main chain moves back.



Glucose
(carbonyl group on top)

Pyranose rings are often drawn in a chair conformation, similar to cyclohexane rings (Organic Chemistry I: Section 4-6), with substituents positioned either in an axial or equatorial position. The pyranose ring is formed by attack of the hydroxyl on carbon 5 of glucose on the aldehyde carbon (also called the anomeric carbon in carbohydrate terminology). The anomeric carbon is a new chirality center (former carbonyl carbon), and two possible diastereomers, called anomers, are produced. The two isomeric forms are referred to by the Greek letters alpha (α) and beta (β). Pyranose rings undergo ring flipping to change between chair conformations.

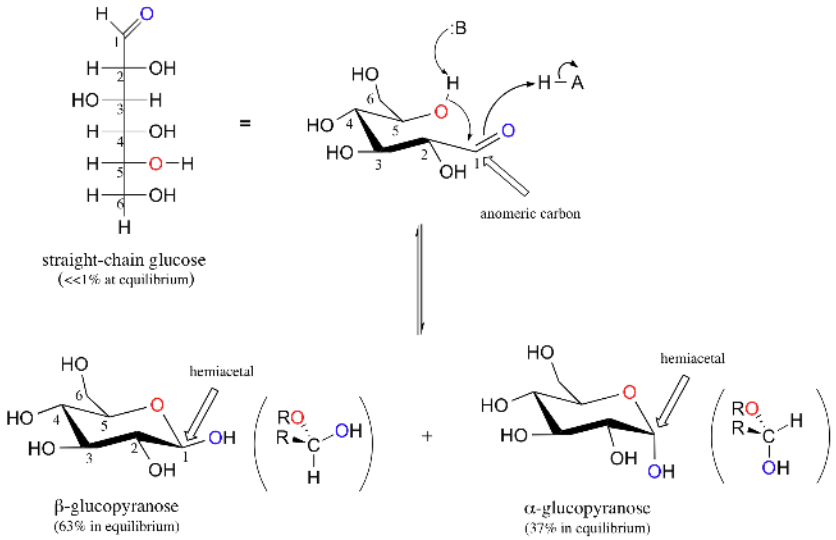
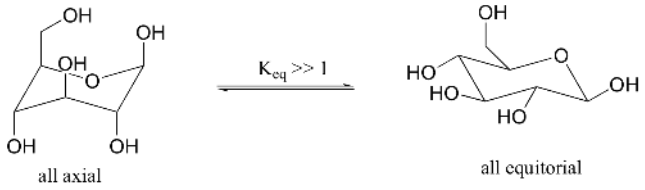


Figure 11.5.2: Glucose in its cyclic pyranose forms. As explained in the text, two anomers are formed by cyclization of glucose. The molecule whose newly formed –OH group at C1 is cis to the oxygen atom on the lowest chirality center (C5) in a Fischer projection is the α anomer. The molecule whose newly formed –OH group is trans to the oxygen atom on the lowest chirality center in a Fischer projection is the β anomer.

By convention, in the drawing of a pyranose, the ring oxygen is placed to the right and the rear of the structure, with the bonds down (top right of the drawing). This is because β-D-glucose (the most abundant sugar) has all the substituents in the equatorial position, indicating the lowest energy structure.

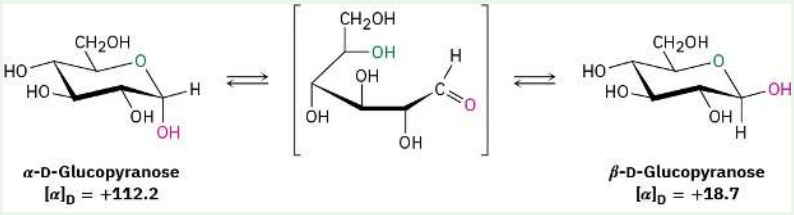


Mutarotation

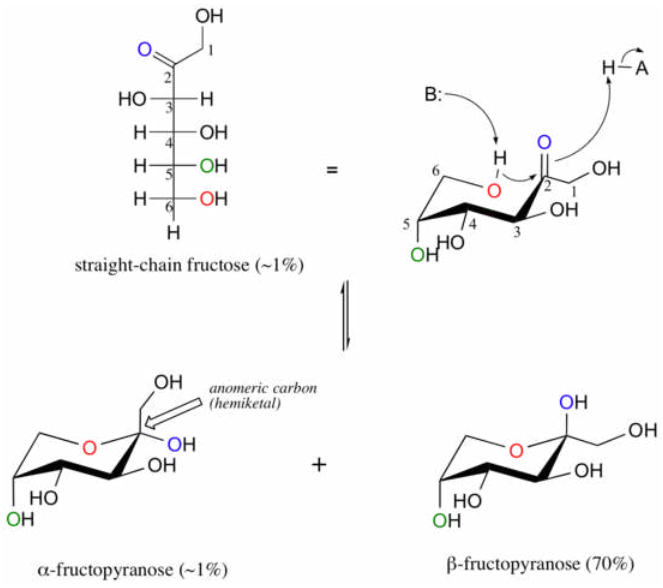
It is possible to obtain a sample of crystalline glucose in which all the molecules have the α structure or all have the β structure. The α form melts at 146°C and has a specific rotation of +112°, while the β form melts at 150°C and has a specific rotation of +18.7°. When the sample is dissolved in water, however, a mixture is soon produced containing both anomers as well as the straight-chain form, in dynamic equilibrium. The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation (Latin *mutare*, meaning "to change").

Mutarotation is the change in specific rotation of a chiral compound due to epimerization.

At equilibrium, the mixture consists of about 36% α-D-glucose, 64% β-D-glucose, and less than 0.02% of the open-chain aldehyde form. The observed rotation of this solution is +52.7°. The beta anomer is preferred because β-D-glucopyranose is the only aldohexose which can be drawn with all its bulky substituents (-OH and -CH_2OH) in equatorial positions, making it the most stable of the eight D-aldohexoses, which probably accounts for its widespread prevalence in nature.



The most abundant form of fructose in aqueous solution is also a six-membered ring. Fructose in aqueous solution forms a six-membered cyclic hemiketal called **fructopyranose** when the hydroxyl oxygen on carbon #6 attacks the ketone carbon (carbon #2, the anomeric carbon in fructose).

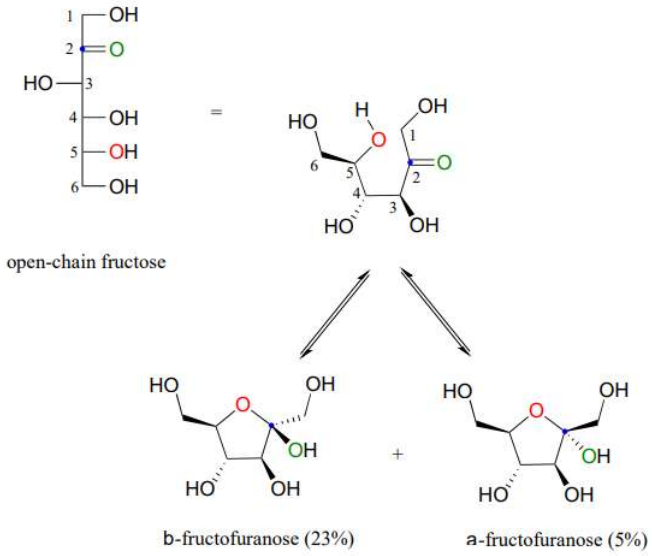


In this case, the β anomer is heavily favored in equilibrium by a ratio of 70:1, because it is the lower energy chair conformation, which has three of the five substituents (including the bulky CH_2OH group) in the equatorial position. In the minor α anomer, the bulkier -CH_2OH group and one more -OH occupy an axial position.

Notice in the above figure that the percentages of α and β anomers present at equilibrium do not add up to 100%. Fructose also exists in solution as a five-membered cyclic hemiketal, referred to in carbohydrate nomenclature as fructofuranose. In the formation of fructofuranose from open-chain fructose, the hydroxyl group on the fifth carbon attacks the ketone.

Furanose Rings

Fructose also exists in solution as a five-membered cyclic hemiketal, referred to in carbohydrate nomenclature as **fructofuranose**. In forming fructofuranose from open-chain fructose, the hydroxyl group on the fifth carbon attacks the ketone.



In aqueous solution, then, fructose exists as an equilibrium mixture of 70% β-fructopyranose, 23% β-fructofuranose, and smaller percentages of the open chain and cyclic α-anomers (Figure 11.5.3). The β-pyranose form of fructose is one of the sweetest compounds known, and is the main component of high-fructose corn syrup. The β-furanose form is much less sweet.

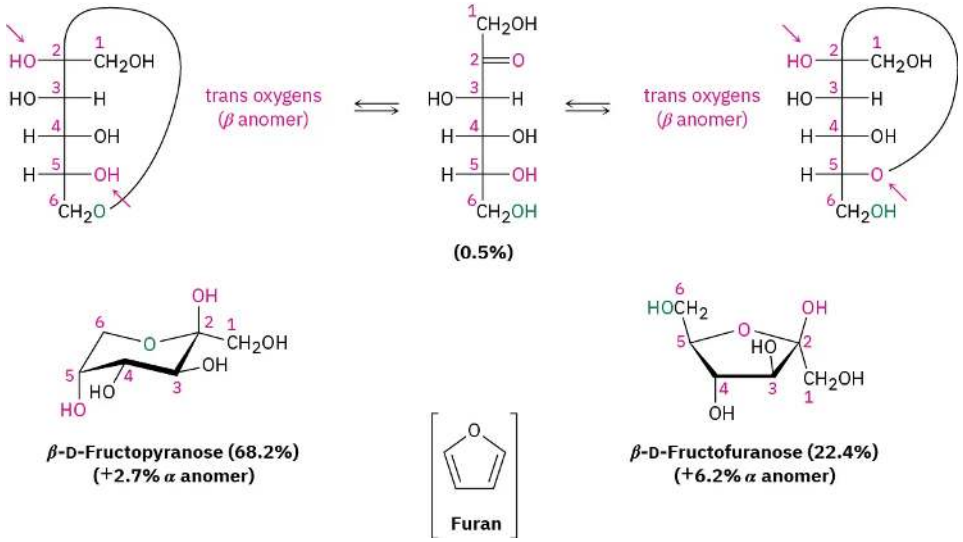


Figure 11.5.3: Pyranose and furanose forms of fructose in aqueous solution. The two pyranose anomers result from addition of the C6 –OH group to the C2 carbonyl; the two furanose anomers result from addition of the C5 –OH group to the C2 carbonyl.

Although we have been looking at specific examples for glucose and fructose, other five- and six-carbon monosaccharides also exist in solution as equilibrium mixtures of open chains and cyclic hemiacetals and hemiketals. Shorter monosaccharides (four-

carbon monosaccharides or smaller) are unlikely to undergo analogous ring-forming reactions due to the inherent instability of three- and four-membered rings.

The naturally occurring form of D-Ribose ($C_5H_{10}O_5$) is a component of the ribonucleotides from which RNA is built, and so this compound is necessary for coding, decoding, regulating, and expressing genes.

At room temperature in solution, about 79% of d-ribose is present in pyranose forms β-d-ribopyranose (59%), α-d-ribopyranose (20%) and 20% in the furanose forms β-d-ribofuranose (13%), α-d-ribofuranose (7%) with only about 0.1% of the linear form present.[1]

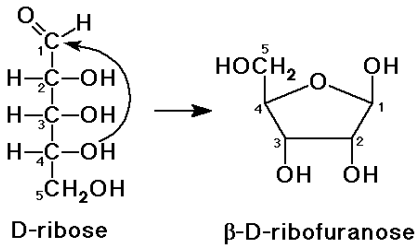


Figure 11.5.4: β-d-ribofuranose is the configuration present in ribonucleotides.

Drawing Cyclic Structures of Monosaccharides

The cyclic forms of sugars are commonly depicted as **Haworth projections**. This convention, first suggested by the English chemist Walter N. Haworth, shows molecules drawn as planar rings with darkened edges representing the side facing toward the viewer. The structure is simplified to show only the functional groups attached to the carbon atoms. Any group written to the *right* in a Fischer projection appears *below (bottom face)* the plane of the ring in a Haworth projection, and any group written to the *left* in a Fischer projection appears *above* (top face) the plane in a Haworth projection.

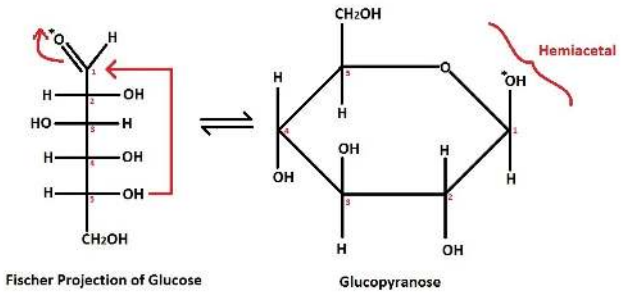
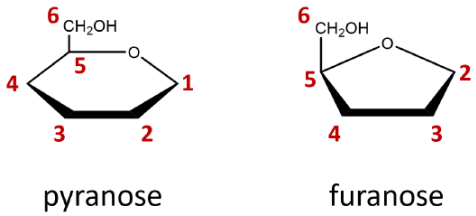


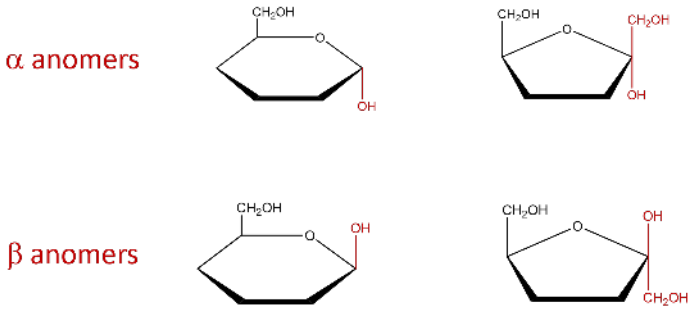
Figure: Conversion of the Fischer projection of D-glucose to the Haworth projection of ß-D-glucose

1. When converting a Fischer projection (line) to a Haworth projection, you must first identify the type of monosaccharide involved. If the carbohydrate represents an aldohexose, the **pyranose** ring is typically used. A pyranose is a cyclic structure that contains five carbon atoms and an oxygen. If the carbohydrate represents aldopentose, the **furanose** ring is typically used. The furanose ring contains four carbon atoms and an oxygen.

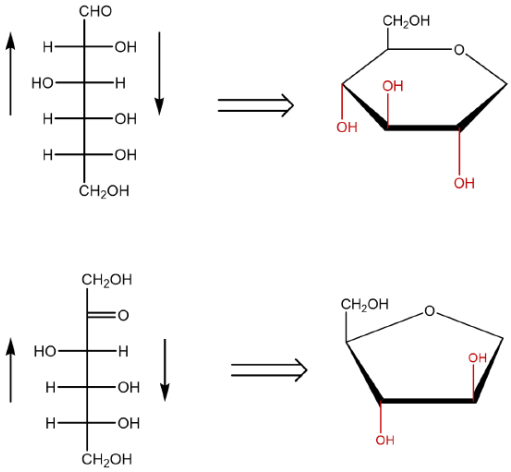


2. Indicate the arrangement of the hydroxyl group attached to the anomeric carbon to identify the sugar as an alpha or beta anomer. The *α* and *β* anomers are determined with respect to carbon 6. If the molecule represents a D-sugar, carbon 6 will be

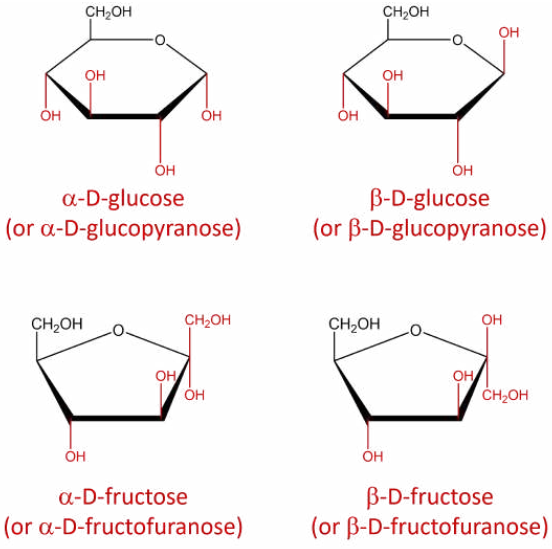
above the plane of the ring (top face) and form an L-sugar, carbon 6 will be below the plane of the ring (ring). The α anomer occurs when the OH on the anomeric carbon is trans to carbon 6 and the β anomer occurs when the OH on the anomeric carbon is cis to carbon 6. If the cyclic structure contains a furanose, since carbon 1 is not included within the ring, that carbon group would be arranged in the opposite direction of the OH group.



3. The remaining chiral centers (carbons 2, 3, and 4 of the pyranose or carbons 3 and 4 of the furanose) are arranged based on the directions of the hydroxyl from the Fischer projection structures. Groups to the left of the Fischer projection would point up (top face), while groups to the right would point down (bottom face).



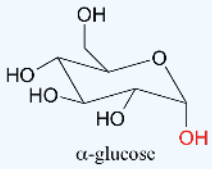
Since the Fischer Projection of any given carbohydrate is always the same, the Haworth Projection is essentially always the same. The only difference between the Haworth Projection of the alpha or beta form of a single carbohydrate is how the OH (and carbon-1 if furanose ring) is arranged around the anomeric carbon to determine whether the molecule is alpha or beta.



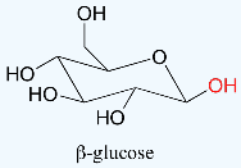
Exercise 11.5.1

D-Glucose is the most abundant aldohexose, and that abundance in nature means stability. Draw α-D-glucopyranose and β-D-glucopyranose, without looking for the structure of glucose.

Answer



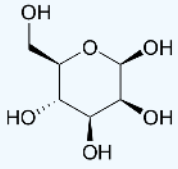
α-glucose



β-glucose

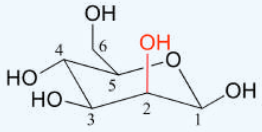
Exercise 11.5.2

Draw the two chair conformations of β-D-mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.

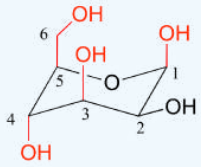


mannose

Answer



major chair form of mannose
(only one substituent axial)



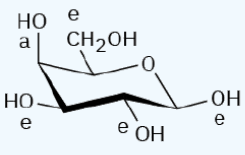
minor chair form of mannose
(four substituents axial)

Exercise 11.5.3

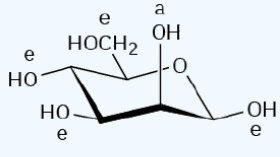
Draw the following in their most stable chair conformation: β-D-galactopyranose and β-D-mannopyranose. Which one is expected to be the more stable chair?

Answer

Because both have one axial OHs, their chair conformations should have roughly the same stability.



β-D-Galactopyranose



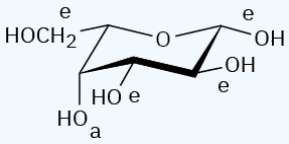
β-D-Mannopyranose

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Exercise 11.5.4

Draw β-L-galactopyranose in its more stable chair conformation, and label the substituents as either axial or equatorial.

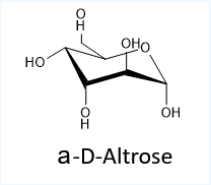
Answer



Exercise 11.5.5

Draw the cyclic structure of α-D-altrose.

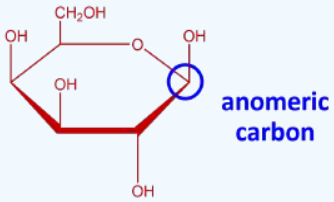
Answer



Exercise 11.5.6

Draw the cyclic structure for β-D-galactose. Identify the anomeric carbon.

Answer

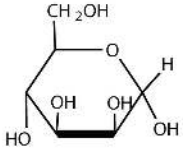


To identify the structure, we should first start with the Fischer projection of D-galactose. Since it is an aldohexose, we will start with the pyranose ring. The beta anomer was requested, so the OH on the anomeric carbon (C1) is cis to C6. Since C6 is top face (pointing up), the OH will be top face. Carbons 2, 3, and 4 are then arranged based on the Fischer projection arrangement at those carbons (C2 right, C3 left, and C4 left).

Exercise 11.5.7

Given that the aldohexose D-mannose differs from D-glucose only in the configuration at the second carbon atom, draw the cyclic structure for α-D-mannose.

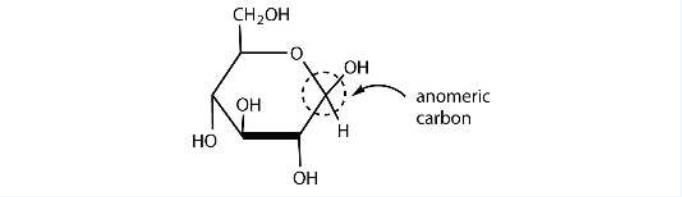
Answer



Exercise 11.5.8

Draw the cyclic structure for β-D-glucose. Identify the anomeric carbon.

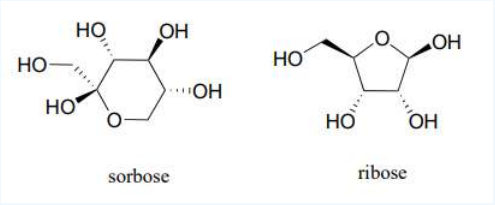
Answer



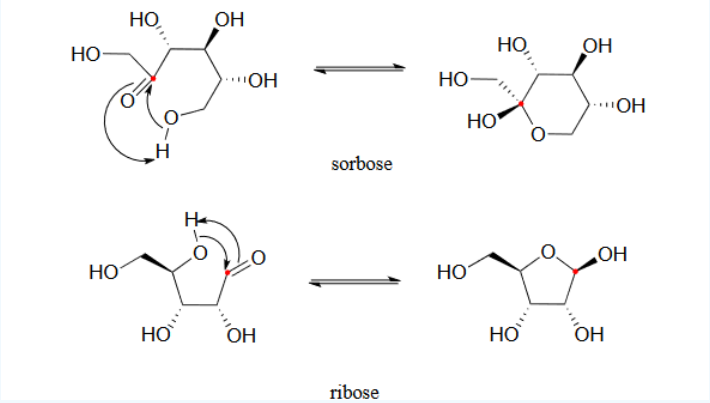
Exercise 11.5.9

a) Identify the anomeric carbon of each of the sugars shown below, and specify whether the structure shown is a hemiacetal or hemiketal.

b) Draw mechanisms for the cyclization of the open-chain forms to the cyclic forms shown.



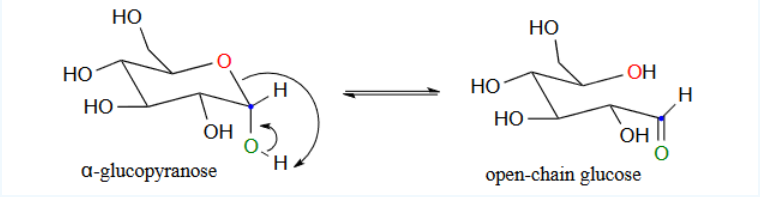
Answer



Exercise 11.5.10

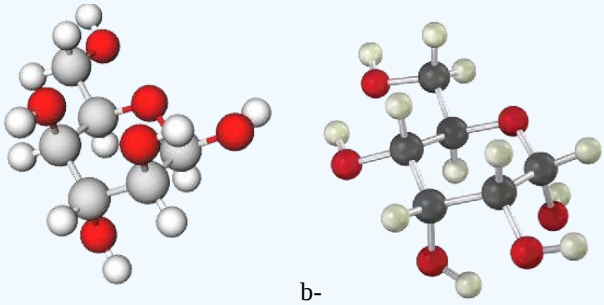
Draw a mechanism for the conversion of α-glucopyranose to open-chain glucose.

Answer



Exercise 11.5.11

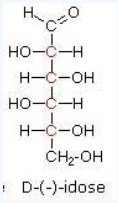
Identify the following monosaccharide, write its full name, and draw its open-chain form as a Fischer projection.



a- b-

Answer

a- β-D-idopyranose. b-α-D-Allopyranose



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11.6: Reactions of Monosaccharides

Objectives

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- aldaric acid, aldonic acid, alditol, glycoside, reducing sugar
- Kiliani-Fischer synthesis, Wohl degradation, neighboring group effect

Study Notes

While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 5.10

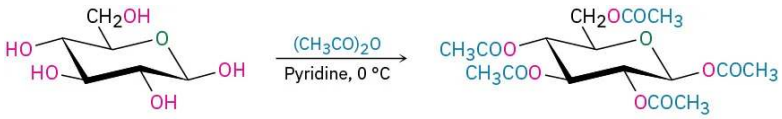
Monosaccharides contain both alcohol and carbonyl functional groups. This allows monosaccharides to undergo many of the reactions typical for these functional groups. In particular, alcohols can be converted to esters, converted to ethers, converted to

acetals, or oxidized. Carbonyls can be reacted with nucleophiles, be reduced to form alcohols, or be oxidized to form carboxylic acids.

Ester and Ether Formation

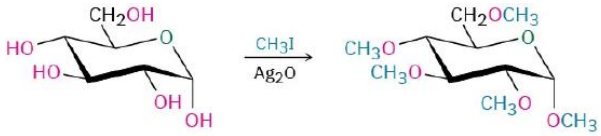
The hydroxyl groups of monosaccharides are often converted to ether or ester groups to increase solubility in organic solvents. Also, the conversion allows the sugar to be easily purified and crystallized.

Esterification is normally carried out by treating a carbohydrate with an acid chloride or acid anhydride in the presence of a base (Section 7.5 and Section 7.6). All the –OH groups react, including the anomeric one. For example, *β*-D-glucopyranose is converted into its pentaacetate by treatment with acetic anhydride in pyridine solution.



β-D-Glucopyranose — **Penta-*O*-acetyl-β-D-glucopyranose (91%)**

Carbohydrates are converted into ethers by treatment with an alkyl halide in the presence of base—the Williamson ether synthesis (Section 4.3). Standard Williamson conditions using a strong base tend to degrade sensitive sugar molecules, but silver oxide works well as a mild base and gives high yields of ethers. For example, *α*-D-glucopyranose is converted into its pentamethyl ether in 85% yield on reaction with iodomethane and Ag_2O.

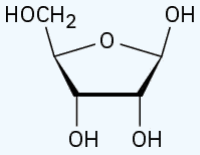


α-D-Glucopyranose — **α-D-Glucopyranose pentamethyl ether (85%)**

? Exercise 11.6.1

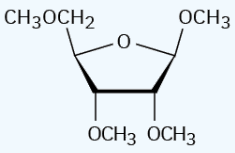
Draw the products you would obtain by the reaction of β-D-ribofuranose with:

a. CH_3I, Ag_2O
b. $(CH_3CO)_2O$, pyridine

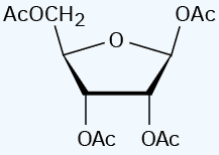


β-D-Ribofuranose

Answer



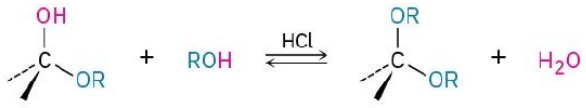
a.



b.

Glycoside Formation

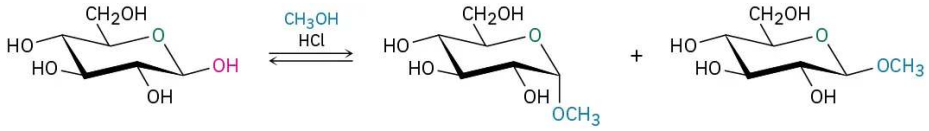
Reacting a hemiacetal with an alcohol and an acid catalyst produces an acetal in which the anomeric hydroxide has been replaced by an ether group.



A hemiacetal **An acetal**

Monosaccharide acetal derivatives, called glycosides, are formed when a hemiacetal reacts with an alcohol in the presence of an acid catalyst. During the reaction the -OH group from the anomeric carbon is replaced by a -OR group from the alcohol. A mixture of alpha and beta products are formed regardless of the conformation of the reactant. This reaction is illustrated below for D-glucopyranose and methanol which forms a mixture of alpha and beta methyl-glucopyranosides Figure \(\PageIndex{1}\). In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first.

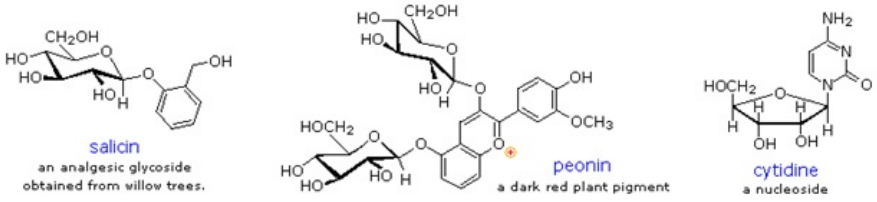
As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. Since this acid-catalyzed reaction is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid. The acetal product is stable to base and alkaline oxidants such as Tollen's reagent. In tbasic condition, it is not in equilibrium with the open-chain form and thus does not undergo mutarotation.



β-D-Glucopyranose (a cyclic hemiacetal) **Methyl α-D-glucopyranoside (66%)** **Methyl β-D-glucopyranoside (33%)**

Figure \(\PageIndex{1}\): The Reaction of β-D-glucopyranose with methanol gives a mixture of α and β methyl D-glucopyranosides.

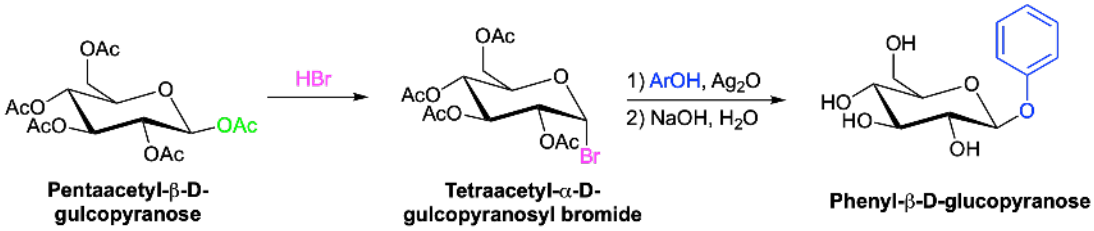
Two examples of naturally occurring glycosides and one example of an amino derivative are displayed below.



- Salicin, one of the oldest herbal remedies known, was the model for the synthetic analgesic aspirin.
- A large class of hydroxylated, aromatic oxonium cations called anthocyanins provide the red, purple and blue colors of many flowers, fruits and some vegetables. Peonin is one example of this class of natural pigments, which exhibit a pronounced pH color dependence. The oxonium moiety is only stable in acidic environments, and the color changes or disappears when base is added. The complex changes that occur when wine is fermented and stored are in part associated with glycosides of anthocyanins.
- Amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

Koenigs–Knorr Reaction

The presence of multiple -OH groups on a sugar molecular makes the synthesis of glycosides particularly difficult. One of the oldest glycosylation reactions, called the **Koenigs–Knorr reaction**, is effective for preparing the beta-glycosides of glucose. The pathway starts with the reaction of glucose pentaacetate with HBr to form a pyranosyl bromide. Addition of silver oxide allows for the nucleophilic addition of the chosen alcohol. Hydrolysis of the remaining acetal groups forms the beta-glucopyranoside.



Although the final step of the reaction appears to show the inversion characteristic of an S_N2 reaction, the same product forms if either the alpha or beta anomers of the glucopyranosyl bromide is used. This provides evidence that stereochemical control is lost at some point during the mechanism of the reaction.

Koenigs–Knorr Reaction Mechanism

The mechanism starts with the S_N1 like removal of the bromine leaving group which is promoted by the formation of an oxonium ion intermediate. Either anomer of the glucopyranosyl bromide will produce the same oxonium intermediate. Lone pair electrons from the carbonyl oxygen of an adjacent acetate group adds to the oxonium ion in an internal ring-forming reaction. Because the adjacent acetate was on the bottom of the glucose ring the newly form C-O bond is also on the bottom. During this step a new oxonium ion is formed. The alcohol then displaces the oxonium ion as a leaving groups during an S_N2 reaction. The inversion of configuration of the S_N2 reaction produces a beta-glycoside. Participation of an adjacent acetate group in the mechanism of the Koenigs–Knorr reaction is called a **neighboring-group effect**.

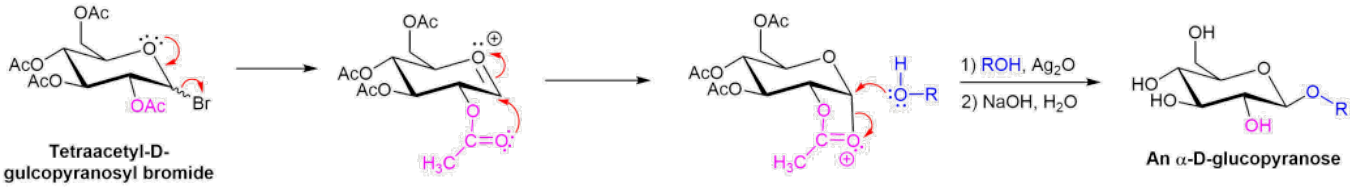


Figure 11.6.2: Mechanism of the Koenigs–Knorr reaction, showing the neighboring-group effect of a nearby acetate.

Biological Ester Formation: Phosphorylation

In living organisms, carbohydrates occur not only in the free form but also linked through their anomeric center to other molecules such as lipids (glycolipids) or proteins (glycoproteins). Collectively called **glycoconjugates**, these sugar-linked molecules are components of cell walls that are crucial to the mechanism by which different cell types recognize one another.

Glycoconjugate formation occurs by reaction of the lipid or protein with a glycosyl nucleoside diphosphate. This diphosphate is itself formed by initial reaction of a monosaccharide with adenosine triphosphate (ATP) to give a glycosyl monophosphate, followed by reaction with uridine triphosphate (UTP), to give a glycosyl uridine diphosphate. (We'll see the structures of nucleoside phosphates in Section 14.1.) The purpose of the phosphorylation is to activate the anomeric –OH group of the sugar and make it a better leaving group in a nucleophilic substitution reaction by a protein or lipid (Figure 11.6.3).

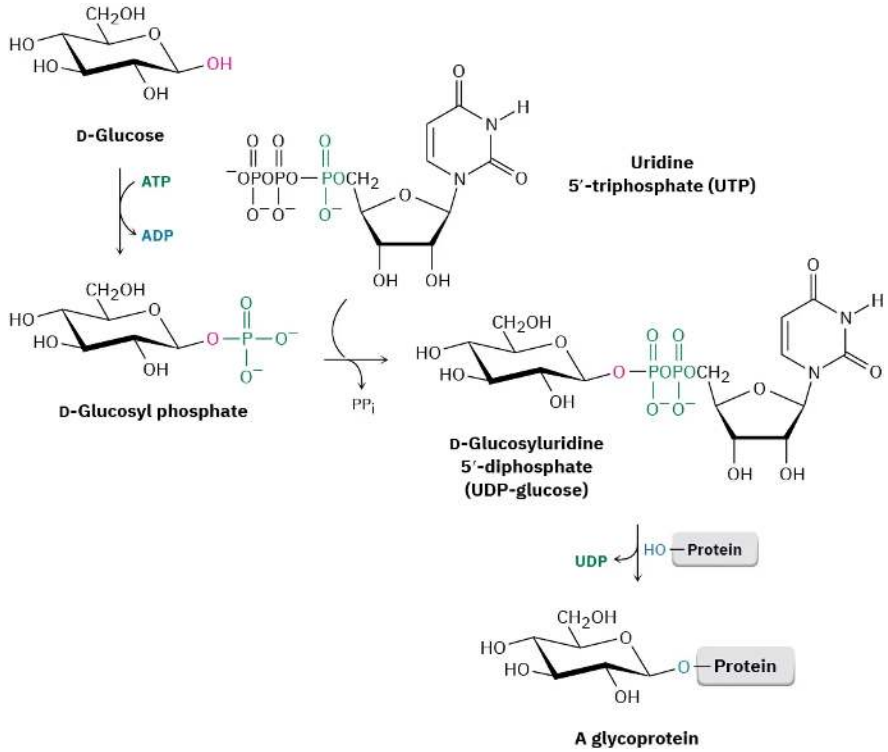
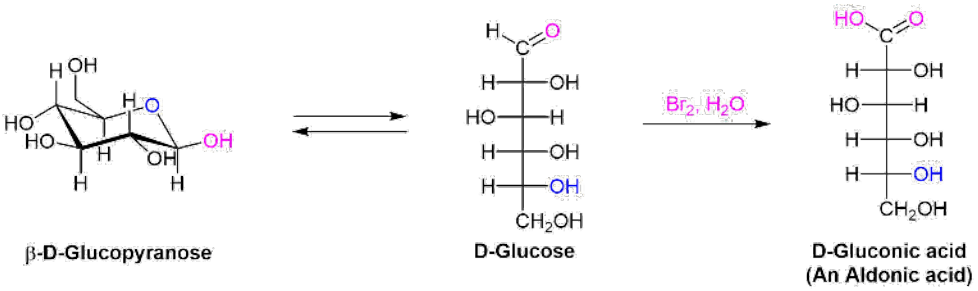


Figure 11.6.3: Glycoprotein formation occurs by initial phosphorylation of the starting carbohydrate with ATP to a glycosyl monophosphate, followed by reaction with UTP to form a glycosyl uridine 5′-diphosphate. Nucleophilic substitution by an –OH (or $–NH_2$) group on a protein then gives the glycoprotein.

Oxidation of Monosaccharides

When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2º hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as aqueous Br_2 can be used for this conversion. The oxidation occurs by reaction of the open-chain form of the sugar. Because of the equilibrium between the open and ring form of the sugar, eventually the entire sample will undergo the reaction.



Historically sugars have been classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'** (Ag^+ in NH_3) or **Benedict's** (Cu^{2+} and sodium citrate) reagents. If a sugar is oxidized by these reagents it is called a reducing sugar, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

All aldoses are reducing sugars because they contain an aldehyde group, but some ketoses are reducing sugars as well. Fructose reduces Tollens' reagent, for example, even though it contains no aldehyde group. Reduction occurs because fructose is readily isomerized to a mixture of aldoses (glucose and mannose) in basic solution by a series of keto–enol tautomeric shifts (Figure 11.6.3). Glycosides, however, are nonreducing because the acetal group is not hydrolyzed to an aldehyde under basic conditions.

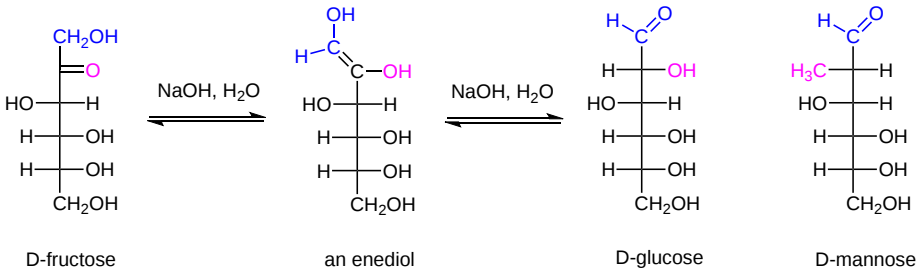
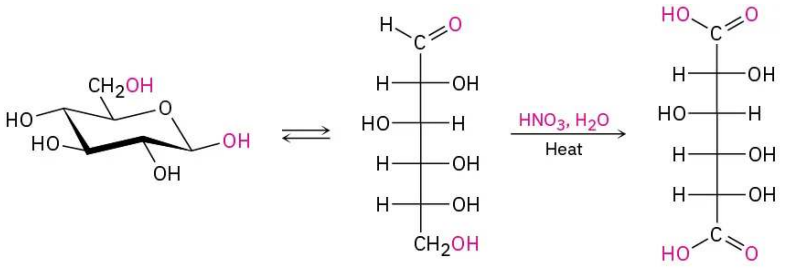


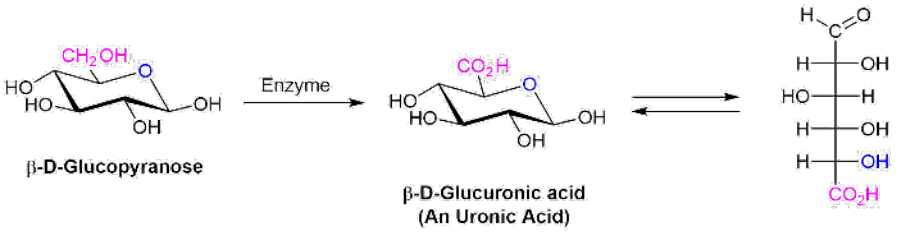
Figure 11.6.3: Fructose, a ketose, is a reducing sugar because it undergoes two base-catalyzed keto–enol tautomerizations that result in conversion to a mixture of aldoses.

Aldoses can be oxidized to a dicarboxylic acid by dilute nitric acid. Nitric acid is a strong enough oxidizing agent to cause both the aldehyde carbonyl and the -CH_2OH group to be oxidized to carboxylic acids. If both ends of an aldose chain are oxidized to carboxylic acids, the product is called an aldaric acid.

By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical. Such an operation will disclose any latent symmetry in the remaining molecule and possibly form an achiral meso compound. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown below.



If the -CH_2OH group of an aldose is oxidized to a carboxylic acid while the aldehyde carbonyl is not affected, the monocarboxylic acid product is called a uronic acid. This selective oxidation is difficult to accomplish and can only be done enzymatically.

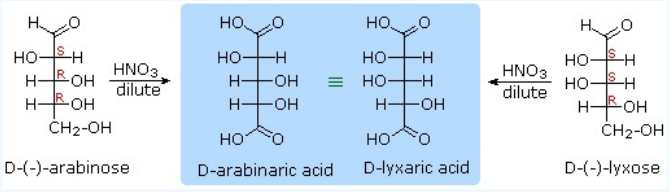


? Exercise 11.6.2

D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

Answer

The Fischer projection formula may be rotated by 180º in the plane of projection without changing its configuration.



? Exercise 11.6.3

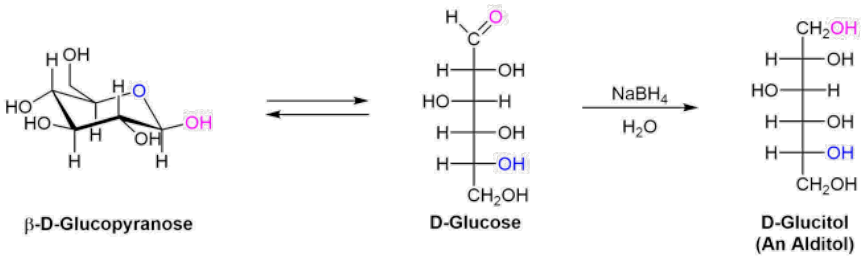
Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer

D-Allose and D-galactose.

Reduction of Monosaccarides

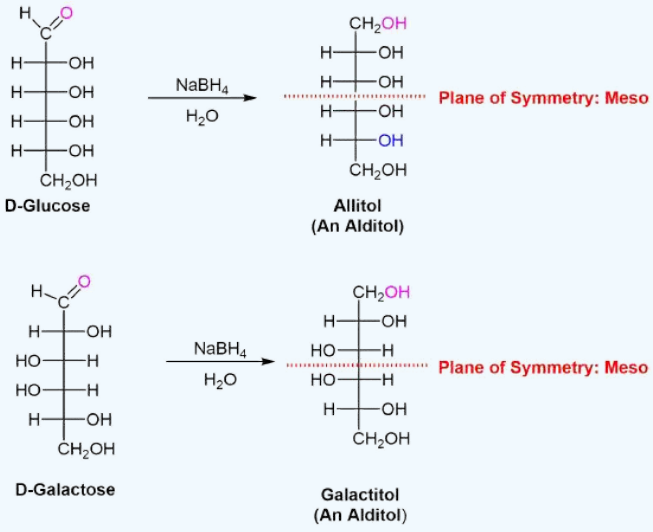
Treatment of an aldose or ketose with sodium borohydride reduces it to a polyalcohol called alditol. The reduction occurs by reaction of the open-chain form. Although only a small amount of the open-chain form is present at any given time, that small amount is reduced, more is produced by opening of the pyranose form, that additional amount is reduced, and so on, until the entire sample has undergone reaction. The reaction products can be formally named by removing the **-ose** ending from the open-chain sugar and replacing it with **-itol**. Note! The alditol products have identical end groups, $HOCH_2(CHOH)_nCH_2OH$ which means that forming an achiral meso compound is possible.



? Exercise 11.6.4

Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

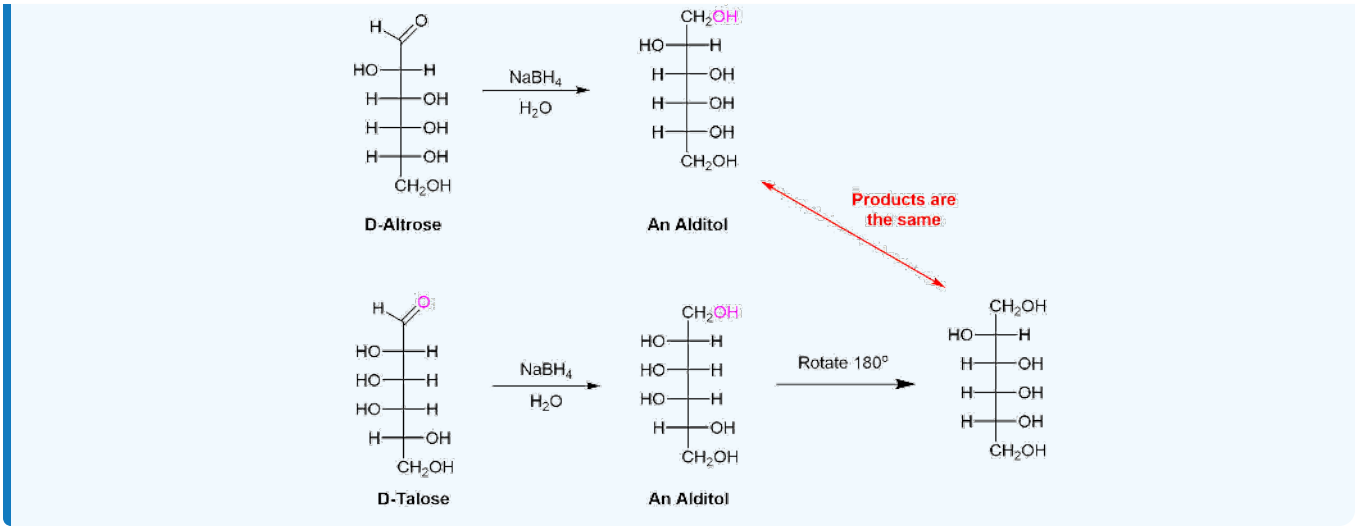
Answer



? Exercise 11.6.5

Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

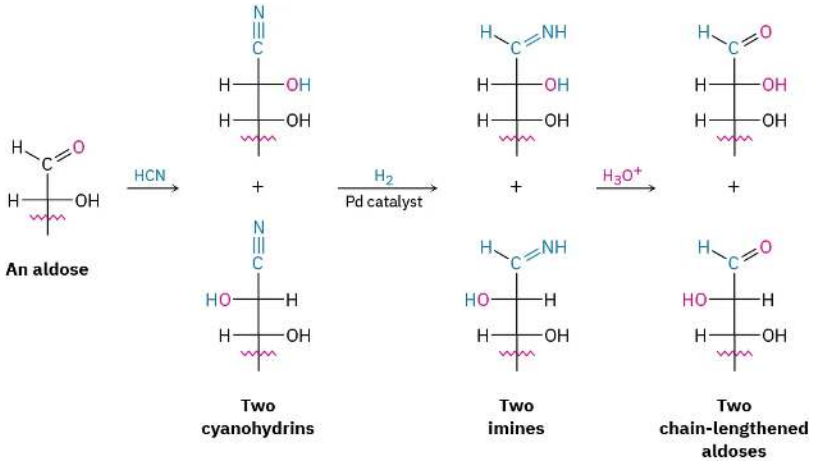
Answer



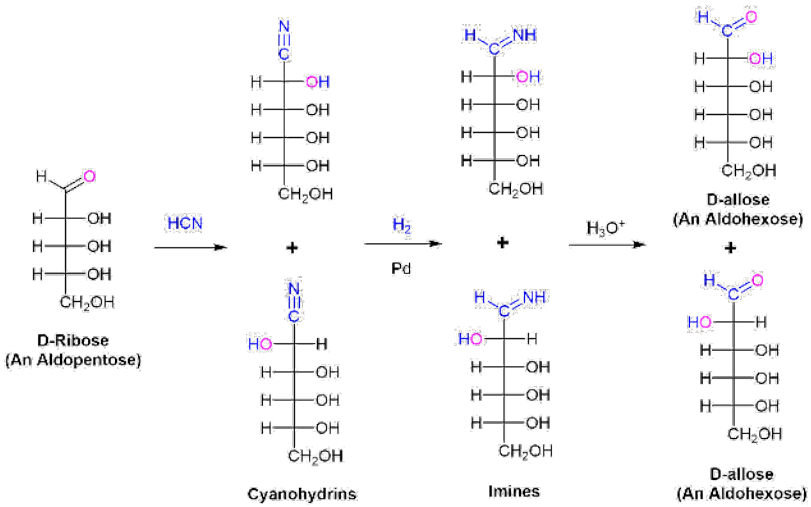
Chain Lengthening: The Kiliani–Fischer Synthesis

Much early activity in carbohydrate chemistry was devoted to unraveling the stereochemical relationships among monosaccharides. One of the most important methods used was the *Kiliani–Fischer synthesis*, which results in the lengthening of an aldose chain by one carbon atom. The C1 aldehyde group of the starting sugar becomes C2 of the chain-lengthened sugar, and a new C1 carbon is added. In doing this, two new sugar epimers are created. For example, an aldopentose is converted by Kiliani–Fischer synthesis into two aldohexoses.

1. The synthesis starts by reacting an aldose with HCN. Nucleophilic addition adds the cyanide nucleophile to the electrophilic carbon of the aldose aldehyde forming a cyanohydrin intermediate. The cyanide nucleophile adds a carbon. Stereochemical control is lost, so a racemic mixture of two cyanohydrins differing in the stereochemistry at C2 is formed.
2. The nitrile group of the cyanohydrin is reduced to an imine intermediate by hydrogenation over a palladium catalyst.
3. Finally, the imine is hydrolyzed to an aldehyde to create two new aldoses with an additional carbon.



For example, performing the Kiliani–Fischer synthesis on D-ribose produces a mixture of D-allose and D-altrose.



? Exercise 11.6.5

What products would you expect from Kiliani–Fischer reaction of D-xylose?

Answer

D-Gulose and D-idose

? Exercise 11.6.6

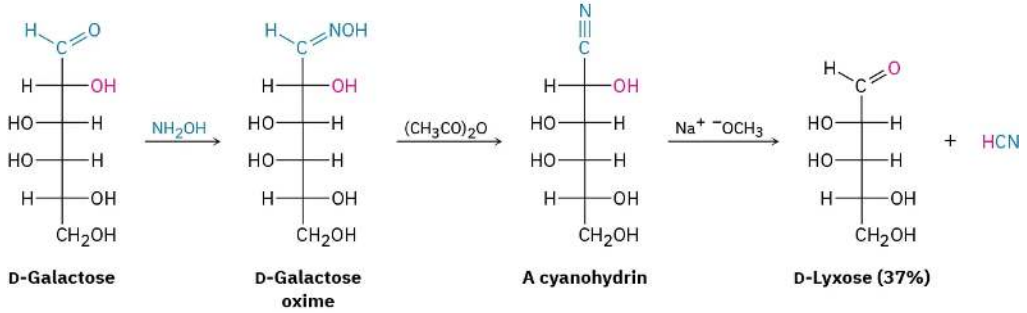
What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer

D-Threose

Chain Shortening: The Wohl Degradation

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This is commonly accomplished the **Wohl degradation**, which is virtually the reverse of the Kiliani–Fischer synthesis. The aldose aldehyde is converted to an oxime (Section 5-9) by treatment with hydroylamine (NH_2OH). Dehydration of the oxime with acetic anhydride forms a cyanohydrin. Under basic conditions, the cyanohydrine loses HCN to reform an aldehyde carbonyl. For example, D-galactose is converted by Wohl degradation into D-lyxose.

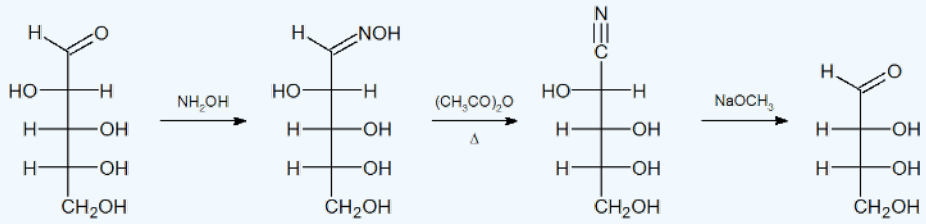


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Exercise 11.6.7

Illustrate the equation of how Wohl degradation is applied to the aldopentose, D-arabinose, to form the aldotetrose, D-erythrose.

Answer



Exercise 11.6.8

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer

D-Ribose and D-arabinose

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11.7: The Eight Essential Monosaccharides + Fructose

Objectives

1. Identify and draw the eight essential monosaccharides

Humans need to obtain eight monosaccharides for proper functioning. Although all eight can be biosynthesized from simpler precursors if necessary, it's more energetically efficient to obtain them from the diet. The eight are L-fucose (6-deoxy-L-galactose), D-galactose, D-glucose, D-mannose, D-Fructose, *N*-acetyl-D-glucosamine, *N*-acetyl-D-galactosamine, D-xylose, and *N*-acetyl-D-neuraminic acid (Figure 11.7.1). All are used for the synthesis of the **glycoconjugate** components of cell membranes, and glucose is also the body's primary source of energy.

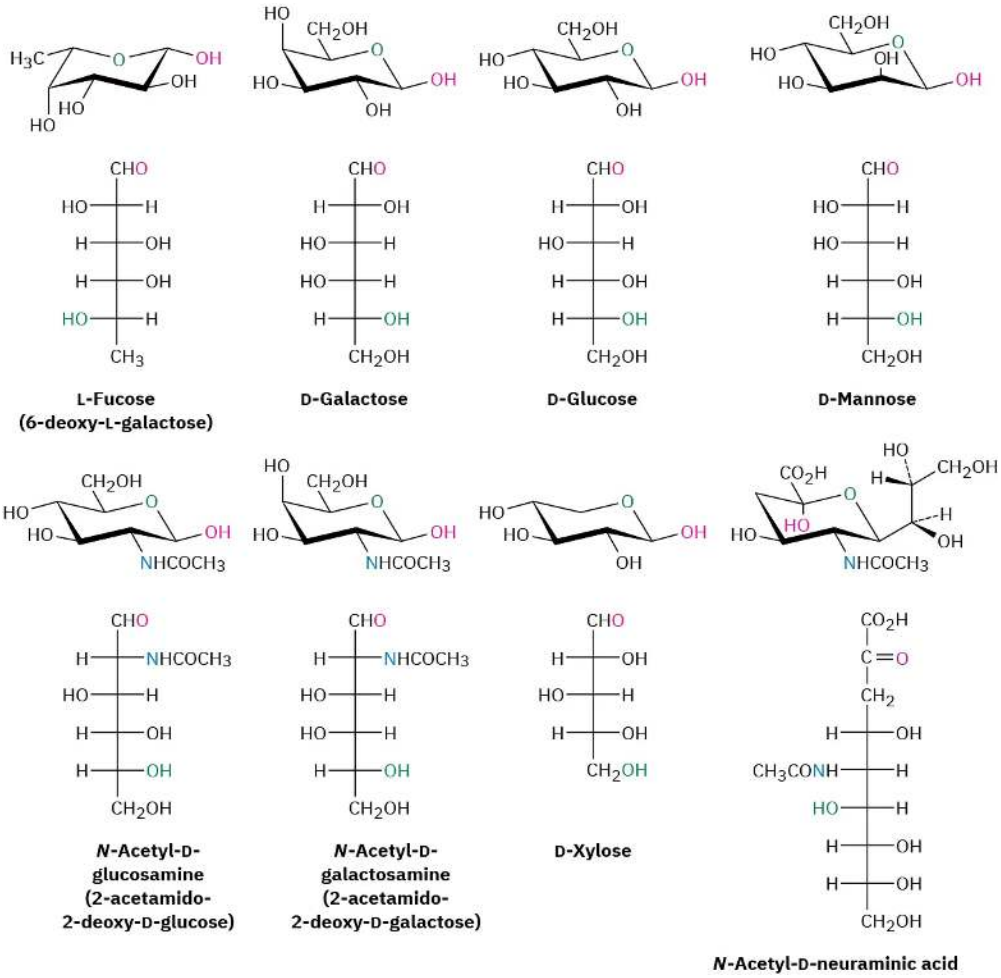


Figure 11.7.1: Structures of the eight monosaccharides essential to humans.

Of the eight essential monosaccharides, galactose, glucose, and mannose are simple aldohexoses, while xylose is an aldopentose and Fructose a ketohexose.

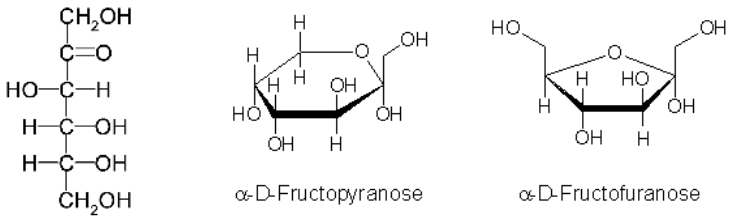


Figure 11.7.2: Structures of D-Fructose.

Fucose is a deoxy sugar, meaning that it has an oxygen atom “missing.” That is, in L-galactose the –OH group of C-6 is replaced by an –H. Figure 11.7.3.

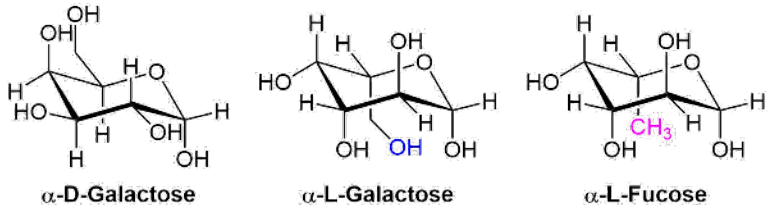
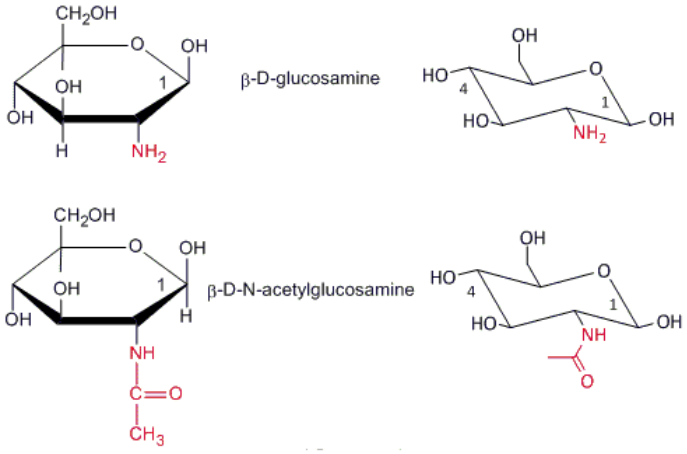
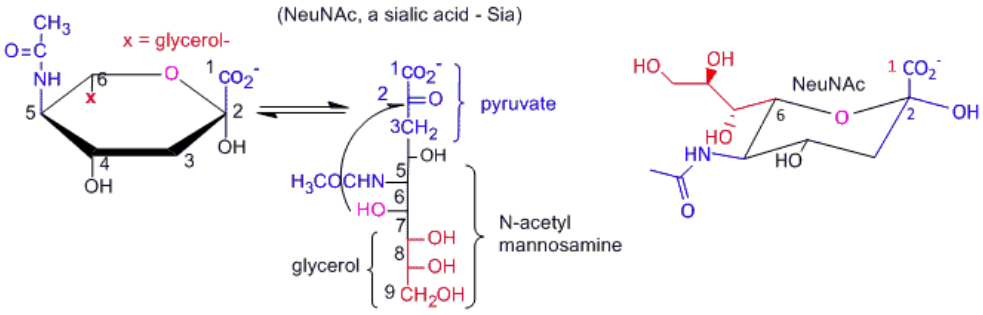


Figure 11.7.3: L-Fucose is a deoxy sugar. Fucose is the monosaccharide L-galactose with the -OH group on C6 replaced with an -H.

N-Acetylglucosamine and *N*-acetylgalactosamine are amide derivatives of amino sugars in which the –OH at C2 is replaced by an –NH_2 group (forming de corresponding amino-sugar) and converted to amides by N-acylation.



Neuraminic acid is crucial to the mechanism by which an influenza virus spreads. *N*-Acetylneuraminic acid is a nine-carbon sugar created by an aldol reaction between *N*-acetymannosamine and pyruvate ($CH_3COCO_2^-$). N-acetylneuaminic acid forms a pyranose ring by a intramolecular hemiacetal formation between the -OH on C6 and the ketone functional group in the pyruvate moiety.



All the essential monosaccharides arise from glucose, by the conversions summarized in Figure 11.7.4. We’ll not look specifically at these conversions, but might note that Problems 25-30 through 25-32 and 25-35 at the end of the chapter lead you through several of the biosynthetic pathways.

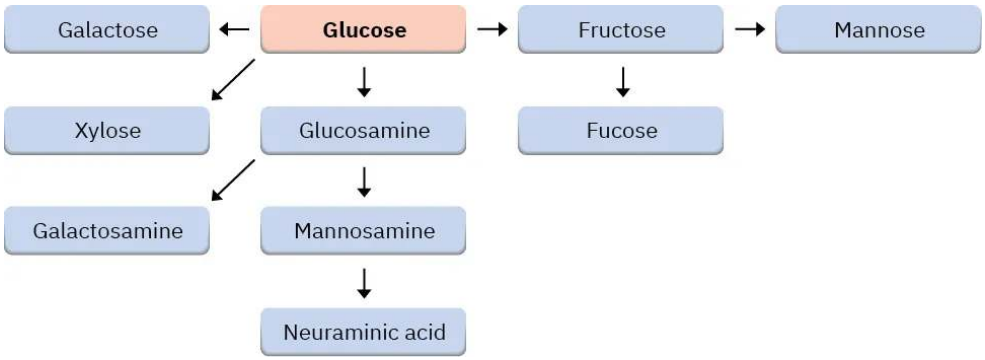
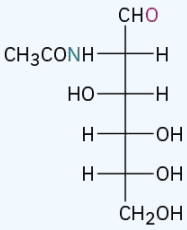


Figure 11.7.4: An overview of biosynthetic pathways for the eight essential monosaccharides.

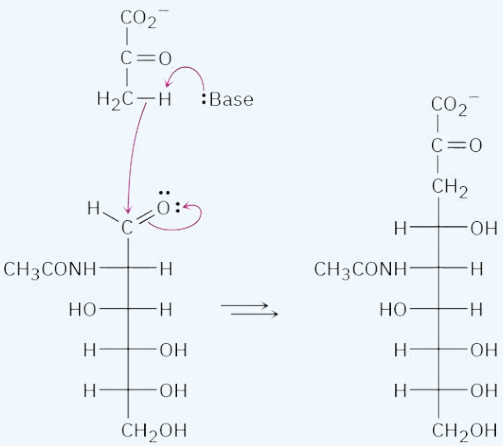
Exercise 11.7.1

1) Please show the mechanism of the aldol reaction between *N*-acetylmannosamine and pyruvate to form neuraminic acid.



***N*-Acetylmannosamine**

Answer



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11.8: Disaccharides

Objectives

After completing this section, you should be able to

1. identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
2. identify the two monosaccharide units in a given disaccharide.
3. identify the type of glycoside link (e.g., 1,4′-β) present in a given disaccharide structure.
4. draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.

   Note: If α- or β-D-glucose were one of the monosaccharide units, its structure would not be provided.
5. identify the structural feature that determines whether or not a given disaccharide behaves as a reducing sugar and undergoes mutarotation, and write equations to illustrate these phenomena.
6. identify the products formed from the hydrolysis of a given disaccharide.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- 1,4′ link
- disaccharide (see Section 25.1)
- invert sugar

Study Notes

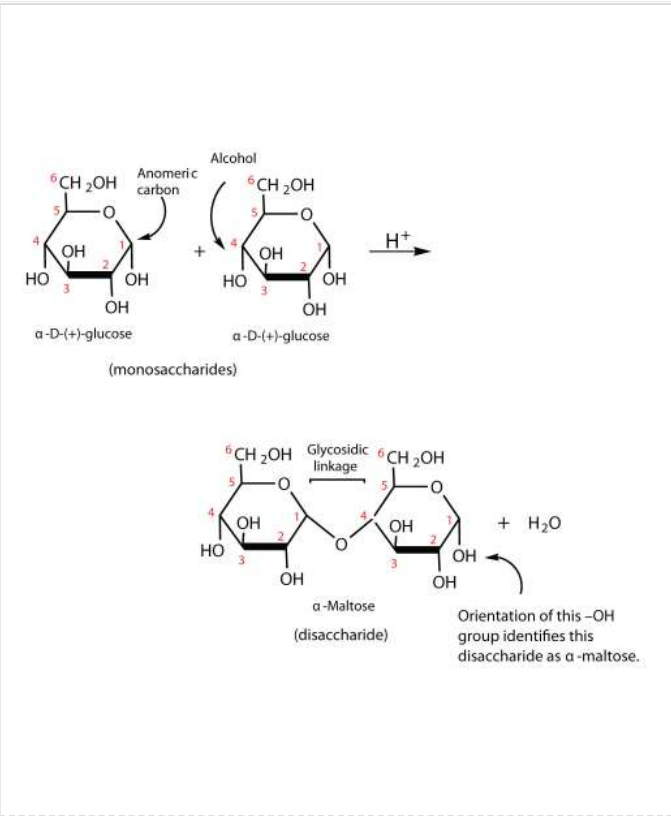
Notice that most of the disaccharides discussed in this section contain one unit of D-glucose. You are not expected to remember the detailed structures of maltose, lactose and sucrose. Similarly, we do not expect you to remember the systematic names of these substances.

Previously, you learned that monosaccharides can form cyclic structures by the reaction of the carbonyl group with an OH group. These cyclic molecules can in turn react with another alcohol to form a glycoside. When the alcohol component of a glycoside is provided by a hydroxyl function on another monosaccharide, the compound is called a disaccharide. Disaccharides ($C_{12}H_{22}O_{11}$) are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage. This linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide. The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them. There are three common disaccharides: maltose, lactose, and sucrose. All three are white crystalline solids at room temperature and are soluble in water.

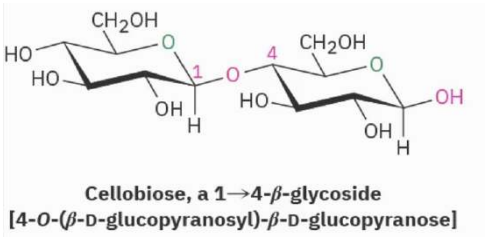
Maltose

Maltose occurs to a limited extent in sprouting grain. It is formed most often by the partial hydrolysis of starch and glycogen. In the manufacture of beer, maltose is liberated by the action of malt (germinating barley) on starch; for this reason, it is often referred to as *malt sugar*. Maltose is about 30% as sweet as sucrose. The human body is unable to metabolize maltose or any other disaccharide directly from the diet because the molecules are too large to pass through the cell membranes of the intestinal wall. Therefore, an ingested disaccharide must first be broken down by hydrolysis into its two constituent monosaccharide units. In the body, such hydrolysis reactions are catalyzed by enzymes such as *maltase*. The same reactions can be carried out in the laboratory with dilute acid as a catalyst, although in that case the rate is much slower, and high temperatures are required. Whether it occurs in the body or a glass beaker, the hydrolysis of maltose produces two molecules of D-glucose

The glucopyranose units in maltose are joined in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucopyranose molecule to the fourth carbon atom of the second glucopyranose molecule (an α-1,4-glycosidic linkage). The bond from the anomeric carbon of the first monosaccharide unit is directed downward, which is why this is known as an α-glycosidic linkage. The OH group on the anomeric carbon of the second glucopyranose can be in either the α or the β position.



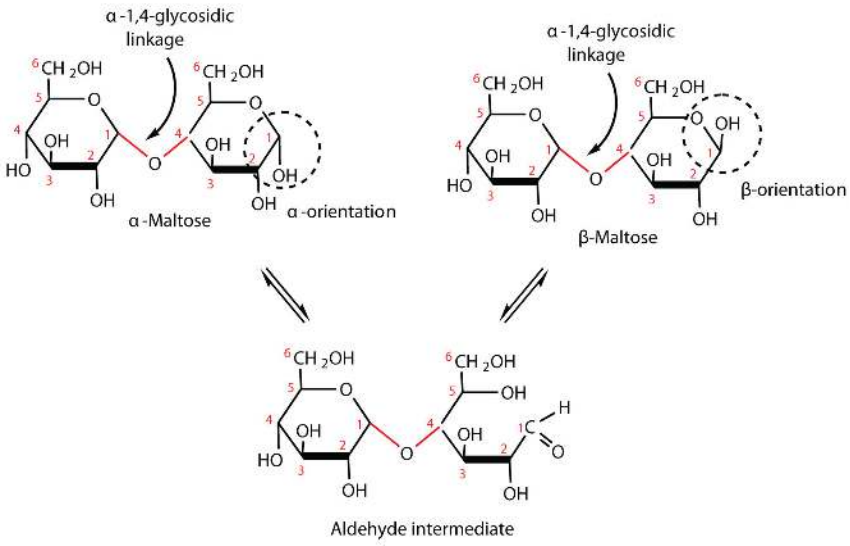
Cellobiose is a disaccharide made up of two D-glucopyranose molecules linked with a β-1,4-glycosidic linkage. Like maltose, the OH group on the anomeric carbon of the second glucopyranose of cellobiose can be in either the α or the β position.



Cellobiose, a 1→4-*β*-glycoside
[4-*O*-(*β*-D-glucopyranosyl)-*β*-D-glucopyranose]

Reactivity

- Maltose and Cellobiose are both reducing sugars. Thus, its two D-glucopyranose molecules must be linked in such a way as to leave one anomeric carbon that can open to form an aldehyde group. Although one anomeric carbon in maltose and cellobiose is used to form the 1,4-glycosidic linkage, the anomeric carbons on the second glucopyranose remain a hemiacetal. Like an individual monosaccharide, the second glucopyranose subunit undergoes mutarotation and thus is in equilibrium with its aldehyde and both anomer forms. For this reason, maltose and cellobiose contain a mixture of α and β anomers of the second glucopyranose.

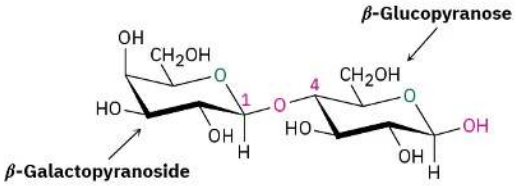


- Despite the similarities of their structures, cellobiose and maltose have dramatically different biological properties. Humans can't digest Cellobiose and can't be fermented by yeast. Maltose, however, is digested without difficulty and is fermented readily.

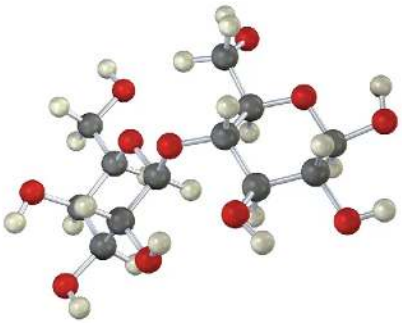
Lactose

Lactose is known as *milk sugar* because it occurs in the milk of humans, cows, and other mammals. In fact, the natural synthesis of lactose occurs only in mammary tissue, whereas most other carbohydrates are plant products. Human milk contains about 7.5% lactose, and cow's milk contains about 4.5%. This sugar is one of the lowest ranking in terms of sweetness, being about one-sixth as sweet as sucrose. Lactose is produced commercially from whey, a by-product of cheese manufacturing. It is important as an infant food and in the production of penicillin.

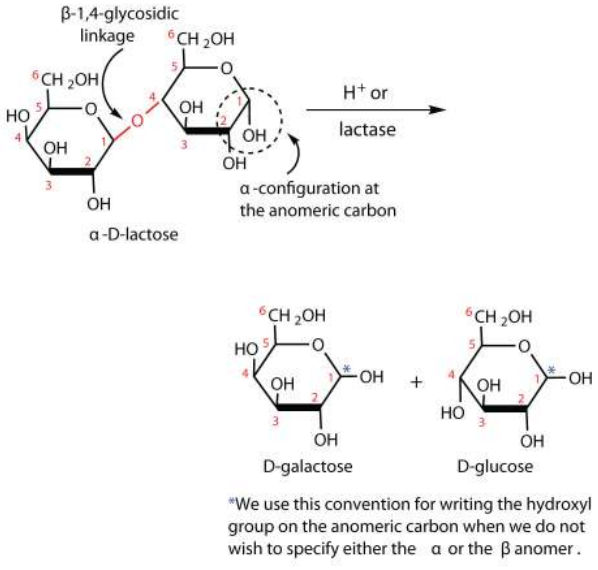
Lactose is a disaccharide composed of one molecule of D-galactopyranose and one molecule of D-glucopyranose joined by a **β-1,4-glycosidic bond** between the 1 of D-galactopyranose and the C4 of glucose.

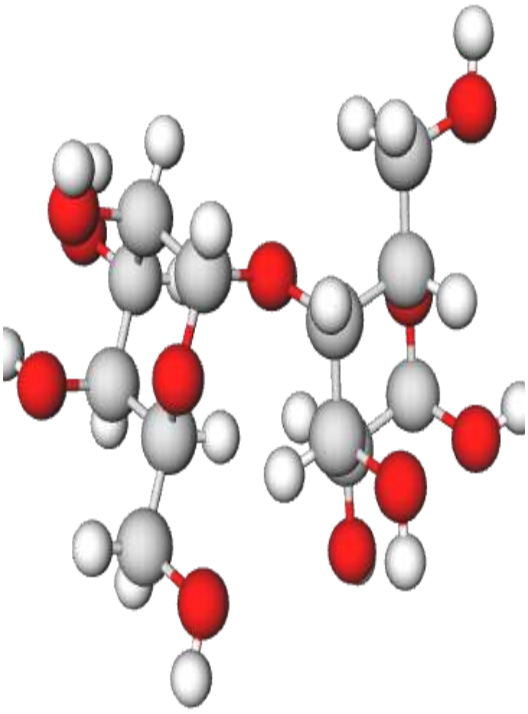


Lactose, a 1→4-β-glycoside
[4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranose]



Lactose is a reducing sugar and undergoes mutarotation to exhibit both anomers of the D-glucopyranose subunit. The two monosaccharides are obtained from lactose by acid hydrolysis or the catalytic action of the enzyme *lactase*.





- Many adults and some children suffer from a deficiency of lactase. These individuals are said to be lactose intolerant because they cannot digest the lactose found in milk. A more serious problem is the genetic disease galactosemia, which results from the absence of an enzyme needed to convert galactose to glucose. Certain bacteria can metabolize lactose, forming lactic acid as one of the products. This reaction is responsible for the “souring” of milk.

To Your Health: Lactose Intolerance and Galactosemia

Lactose makes up about 40% of an infant’s diet during the first year of life. Infants and small children have one form of the enzyme lactase in their small intestines and can digest the sugar easily; however, adults usually have a less active form of the enzyme, and about 70% of the world’s adult population has some deficiency in its production. As a result, many adults experience a reduction in the ability to hydrolyze lactose to galactose and glucose in their small intestine. For some people, the inability to synthesize sufficient enzymes increases with age. Up to 20% of the US population suffers from some degree of lactose intolerance.

In people with lactose intolerance, some of the unhydrolyzed lactose passes into the colon, where it tends to draw water from the interstitial fluid into the intestinal lumen by osmosis. At the same time, intestinal bacteria may act on the lactose to produce organic acids and gases. The buildup of water and bacterial decay products leads to abdominal distention, cramps, and diarrhea, which are symptoms of the condition.

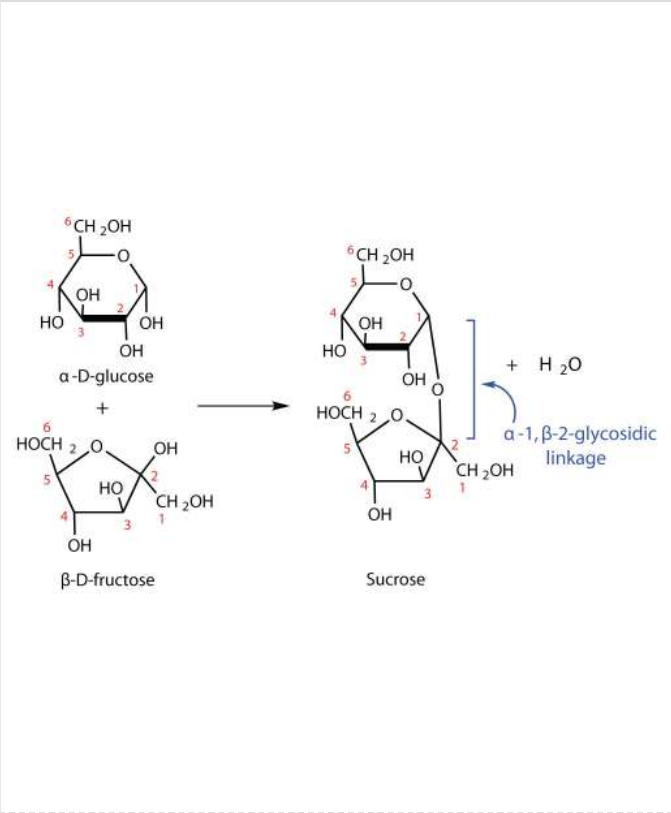
The symptoms disappear if milk or other sources of lactose are excluded from the diet or consumed only sparingly. Alternatively, many food stores now carry special brands of milk that have been pretreated with lactase to hydrolyze the lactose. Cooking or fermenting milk causes at least partial hydrolysis of the lactose, so some people with lactose intolerance are still able to enjoy cheese, yogurt, or cooked foods containing milk. The most common treatment for lactose intolerance, however, is the use of lactase preparations (e.g., Lactaid), which are available in liquid and tablet form at drugstores and grocery stores. These are taken orally with dairy foods—or may be added to them directly—to assist in their digestion.

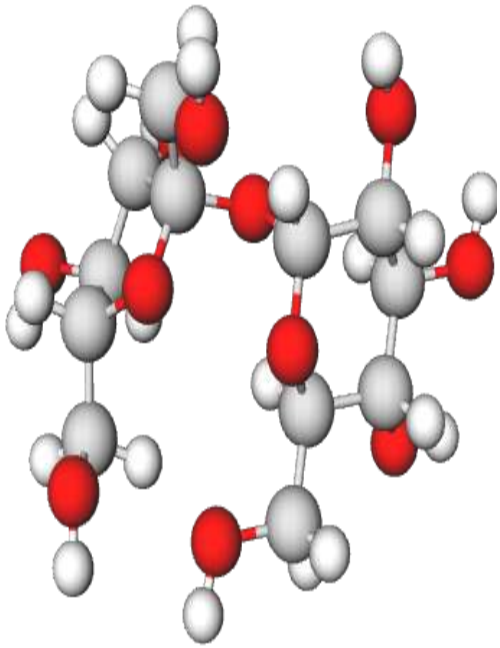
Galactosemia is a condition in which one of the enzymes needed to convert galactose to glucose is missing. Consequently, the blood galactose level is markedly elevated, and galactose is found in the urine. An infant with galactosemia experiences a lack of appetite, weight loss, diarrhea, and jaundice. The disease may result in impaired liver function, cataracts, mental retardation, and even death. If galactosemia is recognized in early infancy, its effects can be prevented by the exclusion of milk and all other sources of galactose from the diet. As a child with galactosemia grows older, he or she usually develops an alternate pathway for metabolizing galactose, so the need to restrict milk is not permanent. The incidence of galactosemia in the United States is 1 in every 65,000 newborn babies.

Sucrose

Sucrose, probably the largest-selling pure organic compound in the world, is known as *beet sugar*, *cane sugar*, *table sugar*, or simply *sugar*. Most of the sucrose sold commercially is obtained from sugar cane and sugar beets (whose juices are 14%–20% sucrose) by evaporation of the water and recrystallization. The dark brown liquid that remains after the recrystallization of sugar is sold as molasses.

The sucrose molecule is unique among the common disaccharides in having an α-1,β-2-glycosidic (head-to-head) linkage. Because this glycosidic linkage is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.





This linkage gives sucrose certain properties that are quite different from those of maltose and lactose. As long as the sucrose molecule remains intact, neither monosaccharide is in equilibrium with its open-chain form. Thus, sucrose is incapable of mutarotation and exists in only one form both in the solid state and in solution. In addition, sucrose does not undergo reactions that are typical of aldehydes and ketones. Therefore, sucrose is a nonreducing sugar.

The hydrolysis of sucrose in dilute acid or through the action of the enzyme *sucrase* (also known as invertase) gives an equimolar mixture of glucose and fructose. This 1:1 mixture is referred to as *invert sugar* because it rotates plane-polarized light in the opposite direction than sucrose. The hydrolysis reaction has several practical applications. Sucrose readily recrystallizes from a solution, but invert sugar has a much greater tendency to remain in solution. In the manufacture of jelly and candy and in the canning of fruit, the recrystallization of sugar is undesirable. Therefore, conditions leading to the hydrolysis of sucrose are employed in these processes. Moreover, because fructose is sweeter than sucrose, the hydrolysis adds to the sweetening effect. Bees carry out this reaction when they make honey.

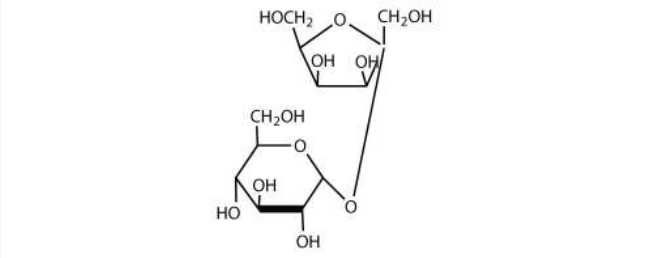
The average American consumes more than 100 lb of sucrose every year. About two-thirds of this amount is ingested in soft drinks, presweetened cereals, and other highly processed foods. The widespread use of sucrose is a contributing factor to obesity and tooth decay. Carbohydrates such as sucrose, are converted to fat when the caloric intake exceeds the body's requirements, and sucrose causes tooth decay by promoting the formation of plaque that sticks to teeth.

Example 11.8.1

For this disaccharide:

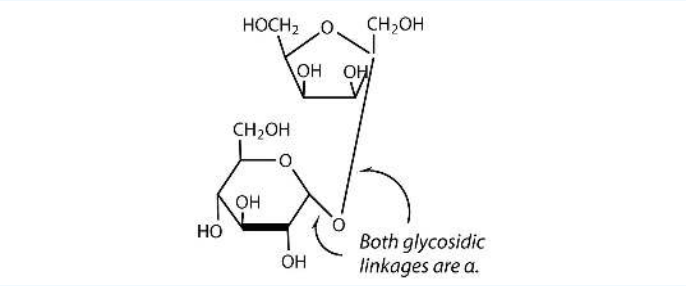
a- indicate whether the glycosidic linkage is α or β.

b- Identify the disaccharide as a reducing or non-reducing sugar.



Solution

a-



b- non-reducing

Exercise 11.8.1

What monosaccharides are obtained by the hydrolysis of each disaccharide?

a. sucrose
b. maltose
c. lactose

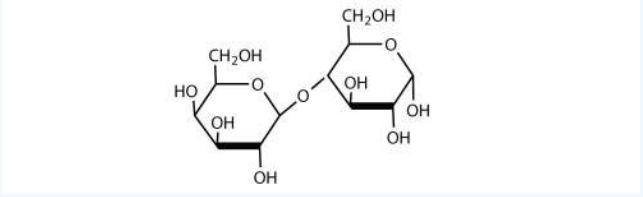
Answer

a. D-glucose and D-fructose
b. two molecules of D-glucose
c. D-glucose and D-galactose

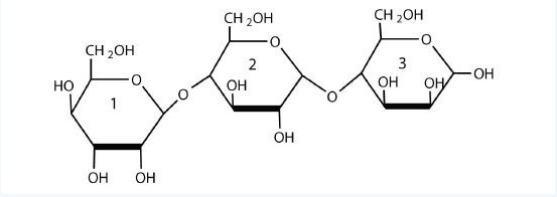
Exercise 11.8.2

For each saccharide, indicate whether the glycosidic linkage is α or β.

a.

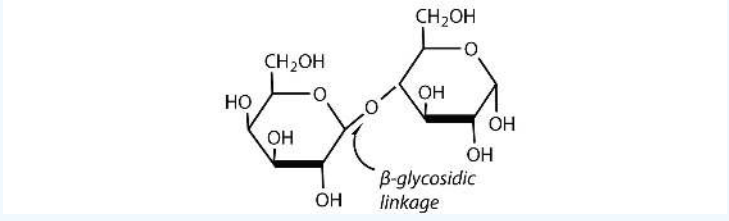


b.



Answer

a.



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b. The glycosidic linkage between sugars 1 and 2 is β because the bond is directed up from the anomeric carbon. The glycosidic linkage between sugars 2 and 3 is α because the bond is directed down from the anomeric carbon.

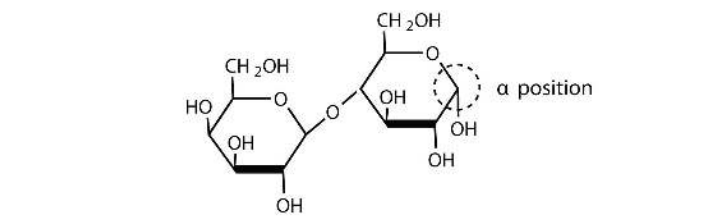
Exercise 11.8.3

Identify each saccharide in Exercise 2 as a reducing or nonreducing sugar. If it is a reducing sugar, draw its structure and circle the anomeric carbon. State if the OH group at the anomeric carbon is in the α or the β position.

Answer

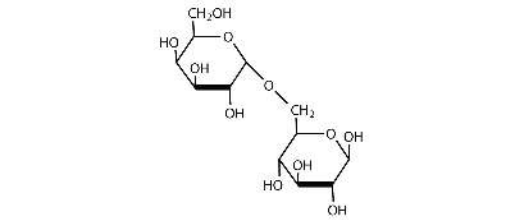
a) reducing

b) reducing



Exercise 11.8.4

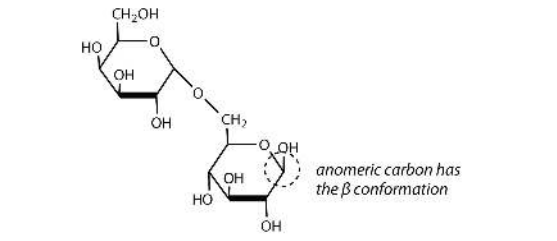
Melibiose is a disaccharide that occurs in some plant juices. Its structure is as follows:



a. What monosaccharide units are incorporated into melibiose?
b. What type of linkage (α or β) joins the two monosaccharide units of melibiose?
c. Melibiose has a free anomeric carbon and is thus a reducing sugar. Circle the anomeric carbon and indicate whether the OH group is α or β

Answer

a) galactose and glucose



b) α-glycosidic linkage

c) β.

Exercise 11.8.5

Show the product you would obtain from the reaction of cellobiose with the following reagents:

a. $NaBH_4$
b. Br_2, H_2O
c. CH_3COCl, pyridine

Answer

a. The hemiacetal ring is reduced.
b. The hemiacetal ring is oxidized.
c. All hydroxyl groups are acetylated.

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11.9: Polysaccharides and Their Synthesis

Objectives

After completing this section, you should be able to

1. identify the structural difference between cellulose and the cold-water-insoluble fraction of starch (amylose), and identify both of these substances as containing many glucose molecules joined by 1,4′-glycoside links.
2. identify the cold-water-soluble fraction of starch (amylopectin) as having a more complex structure than amylose because of the existence of 1,6′-glycoside links in addition to the 1,4′-links.
3. compare and contrast the structures and uses of starch, glycogen and cellulose.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- amylopectin, amylose, polysaccharide

The polysaccharides are the most abundant carbohydrates in nature and serve a variety of functions, such as energy storage or as components of plant cell walls. Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages. The three most abundant polysaccharides are starch, glycogen, and cellulose. These three are referred to as *homopolymers* because each yields only one type of monosaccharide (glucose) after complete hydrolysis. *Heteropolymers* may contain sugar acids, amino sugars, or noncarbohydrate substances in addition to monosaccharides. Heteropolymers are common in nature (gums, pectins, and other substances) but will not be discussed further in this textbook. The polysaccharides are nonreducing carbohydrates, are not sweet tasting, and do not undergo mutarotation.

Starch

Starch is the most important source of carbohydrates in the human diet and accounts for more than 50% of our carbohydrate intake. It occurs in plants in the form of granules, and these are particularly abundant in seeds (especially the cereal grains) and tubers, where they serve as a storage form of carbohydrates. The breakdown of starch to glucose nourishes the plant during periods of reduced photosynthetic activity. We often think of potatoes as a “starchy” food, yet other plants contain a much greater percentage of starch (potatoes 15%, wheat 55%, corn 65%, and rice 75%). Commercial starch is a white powder.

Starch is a mixture of two polymers: amylose and amylopectin. Natural starches consist of about 10%–30% amylose and 70%–90% amylopectin. Amylose is a linear polysaccharide composed entirely of D-glucose units joined by the α-1,4-glycosidic linkages we saw in maltose (part (a) of Figure 11.9.1). Experimental evidence indicates that amylose is not a straight chain of glucose units but instead is coiled like a spring, with six glucose monomers per turn (part (b) of Figure 11.9.1). When coiled in this fashion, amylose has just enough room in its core to accommodate an iodine molecule. The characteristic blue-violet color that appears when starch is treated with iodine is due to the formation of the amylose-iodine complex. This color test is sensitive enough to detect even minute amounts of starch in solution.

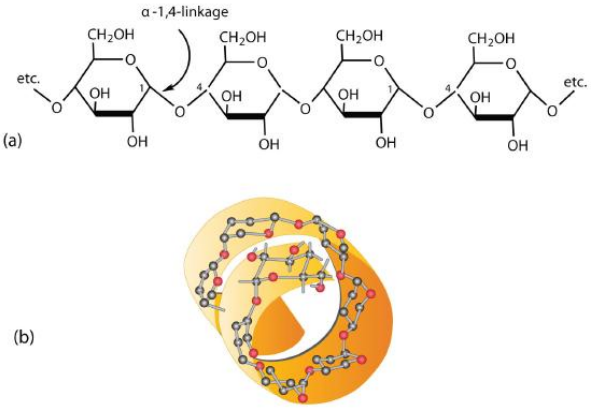


Figure 11.9.1: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

Amylopectin is a branched-chain polysaccharide composed of glucose units linked primarily by α-1,4-glycosidic bonds but with occasional α-1,6-glycosidic bonds, which are responsible for the branching. A molecule of amylopectin may contain many thousands of glucose units with branch points occurring about every 25–30 units (Figure 11.9.2). The helical structure of amylopectin is disrupted by the branching of the chain, so instead of the deep blue-violet color amylose gives with iodine, amylopectin produces a less intense reddish brown.

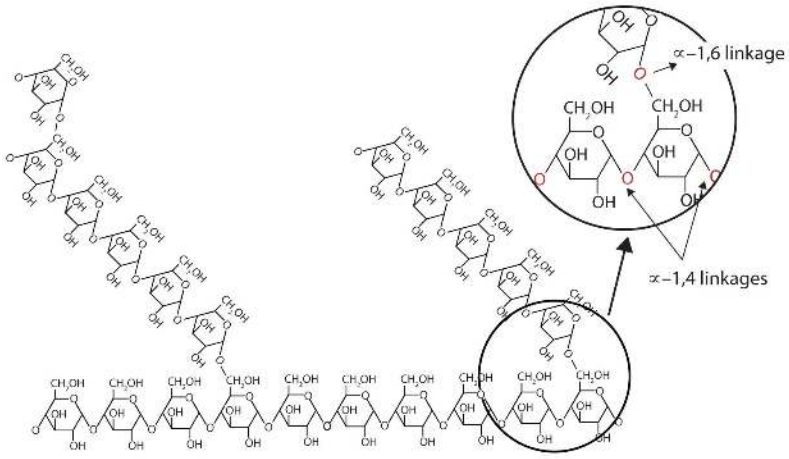


Figure 11.9.2: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

Dextrins are glucose polysaccharides of intermediate size. The shine and stiffness imparted to clothing by starch are due to the presence of dextrins formed when clothing is ironed. Because of their characteristic stickiness with wetting, dextrins are used as adhesives on stamps, envelopes, and labels; as binders to hold pills and tablets together; and as pastes. Dextrins are more easily digested than starch and are therefore used extensively in the commercial preparation of infant foods.

The complete hydrolysis of starch yields, in successive stages, glucose:

$$\text{starch} \rightarrow \text{dextrins} \rightarrow \text{maltose} \rightarrow \text{glucose}$$

In the human body, several enzymes known collectively as amylases degrade starch sequentially into usable glucose units.

Glycogen

Glycogen is the energy reserve carbohydrate of animals. Practically all mammalian cells contain some stored carbohydrates in the form of glycogen, but it is especially abundant in the liver (4%–8% by weight of tissue) and in skeletal muscle cells (0.5%–1.0%).

Like starch in plants, glycogen is found as granules in liver and muscle cells. When fasting, animals draw on these glycogen reserves during the first day without food to obtain the glucose needed to maintain metabolic balance.

> About 70% of the total glycogen in the body is stored in muscle cells. Although the percentage of glycogen (by weight) is higher in the liver, the much greater mass of skeletal muscle stores a greater total amount of glycogen.

Glycogen is structurally quite similar to amylopectin, although glycogen molecules are larger than those of amylopectin—up to 100,000 glucose units—, contain even more branches, and the branches are shorter.

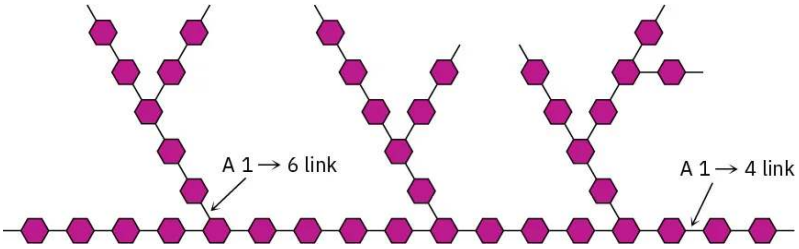


Figure 11.9.3: A representation of the structure of glycogen. The hexagons represent glucose units linked by 1→4 and 1→6 glycoside bonds.

When treated with iodine, glycogen gives a reddish brown color. Glycogen can be broken down into its D-glucose subunits by acid hydrolysis or by the same enzymes that catalyze the breakdown of starch. In animals, the enzyme phosphorylase catalyzes the breakdown of glycogen to phosphate esters of glucose.

Cellulose

Cellulose, a fibrous carbohydrate found in all plants, is the structural component of plant cell walls. Because the earth is covered with vegetation, cellulose is the most abundant of all carbohydrates, accounting for over 50% of all the carbon found in the vegetable kingdom. Cotton fibrils and filter paper are almost entirely cellulose (about 95%), wood is about 50% cellulose, and the dry weight of leaves is about 10%–20% cellulose. The largest use of cellulose is in the manufacture of paper and paper products. Although the use of non-cellulose synthetic fibers is increasing, rayon (made from cellulose) and cotton still account for over 70% of textile production.

Like amylose, cellulose is a linear polymer of glucose. It differs, however, in that the glucose units are joined by β-1,4-glycosidic linkages, producing a more extended structure than amylose (part (a) of Figure 11.9.4). This extreme linearity allows a great deal of hydrogen bonding between OH groups on adjacent chains, causing them to pack closely into fibers (part (b) of Figure 11.9.4). As a result, cellulose exhibits little interaction with water or any other solvent. Cotton and wood, for example, are completely insoluble in water and have considerable mechanical strength. Because cellulose does not have a helical structure, it does not bind to iodine to form a colored product.

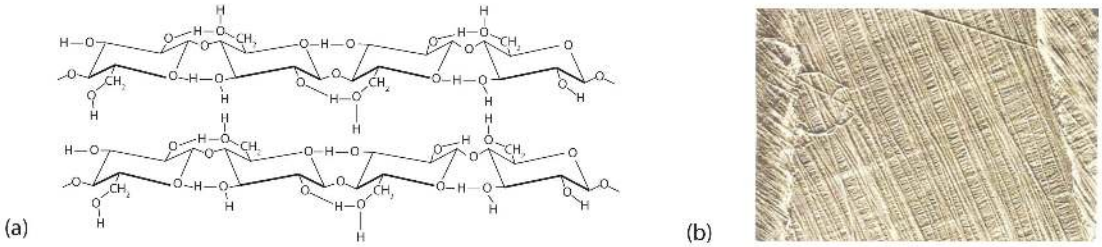


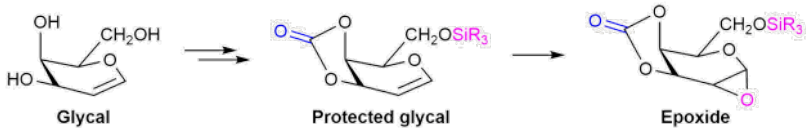
Figure 11.9.4: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

Cellulose yields D-glucose after complete acid hydrolysis, yet humans are unable to metabolize cellulose as a source of glucose. Our digestive juices lack enzymes that can hydrolyze the β-glycosidic linkages found in cellulose, so although we can eat potatoes, we cannot eat grass. However, certain microorganisms can digest cellulose because they make the enzyme cellulase, which catalyzes the hydrolysis of cellulose. The presence of these microorganisms in the digestive tracts of herbivorous animals (such as cows, horses, and sheep) allows these animals to degrade the cellulose from plant material into glucose for energy. Termites also

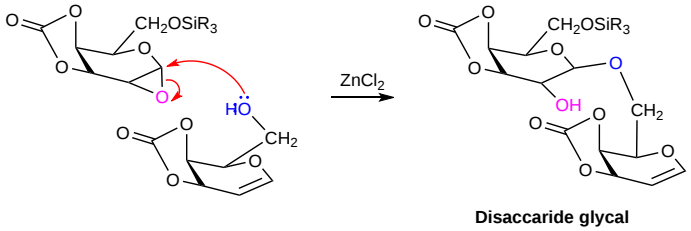
contain cellulase-secreting microorganisms and thus can subsist on a wood diet. This example once again demonstrates the extreme stereospecificity of biochemical processes.

Polysaccaride Synthesis

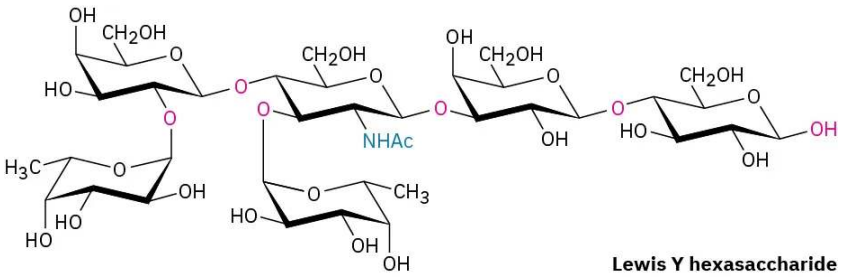
The presence of multiple -OH groups in monosaccarides makes the laboratory synthesis of polysaccharides difficult. One modern method for the synthesis of polysaccharides is called the **glycal assembly method**. A glycal is a sugar which has been dehydrated to form a double bond. Glycals are typically prepared from the corresponding monosaccharide. As part of the synthesis pathway, the primary alcohol of the glycal is protected by forming a silyl ether (Section 17-8). Also, two adjacent secondary alcohols are protected by forming a cyclic carbonate ester. Now there are no -OH groups remanding in the protected glycal. The double bond of the protected glycal is then converted into a epoxide functional groups.



Epoxides ring can be opened by the acid-catalyzed S_N2 backside attack by an alcohol (section 18-6). This reaction is exploited by reacting a protected glycal epoxide with a second glycal with an unprotected primary alcohol in the presence $ZnCl_2$ as a Lewis acid. The disaccharide formed in this reaction is a glycal so it can be epoxidized and coupled with another glycal to form a trisaccharide etc. Once the monosaccharides are combined to form a chain of the desired length, the remaining silyl ether and cyclic carbonate protecting groups are removed by hydrolysis and the polysaccharide is formed.



Among the numerous complex polysaccharides that have been synthesized in the laboratory are several tumor-associated carbohydrate antigens (TACAs) that are currently being tested as potential vaccines for breast, prostate, lung, colon, and ovarian cancers.



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11.10: Other Important Carbohydrates

Objectives

After completing this section, you should be able to identify deoxy and amino sugars, given their structures.

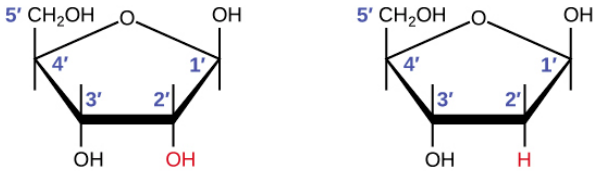
Key Terms

Make certain that you can define, and use in context, the key terms below.

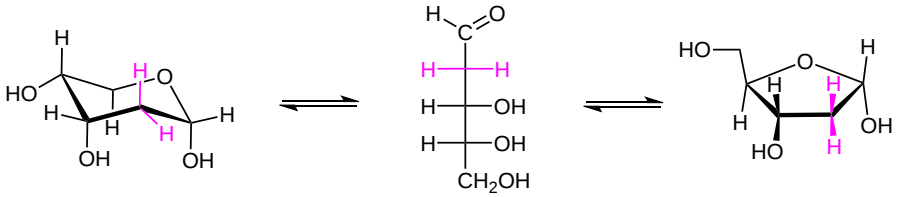
- amino sugar
- deoxy sugar

Deoxy Sugars

As shown in **Section 11-8**, deoxy sugars are missing an oxygen atom. The most common deoxy sugar is 2-deoxyribose, a modified form of another sugar called ribose. When compared to ribose, 2-deoxyribose has an -OH group replaced with an -H at the 2 position. 2-deoxyribose is best known for being the sugar found in the structure of deoxyribonucleic acid (DNA).



In water, 2-deoxyribose is an equilibrium mixture of both the furanose and pyranose ring forms. The pyranose form the most stable (40% alpha anomer and 35% beta anomer), followed by the furanose structures (13% alpha anomer and 12% beta), with the uncyclized form making up the remaining 0.7%.

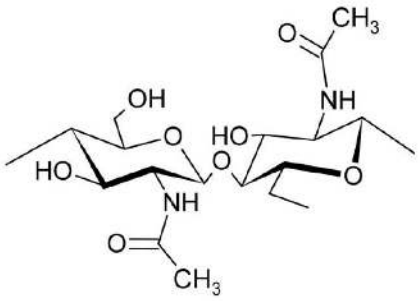


Pyranose, uncyclized and furanose forms of 2-deoxyribose. The more stable alpha isomer is shown for both the pyranose and furanose forms. Note the missing hydroxide at the 2 position (highlighted magenta)

Amino Sugars

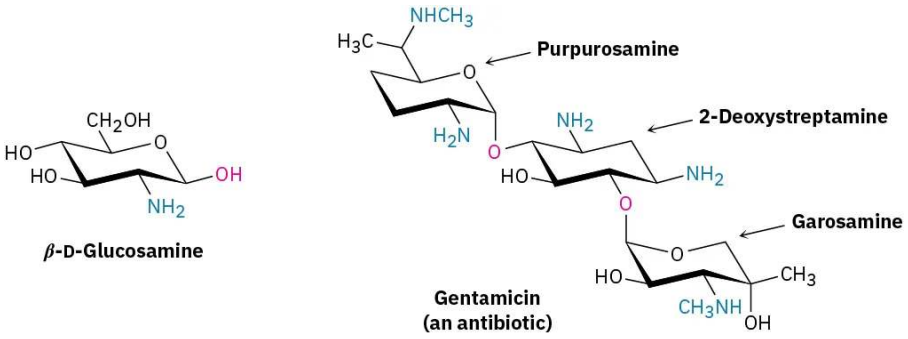
An amino sugar (or more technically a 2-amino-2-deoxysugar) is a sugar molecule in which a hydroxyl group has been replaced with an amine group. More than 60 amino sugars are known, with one of the most abundant being *N*-acetylglucosamine, which is the main component of chitin.

Chitin is a polymer of 2-deoxy-2-N-ethanamidoglucose (N-acetyl-β-D-glucosamine) found in many places throughout the natural world. It is a characteristic component of the cell walls of fungi, the exoskeletons of arthropods such as crustaceans (e.g., crabs, lobsters and shrimps) and insects, the radulae of molluscs, and the beaks and internal shells of cephalopods, including squid and octopuses and on the scales and other soft tissues of fish and lissamphibians.



Chitin Structure, polymer of 2-deoxy-2-N-ethanamidoglucose (N-acetyl-β-D-glucosamine)

Other amino sugars are found in antibiotics such as streptomycin, gentamicin, amikacin, and tobramicin.



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11.11: Cell-Surface Carbohydrates and Influenza Viruses

Objectives

After completing this section, you should be able to:

1. Explain how carbohydrates are related to blood type.
2. Explain how influenza works and how it is influenced by carbohydrates.

Oligosaccharides

An **oligosaccharide** is a saccharide polymer containing a small number (typically two to ten) of monosaccharides. Oligosaccharides can have many functions; for example, they are commonly found on the plasma membrane of animal cells where they can play a role in cell-cell recognition. In general, they are found attached to compatible amino acid side-chains in proteins or to lipids. Oligosaccharides are often found as components of **glycoproteins** or **glycolipids**. They can be used as chemical markers on the outside of cells, often for cell recognition. Oligosaccharides are also responsible for determining blood type.

Glycoproteins

Carbohydrates are covalently attached to many different biomolecules, including lipids to form glycolipids and proteins to form glycoproteins. Glycoproteins and glycolipids are often found in biological membranes, to which they are anchored through nonpolar interactions. What is the function of these carbohydrates? Two are apparent. First, glycosylation of proteins helps protect them from degradation by enzymes in the body. However, their main functions arises from the fact that covalently attached carbohydrates that "decorate" the surface of glycoproteins or glycolipids provide new binding site interactions that allow interactions with other biomolecules. Hence glycosylation allows for cell: cell, cell: protein, or protein: protein interactions. Unfortunately, bacteria and viruses often recognize glycosylated molecules on cell membranes as well, allowing for their import into the cell.

Blood Type

Cell markers are carbohydrate chains on the surface of cells, where they act as “road signs” allowing molecules to distinguish one cell from another. Blood markers are exclusively made from four monosaccharides: D-galactose, L-fucose, N-acetylgalactosamine, and N-acetylglucosamine.

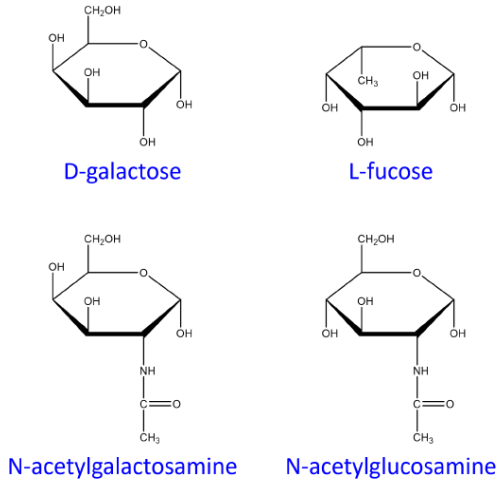


Figure 11.11.1: Structures of monosaccharide units present in ABO blood markers

ABO blood markers found on red blood cells are made up of oligosaccharides that contain either three or four sugar units, as shown below. Oligosaccharides attached to red blood cells determine the ABO blood type.

Of the four blood types, type O has the fewest types of saccharides attached to it, while type AB has the most. As a result, type O blood is considered the universal donor because it doesn't have any saccharides present that will appear as foreign when transfused

into the blood of another type. The reverse is not true. For example:

- If type A blood is given to a patient with type O blood, it will be rejected by the body because there is an unknown species being introduced to the body. Type A blood cells contain N-acetylgalactosamine which is not present in type O blood.
- Since type AB blood has all possible saccharides, type AB blood is considered the **universal acceptor**.

The Rhesus factor (Rh) in blood also affects donor and acceptor properties, but it does not depend on carbohydrates. The Rh factor is determined by the presence (Rh+) or absence (Rh-) of a specific protein on the surface of red blood cells.

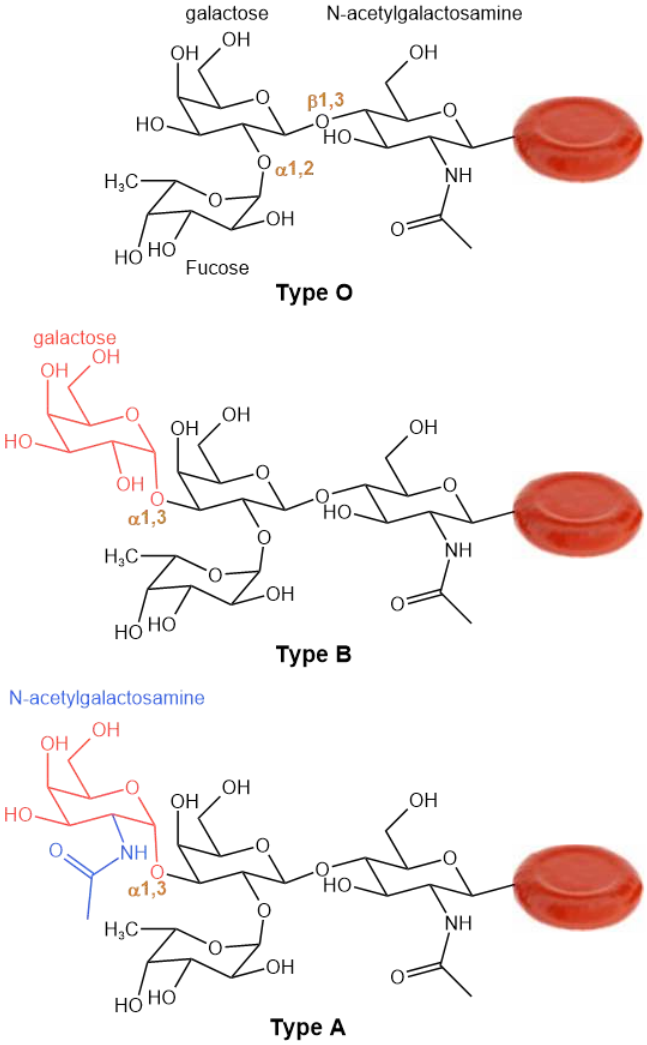


Figure 11.11.2: Oligosaccharide structures of blood type O, type B, and type A. Type AB has type A + type B in it. (Copyright; Public domain)

Virus

Influenza and the Avian Flu

Three pandemics of influenza have swept the world since the "Spanish" flu of 1918.

- The "Asian" flu pandemic of 1957;
- the "Hong Kong" flu pandemic of 1968;
- the "Swine" flu pandemic that began in April of 2009.

The influenza virus is simple yet deadly. It interacts with human cells through a surface protein, hemagglutinin (HA). The virus binds to host cells through interaction of HA with cell surface carbohydrates. Once bound the virus internalizes, ultimately leading to release of the RNA genome of the virus into the host cell. The HA protein is the most abundant protein on the viral surface (as surmised by antibody formation).

The influenza virus is typically classified by two kinds of glycoproteins on the surface of the virus: HA and neuraminidase. Two viral strains which have been often discussed are H5N1 and H1N1, which stand for hemagglutinin (H: type 5 or type 1) and neuraminidase (N: type 1). 15 avian and mammalian variants have been identified (based on antibody studies). Only 3 adapted to humans in the last 100 yr, giving pandemic strains H1 (1918), H2 (957) and H3 (1968). Three recent avian variants (H5, H7, and H9) have jumped directly to humans recently, but have low human-to-human transmissibility.

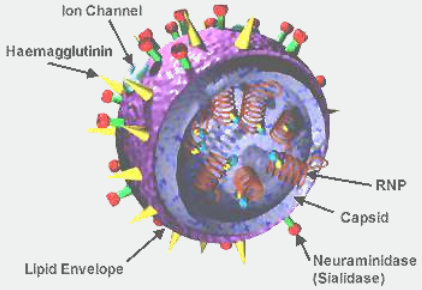
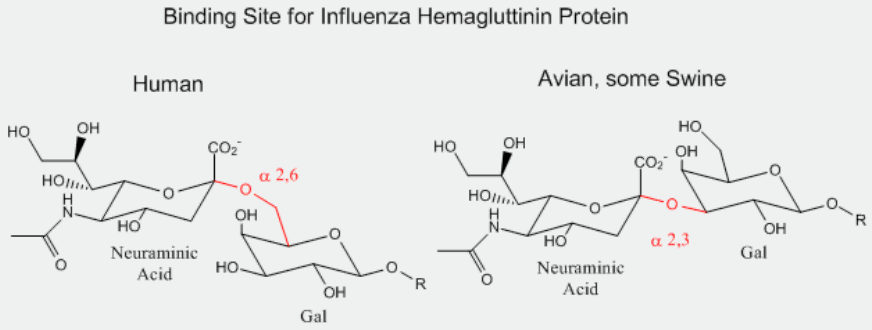
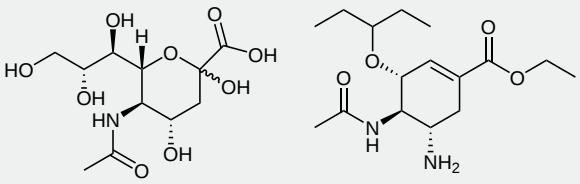


Figure 11.11.3: Structure (3D) of the Influenza Virus: The image depicts the major components of the virus structure, including the neuraminidase. (Public Domain; National Institutes of Health via Wikipedia)

Influenza Virus binds to Cell Surface Glycoproteins with Neu5Ac - A protein on the surface of influenza virus. Hemagluttinin binds to sialic acid (Sia), which is covalently attached to many cell membrane glycoproteins. The sialic acid is usually connected through an alpha (2,3) or alpha (2,6) link to galactose on N-linked glycoproteins. The subtypes found in avian (and equine) influenza isolates bind preferentially to Sia (alpha 2,3) Gal which predominates in avian GI tract where viruses replicate. Human virus of H1, H2, and H3 subtype (cause of the 1918, 1957, and 1968 pandemics) recognize Sia (alpha 2,6) Gal, as the major form in the human respiratory tract. The swine influenza HA bind to Sia (alpha 2,6) Gal and some Sia (alpha 2,3) both of which are commonly found in swine.



Before it leaves the cell, the virus forms a bud on the intracellular side of the cell, with the HA and NA in the host cell membrane. The virus in this state would not leave the cell, since its HA molecules would interact with sialic acid residues on the host cell membrane, thereby holding the virus in the membrane. Neuraminidase hydrolyzes sialic acids on cell-surface glycoproteins, allowing the virus to complete budding and be released from the cell as new viruses. By mimicking the structure of sialic acid, the drugs Oseltamivir (Tamiflu) and zanamivir (Relenza) bind to and inhibit neuraminidase, whose activity is necessary for viral release from infected cells. Tamiflu appears to be effective against N1 in the current H5N1 avian influenza viruses. Governments across the world are stockpiling this drug in case of a pandemic caused by the avian virus jumping directly to humans and becoming transmissible from human to human.



Sialic Acid **Tamiflu**

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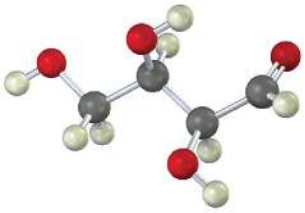
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- **19.3B: Influenza** by John W. Kimball is licensed CC BY 3.0. Original source: https://www.biology-pages.info/.
- **B3. N-linked Glycoproteins** by Henry Jakubowski is licensed CC BY-NC-SA 4.0.

11.12: Additional Problems

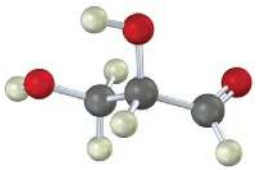
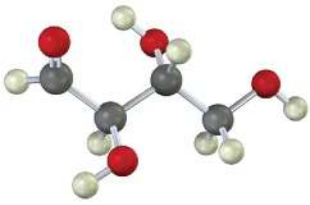
11 • Additional Problems

Visualizing Chemistry

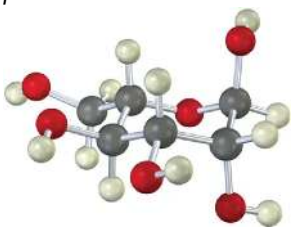
PROBLEM 11.26 Identify the following aldoses, and tell whether each is a D or L sugar:

(a)  (b) 

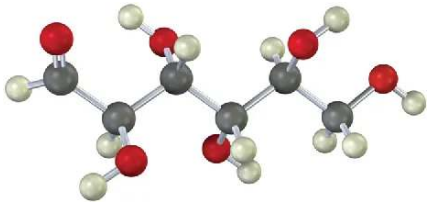
PROBLEM 11.27 Draw Fischer projections of the following molecules, placing the carbonyl group at the top in the usual way. Identify each as a D or L sugar.

(a)  (b) 

PROBLEM 11.28 The following structure is that of an L aldohexose in its pyranose form. Identify it, and tell whether it is an α or β anomer.



PROBLEM 11.29 The following model is that of an aldohexose:

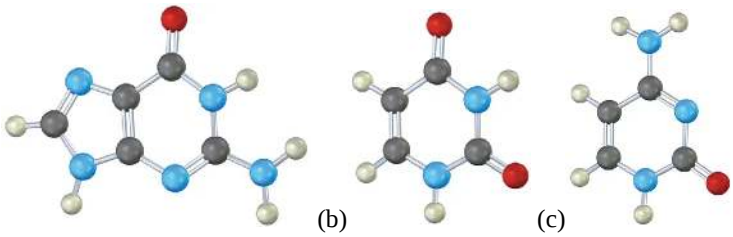


(a) Draw Fischer projections of the sugar, its enantiomer, and a diastereomer.

(b) Is this a D sugar or an L sugar? Explain.

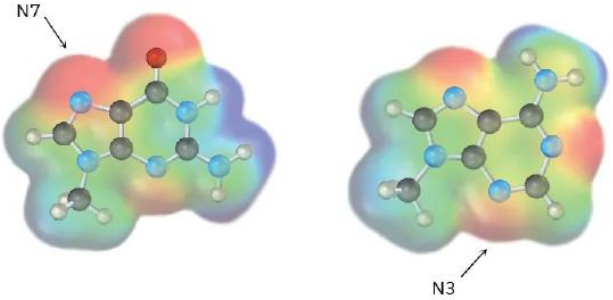
(c) Draw the β anomer of the sugar in its furanose form.

PROBLEM 11.30 Identify the following bases, and tell whether each is found in DNA, RNA, or both:



(a) (b) (c)

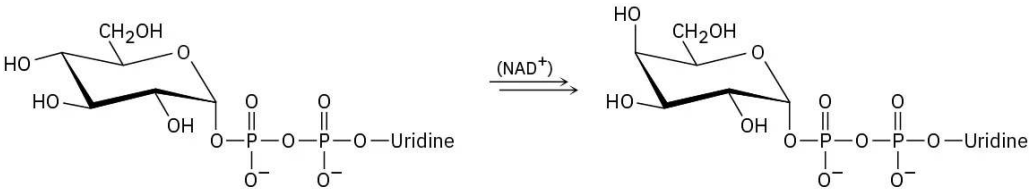
PROBLEM 11.31 Amine bases in nucleic acids can react with alkylating agents in typical S_N2 reactions. Look at the following electrostatic potential maps, and tell which is the better nucleophile, guanine or adenine. The reactive positions in each are indicated.



9-Methylguanine **9-Methyladenine**

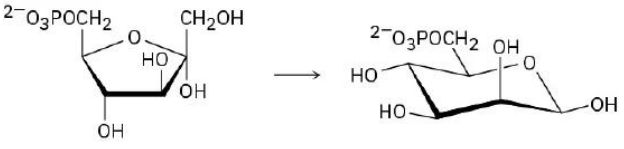
Mechanism Problems

PROBLEM 11.32 Galactose, one of the eight essential monosaccharides (**Section 11.8**), is biosynthesized from UDP-glucose by galactose 4-epimerase, where UDP = uridylyl diphosphate (a ribonucleotide diphosphate; **Section 14.2**). The enzyme requires NAD^+ for activity (**Section 3.8**), but it is not a stoichiometric reactant, and NADH is not a final reaction product. Propose a mechanism.



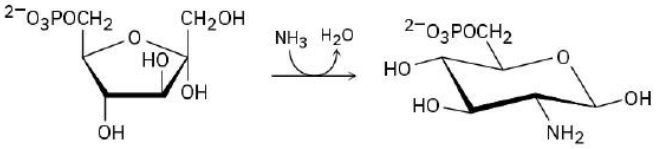
UDP-Glucose **UDP-Galactose**

PROBLEM 11.33 Mannose, one of the eight essential monosaccharides (**Section 11.8**), is biosynthesized as its 6-phosphate derivative from fructose 6-phosphate. No enzyme cofactor is required. Propose a mechanism.



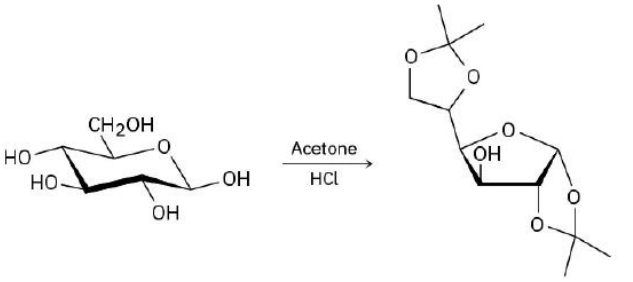
Fructose 6-phosphate **Mannose 6-phosphate**

PROBLEM 11.34 Glucosamine, one of the eight essential monosaccharides (**Section 11.8**), is biosynthesized as its 6-phosphate derivative from fructose 6-phosphate by reaction with ammonia. Propose a mechanism.



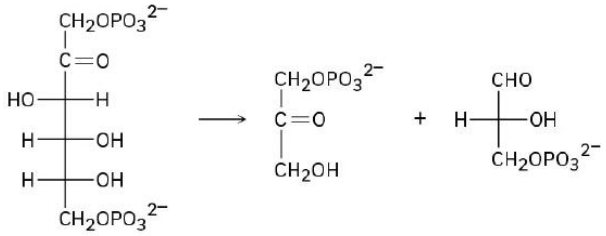
Fructose 6-phosphate **Glucosamine 6-phosphate**

PROBLEM 11.35 D-Glucose reacts with acetone in the presence of acid to yield the nonreducing 1,2 : 5,6-diisopropylidene-D-glucofuranose. Propose a mechanism.



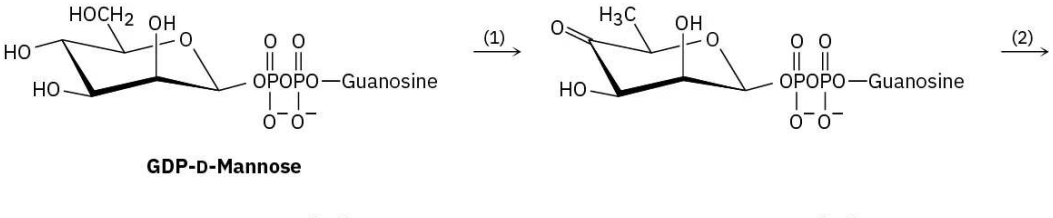
1,2:5,6-Diisopropylidene-D-glucofuranose

PROBLEM 11.36 One of the steps in the biological pathway for carbohydrate metabolism is the conversion of fructose 1,6-bisphosphate into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate. Propose a mechanism for the transformation.

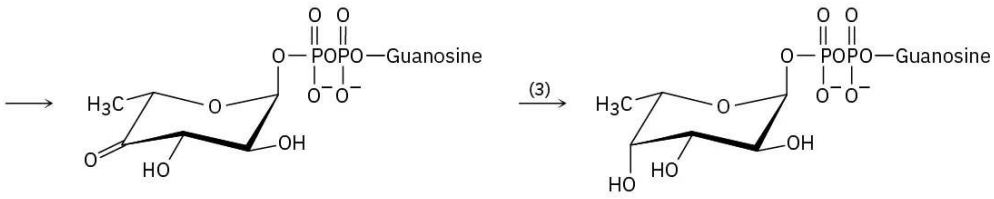


Fructose 1,6-bisphosphate **Dihydroxyacetone phosphate** **Glyceraldehyde 3-phosphate**

PROBLEM 11.37 L-Fucose, one of the eight essential monosaccharides (**Section 11.8**), is biosynthesized from GDP-D-mannose by the following three-step reaction sequence, where GDP = guanosine diphosphate (a ribonucleoside diphosphate; **Section 14.2**):



GDP-D-Mannose



GDP-L-Fucose

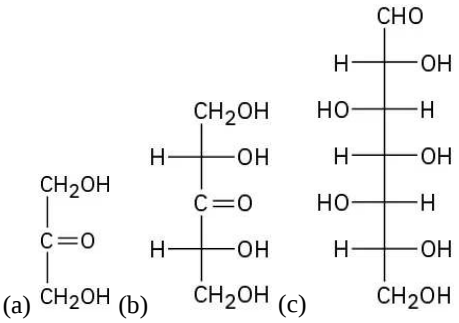
(a) Step 1 involves an oxidation to a ketone, a dehydration to an enone, and a conjugate reduction. The step requires $NADP^+$, but no NADPH is formed as a final reaction product. Propose a mechanism.

(b) Step 2 accomplishes two epimerizations and utilizes acidic and basic sites in the enzyme but does not require a coenzyme. Propose a mechanism.

(c) Step 3 requires NADPH as a coenzyme. Show the mechanism.

Carbohydrate Structures

PROBLEM 11.38 Classify each of the following sugars. (For example, glucose is an aldohexose.)



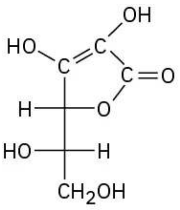
PROBLEM 11.39 Write open-chain structures for the following:

(a) A ketotetrose. (b) A ketopentose. (c) A deoxyaldohexose (d) A five-carbon amino sugar

PROBLEM 11.40 What is the stereochemical relationship of D-ribose to L-xylose? What generalizations can you make about the following properties of the two sugars?

(a) Melting point (b) Solubility in water (c) Specific rotation (d) Density

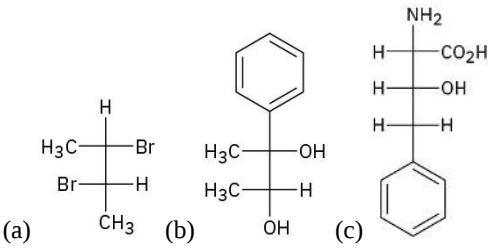
PROBLEM 11.41 Does ascorbic acid (vitamin C) have a D or L configuration?



Ascorbic acid

PROBLEM 11.42 Draw the three-dimensional furanose form of ascorbic acid (Problem 11-41), and assign *R* or *S* stereochemistry to each chirality center.

PROBLEM 11.43 Assign R or *S* configuration to each chirality center in the following molecules:



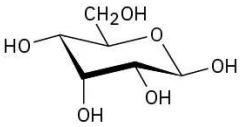
PROBLEM 11.44 Draw Fischer projections of the following molecules:

(a) The *S* enantiomer of 2-bromobutane (b) The *R* enantiomer of alanine, $CH_3CH(NH_2)CO_2H$

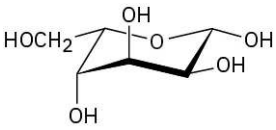
(c) The *R* enantiomer of 2-hydroxypropanoic acid (d) The *S* enantiomer of 3-methylhexane

PROBLEM 11.45 Draw Fischer projections for the two D aldoheptoses whose stereochemistry at C3, C4, C5, and C6 is the same as that of D-glucose at C2, C3, C4, and C5.

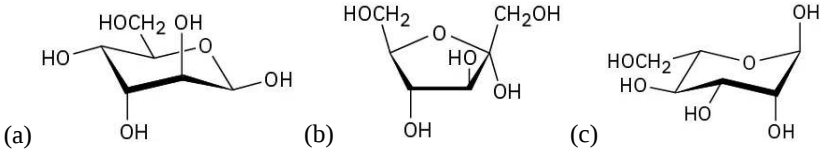
PROBLEM 11.46 The following cyclic structure is that of allose. Is this a furanose or pyranose form? Is it an α or a β anomer? Is it a D or an L sugar?



PROBLEM 11.47 What is the complete name of the following sugar?

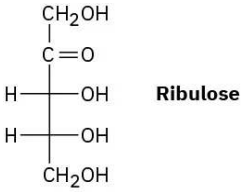


PROBLEM 11.48 Write the following sugars in their open-chain forms:



(a) (b) (c)

PROBLEM 11.49 Draw D-ribulose in its five-membered cyclic β-hemiacetal form.



Ribulose

PROBLEM 11.50 Look up the structure of D-talose in Figure 11.4, and draw the β anomer in its pyranose form. Identify the ring substituents as axial or equatorial.

Carbohydrate Reactions

PROBLEM 11.51 Draw structures for the products you would expect to obtain from the reaction of β- D-talopyranose with each of the following reagents:

(a) $NaBH_4$ in H_2O (b) Warm dilute HNO_3 (c) Br_2, H_2O (d) CH_3CH_2OH, HCl (e) CH_3I, Ag_2O (f) $(CH_3CO)_2O$, pyridine

PROBLEM 11.52 How many D-2-ketohexoses are possible? Draw them.

PROBLEM 11.53 One of the D-2-ketohexoses is called *sorbose*. On treatment with $NaBH_4$, sorbose yields a mixture of gulitol and iditol. What is the structure of sorbose?

PROBLEM 11.54 Another D-2-ketohexose, *psicose*, yields a mixture of allitol and altritol when reduced with $NaBH_4$. What is the structure of psicose?

PROBLEM 11.55 L-Gulose can be prepared from D-glucose by a route that begins with oxidation to D-glucaric acid, which cyclizes to form two six-membered-ring lactones. Separating the lactones and reducing them with sodium amalgam gives D-glucose and L-gulose. What are the structures of the two lactones, and which one is reduced to L -gulose?

PROBLEM 11.56 Gentiobiose, a rare disaccharide found in saffron and gentian, is a reducing sugar and forms only D-glucose on hydrolysis with aqueous acid. Reaction of gentiobiose with iodomethane and Ag_2O yields an octamethyl derivative, which can be hydrolyzed with aqueous acid to give 1 equivalent of 2,3,4,6-tetra-*O*-methyl- D -glucopyranose and 1 equivalent of 2,3,4-tri-*O*-methyl- D -glucopyranose. If gentiobiose contains a β-glycoside link, what is its structure?

General Problems

PROBLEM 11.57 All aldoses exhibit mutarotation. For example, α- D-galactopyranose has $[\alpha]_D$ = +150.7, and β- D -galactopyranose has $[\alpha]_D$ = +52.8. If either anomer is dissolved in water and allowed to reach equilibrium, the specific rotation of

the solution is +80.2. What are the percentages of each anomer at equilibrium? Draw the pyranose forms of both anomers.

PROBLEM 11.58 What other D aldohexose gives the same alditol as D -talose?

PROBLEM 11.59 Which of the eight D aldohexoses give the same aldaric acids as their L enantiomers?

PROBLEM 11.60 Which of the other three D aldopentoses gives the same aldaric acid as D-lyxose?

PROBLEM 11.61 Draw the structure of L-galactose, and then answer the following questions:

(a) Which other aldohexose gives the same aldaric acid as L -galactose on oxidation with warm HNO_3?

(b) Is this other aldohexose a D sugar or an L sugar? (c) Draw this other aldohexose in its most stable pyranose conformation.

PROBLEM 11.62 Amygdalin, or laetrile, is a cyanogenic glycoside first isolated in 1830 from almond and apricot seeds. If acidic hydrolysis of amygdalin liberates HCN, along with benzaldehyde cyanohydrin with gentiobiose (Problem 11-56), what is its structure?

PROBLEM 11.63 Trehalose is a nonreducing disaccharide that is hydrolyzed by aqueous acid to yield 2 equivalents of D-glucose. Methylation followed by hydrolysis yields 2 equivalents of 2,3,4,6-tetra-*O*-methylglucose. How many structures are possible for trehalose?

PROBLEM 11.64 Trehalose (Problem 11-63) is cleaved by enzymes that hydrolyze *α*-glycosides but not by enzymes that hydrolyze *β*-glycosides. What is the structure and systematic name of trehalose?

PROBLEM 11.65 Isotrehalose and neotrehalose are chemically similar to trehalose (Problems 11-61 and 11-62) except that neotrehalose is hydrolyzed only by *β*-glycosidase enzymes, whereas isotrehalose is hydrolyzed by both *α*- and *β*-glycosidase enzymes. What are the structures of isotrehalose and neotrehalose?

PROBLEM 11.66 D-Mannose reacts with acetone to give a diisopropylidene derivative (Problem 11-33) that is still reducing toward Tollens' reagent. Propose a likely structure for this derivative.

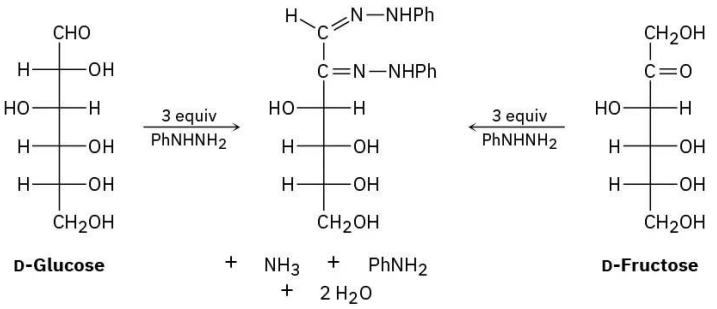
PROBLEM 11.67 Glucose and mannose can be interconverted (in low yield) by treatment with dilute aqueous NaOH. Propose a mechanism.

PROBLEM 11.68 Propose a mechanism to account for the fact that D-gluconic acid and D-mannonic acid are interconverted when either is heated in pyridine solvent.

PROBLEM 11.69 The *cyclitols* are a group of carbocyclic sugar derivatives having the general formulation 1,2,3,4,5,6-cyclohexanehexol. How many stereoisomeric cyclitols are possible? Draw them in their chair forms.

PROBLEM 11.70 Compound **A** is a D-aldopentose that can be oxidized to an optically inactive aldaric acid **B**. On Kiliani–Fischer chain extension, **A** is converted into **C** and **D**; **C** can be oxidized to an optically active aldaric acid **E**, but **D** is oxidized to an optically inactive aldaric acid **F**. What are the structures of **A**–**F**?

PROBLEM 11.71 Simple sugars undergo reaction with phenylhydrazine, $PhNH–NH_2$, to yield crystalline derivatives called *osazones*. The reaction is a bit complex, however, as shown by the fact that glucose and fructose yield the same osazone.



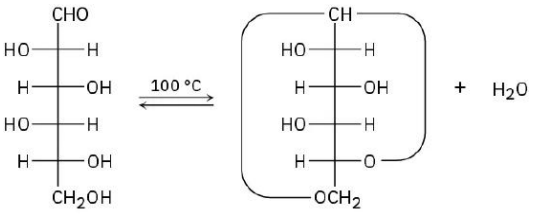
(a) Draw the structure of a third sugar that yields the same osazone as glucose and fructose.

(b) Using glucose as the example, the first step in osazone formation is reaction of the sugar with phenylhydrazine to yield an imine called a *phenylhydrazone*. Draw the structure of the product.

(c) The second and third steps in osazone formation are tautomerization of the phenylhydrazone to give an enol, followed by elimination of aniline to give a keto imine. Draw the structures of both the enol tautomer and the keto imine.

(d) The final step is reaction of the keto imine with 2 equivalents of phenylhydrazine to yield the osazone plus ammonia. Propose a mechanism for this step.

PROBLEM 11.72 When heated to 100 °C, D-idose undergoes a reversible loss of water and exists primarily as 1,6-anhydro- D -idopyranose.



D-Idose 1,6-Anhydro-D-idopyranose

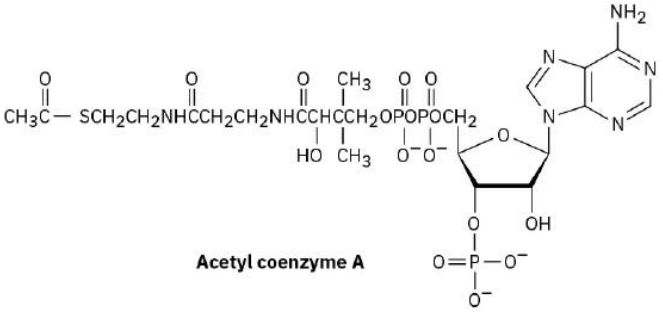
(a) Draw D -idose in its pyranose form, showing the more stable chair conformation of the ring.

(b) Which is more stable, α- D -idopyranose or β- D -idopyranose? Explain.

(c) Draw 1,6-anhydro- D -idopyranose in its most stable conformation.

(d) When heated to 100 °C under the same conditions as those used for D -idose, D -glucose does not lose water and does not exist in a 1,6-anhydro form. Explain.

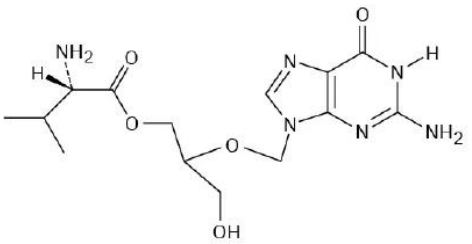
PROBLEM 11.73 Acetyl coenzyme A (acetyl CoA) is the key intermediate in food metabolism. What sugar is present in acetyl CoA?



Acetyl coenzyme A

PROBLEM 11.74 Draw the structure of cyclic adenosine monophosphate (cAMP), a messenger involved in the regulation of glucose production in the body. Cyclic AMP has a phosphate ring connecting the 3′- and 5′-hydroxyl groups on adenosine.

PROBLEM 11.75 Valganciclovir, marketed as Valcyte, is an antiviral agent used for the treatment of cytomegalovirus. Called a *prodrug*, valganciclovir is inactive by itself but is rapidly converted in the intestine by hydrolysis of its ester bond to produce an active drug, called ganciclovir, along with an amino acid.



Valganciclovir

- (a) What is the structure of ganciclovir?
- (b) What atoms present in the nucleotide deoxyguanine are missing from ganciclovir?
- (c) What role do the atoms missing from deoxyguanine play in DNA replication?
- (d) How might valganciclovir interfere with DNA synthesis?

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11.S: Biomolecules- Carbohydrates (Summary)

Concepts & Vocabulary

- fulfill all of the detailed objectives listed under each individual section.
- define, and use in context, any of the key terms introduced in this chapter.

Introduction

- Carbohydrates are composed of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes and ketones.
- Examples of carbohydrates are starch, fibers, sugar, and cellulose.
- Green plants use glucose for energy or making larger carbohydrates.
- Carbohydrates are needed for the synthesis of nucleic acids, proteins, and lipids.
- Animals rely on plants to provide them with carbohydrates, which are used for food and clothing.

11.1 Classification of Carbohydrates

- Carbohydrates originate as products from photosynthesis.
- The generic formula is $C_n(H_2O)_n$.
- Carbohydrates play a vital role in a major food source, but are also used as structural material, recognition sites on cells, and other tasks.
- Carbohydrates are called saccharides and can be classified as simple or complex.

11.2 Fischer Projections

- The Fischer projection is a type of notation often used when multiple chiral centers are present in a molecule.
- In a Fischer projection:
  - the four bonds to a chiral carbon make a cross with the carbon atom at the intersection of the horizontal and vertical lines.
  - the two horizontal bonds are directed toward the viewer (forward of the stereogenic carbon).
  - the two vertical bonds are directed behind the central carbon (away from the viewer).
- Determining whether a chiral carbon is R or S
  - If the lowest priority group is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents.
  - If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer, so you reverse it.
- Epimer is used to designate diastereomers that differ in configuration at only one chiral center.

11.3 D,L Sugars

- To determine absolute configuration for carbohydrates, Emil Fischer started with an arbitrary choice that (+)-glucose would be the D-family and related aldoses.
- The last chiral center in an aldose chain (farthest from the aldehyde group) was chosen by Emil Fischer as the D / L designator site.
- The L-family is the mirror image of the D-family.
- If the hydroxyl group in the projection formula pointed to the right, it was defined as a member of the D-family.
- A left directed hydroxyl group then represented the L-family.
- It is important to recognize that the sign of a compound's specific rotation (an experimental number) does not correlate with its configuration (D or L).
- Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

11.4 Configurations of Aldoses

- The aldose family is composed of three to six carbon atoms.
- Emil Fischer determined a way to determine absolute configuration of aldoses.

- In 1951 x-ray fluorescence studies of (+)-tartaric acid, carried out in the Netherlands by Johannes Martin Bijvoet, proved that Fischer's choice was correct.

11.5 Anomers

- The preferred structural form of monosaccharides is a cyclic hemiacetal, especially for five and six-membered rings due to low angle strain and eclipsing strain.
- Five-membered cyclic sugars are termed furanose and six-membered cyclic sugars are pyranose.
- By convention for the D-family, the five-membered furanose ring is drawn in an edgewise projection with the ring oxygen positioned away from the viewer.
- The cyclic pyranose forms of various monosaccharides are often drawn in a flat projection known as a Haworth formula.
- In the D-family, the alpha and beta bonds have the same orientation defined for the furanose ring.
- The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features.
- Derivatizations of this kind permit selective reactions to be conducted at different locations in these highly functionalized molecules.
- When a straight-chain monosaccharide forms a cyclic structure, the carbonyl oxygen atom may be pushed either up or down, giving rise to two stereoisomers.
    - When the OH group on the first carbon atom projected downward, this is called the *alpha (α) form*.
    - When the OH group on the first carbon atom pointed upward, is the *beta (β) form*.
- These two stereoisomers of a cyclic monosaccharide are known as anomers.
- You can start with a pure crystalline sample of glucose consisting entirely of one anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then reclose to form either the α or the β anomer.
- The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation.

11.6 Reactions of Monosaccharides

- The -OH groups on a monosaccharide can be readily converted to esters and ethers.
- Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides.
- Phosphorylation of the -OH group using ATP.
- Oxidation can occur with monosaccharides, which is why some sugars are classified as reducing sugars.
- When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an aldonic acid.
- If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid.
- Sodium borohydride reduction of an aldose makes the ends of the resulting alditol chain identical like aldaric acid.
- Monosaccharides can react to have the chain length increased or decreased, which can be important in elucidation of the carbohydrate's structure.

11.7 The Eight Essential Monosaccharides

- The eight essential monosaccharides are: L-fructose, D-galactose, D-glucose, D-mannose, N-acetyl-D-glucosamine, N-acetyl-D-galacosamine, D-xylose, N-acetyl-D-neuraminic acid.
- These eight monosaccaharides are obtained through diet.

11.8 Disaccharides

- Disaccharides are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage.
- The glycosidic linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide.
- The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them.
- There are three common disaccharides: maltose, lactose, and sucrose.

- Maltose is two glucose molecules linked in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucose molecule to the fourth carbon atom of the second glucose molecule.
- Lactose is composed of one molecule of D-galactose and one molecule of D-glucose joined by a β-1,4-glycosidic bond.
- Sucrose has an α-1,β-2-glycosidic (head-to-head) linkage, which is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.

11.9 Polysaccharides and Their Synthesis

- Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages.
- The three most abundant polysaccharides are starch, glycogen, and cellulose.

11.10 Other Important Carbohydrates

- The backbone of DNA is based on a repeated pattern of a sugar group and a phosphate group, the sugar present - deoxyribose.
- An amino sugar is a sugar molecule in which a hydroxyl group has been replaced with an amine group.

11.11 Cell-Surface Carbohydrates and Influenza Viruses

- Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins.
- Glycoproteins and glycolipids are often found in biological membranes that allow other biomolecules to interact and bind to the protein.
- Bacteria and viruses often recognize glycosylated molecules on cell membranes, allowing for their import into the cell.
- This is how the influenza virus enters the body.

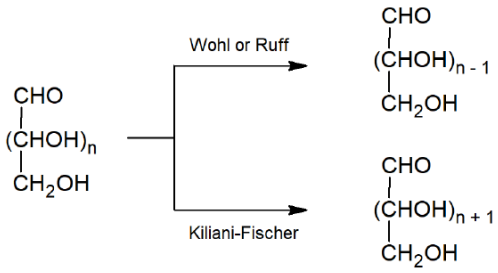
Skills to Master

- Skill 1 Determine which molecules can be classified as carbohydrates.
- Skill 2 Distinguish between monosaccharide, disaccharide, and trisaccharides given the structure.
- Skill 3 Classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.
- Skill 4 Draw the Fischer projection of a monosaccharide, given its wedge-and-broken-line structure or a molecular model.
- Skill 5 Draw the wedge-and-broken-line structure of a monosaccharide, given its Fischer projection or a molecular model.
- Skill 6 Construct a molecular model of a monosaccharide, given its Fischer projection or wedge-and-broken-line structure.
- Skill 7 Identify a specific enantiomer of a monosaccharide as being D or L, given its Fischer projection.
- Skill 8 Assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
- Skill 9 Draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
- Skill 10 Draw configurations of aldoses.
- Skill 11 Determine whether a given monosaccharide will exist as a pyranose or furanose.
- Skill 12 Draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
- Skill 13 Determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
- Skill 14 Describe the phenomenon known as mutarotation.
- Skill 15 Explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
- Skill 16 Predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
- Skill 17 Identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
- Skill 18 Predict the product that would be produced by the Wohl degradation of a given aldose.
- Skill 19 Identify the aldose that would yield a given product following Wohl degradation synthesis.
- Skill 20 Identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
- Skill 21 Identify the two monosaccharide units in a given disaccharide.
- Skill 22 Identify the type of glycoside link (e.g., 1,4′-*β*) present in a given disaccharide structure.

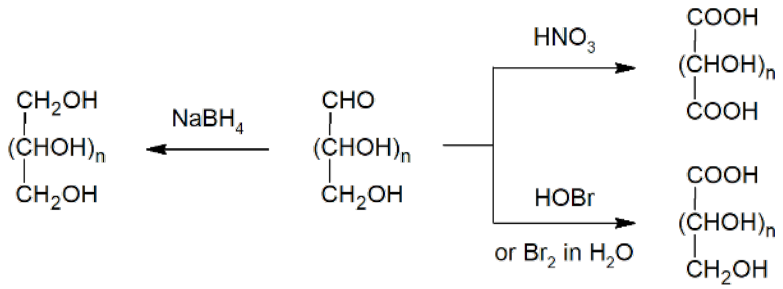
- Skill 23 Draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.
- Skill 24 Identify the products formed from the hydrolysis of a given disaccharide.

Summary of Reactions

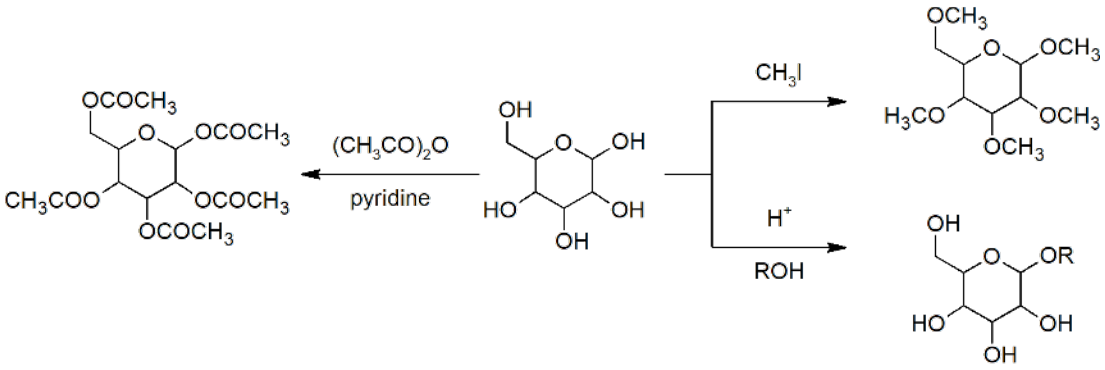
Chain Length



Oxidation - Reduction



Ester and Ether Formation



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CHAPTER OVERVIEW

12: Biomolecules - Amino Acids, Peptides, and Proteins

Learning Objectives

When you have completed Chapter 12, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. use the information provided by an amino acid analysis, an Edman degradation and a carboxypeptidase hydrolysis to determine the structure of an unknown polypeptide.
3. outline the approach that you would use to synthesize a given peptide, providing appropriate mechanistic details if requested to do so.
4. define, and use in context, the key terms introduced in this chapter.

Amino acids are important biochemicals, as they are the building blocks from which proteins and polypeptides are assembled. We begin this chapter with an examination of some of the fundamental chemistry of amino acids: their structures, stereochemistry and synthesis. We then discuss the nature of peptides and of the peptide bond, and present the complex issue of determining the order in which the various amino-acid residues occur in a given peptide. Once a chemist knows the exact order the of the residues in a given peptide, the next challenge is to determine a method by which the same peptide can be prepared in the laboratory. Thus, two sections are devoted to the problem of protein synthesis. The final sections in the chapter deal with the classification, overall structure and denaturation of proteins.

12.0: Introduction
12.1: Structures of Amino Acids
12.2: Amino Acids and Isoelectric Points
12.3: Synthesis of Amino Acids
12.4: Peptides and Proteins
12.5: Peptide Synthesis- Solution-Phase
12.6: Automated Peptide Synthesis - Solid-Phase Technique
12.7: Protein Structure
12.8: Protein Misfolding and Denaturation
12.9: Enzymes and Coenzymes
12.10: Regulation of Enzyme Activity
12.11: How do Enzymes Work? Citrate Synthase
12.12: Additional Problems
12.S: Biomolecules - Amino Acids (Summary)

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12.0: Introduction

Objectives

After completing this section, you should be able to

1. give examples of the various biological roles played by proteins.
2. identify amino acids as being the building blocks from which all proteins are made.
3. show, in a general way, how the joining together of a number of amino acids through the formation of peptide bonds results in the formation of proteins.

Key Terms

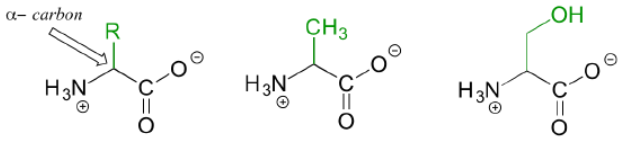
Make certain that you can define, and use in context, the key terms below.

- amino acid
- enzyme
- peptide bond
- protein

Study Notes

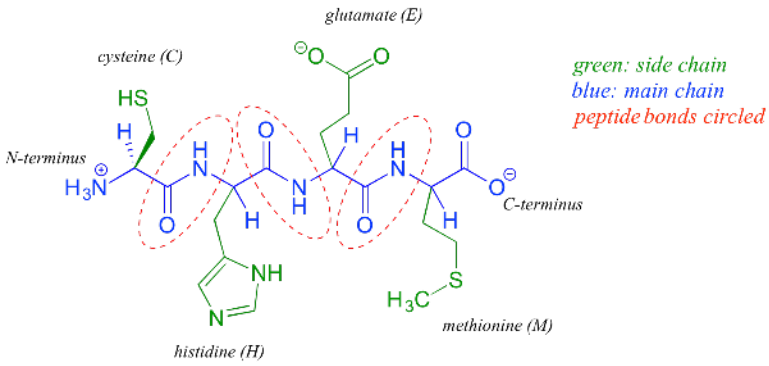
The “peptide bond” or “peptide linkage” that is formed between the amino group of one amino acid and the carboxyl group of a second amino acid is identical to the C-N bond present in amides (see Section 7.8).

Proteins are polymers of **amino acids**, linked by amide groups known as **peptide bond**s. An amino acid can be thought of as having two components: a 'backbone', or 'main chain', composed of an ammonium group, an 'alpha-carbon', and a carboxylate, and a variable 'side chain' (in green below) bonded to the alpha-carbon.



There are twenty different side chains in naturally occurring amino acids, and it is the identity of the side chain that determines the identity of the amino acid: for example, if the side chain is a $-CH_3$ group, the amino acid is alanine, and if the side chain is a $-CH_2OH$ group, the amino acid is serine. Many amino acid side chains contain a functional group (the side chain of serine, for example, contains a primary alcohol), while others, like alanine, lack a functional group, and contain only a simple alkane.

The two 'hooks' on an amino acid monomer are the amine and carboxylate groups. Proteins (polymers of ~50 amino acids or more) and peptides (shorter polymers) are formed when the amino group of one amino acid monomer reacts with the carboxylate carbon of another amino acid to form an amide linkage, which in protein terminology is a **peptide bond**. Which amino acids are linked, and in what order - the protein **sequence** - is what distinguishes one protein from another, and is coded for by an organism's DNA. Protein sequences are written in the amino terminal (N-terminal) to carboxylate terminal (C-terminal) direction, with either three-letter or single-letter abbreviations for the amino acids (see amino acid table). Below is a four amino acid peptide with the sequence "cysteine - histidine - glutamate - methionine". Using the single-letter code, the sequence is abbreviated CHEM.



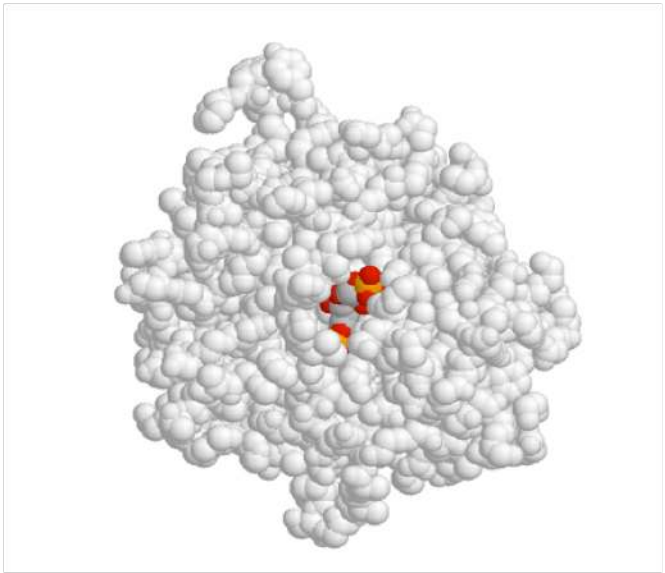
CHEM peptide

When an amino acid is incorporated into a protein it loses a molecule of water and what remains is called a **residue** of the original amino acid. Thus we might refer to the 'glutamate residue' at position 3 of the CHEM peptide above.

Once a protein polymer is constructed, it in many cases folds up very specifically into a three-dimensional structure, which often includes one or more 'binding pockets' in which other molecules can be bound. It is this shape of this folded structure, and the precise arrangement of the functional groups within the structure (especially in the area of the binding pocket) that determines the function of the protein.

Enzymes are proteins which catalyze biochemical reactions. One or more reacting molecules - often called **substrates** - become bound in the **active site** pocket of an enzyme, where the actual reaction takes place. **Receptors** are proteins that bind specifically to one or more molecules - referred to as **ligands** - to initiate a biochemical process. For example, we saw in the introduction to this chapter that the TrpVI receptor in mammalian tissues binds capsaicin (from hot chili peppers) in its binding pocket and initiates a heat/pain signal which is sent to the brain.

Shown below is an image of the glycolytic enzyme fructose-1,6-bisphosphate aldolase (in grey), with the substrate molecule bound inside the active site pocket.



(x-ray crystallographic data are from *Protein Science* **1999**, 8, *291*; pdb code 4ALD. Image produced with JMol First Glance)

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12.1: Structures of Amino Acids

Objectives

After completing this section, you should be able to

1. identify the structural features present in the 20 amino acids commonly found in proteins.

   Note: be prepared to draw the structures of the two simplest members, glycine and alanine.

2. draw the Fischer projection formula of a specified enantiomer of a given amino acid.

   Note: In the *S* enantiomer, the carboxyl group appears at the top of the projection formula and the amino group is on the left.

3. classify an amino acid as being acidic, basic or neutral, given its Kekulé, condensed or shorthand structure.
4. draw the zwitterion form of a given amino acid.
5. account for some of the typical properties of amino acids (e.g., high melting points, solubility in water) in terms of zwitterion formation.
6. write appropriate equations to illustrate the amphoteric nature of amino acids.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- *α*-amino acids; amphoteric; essential amino acids; zwitterion

Study Notes

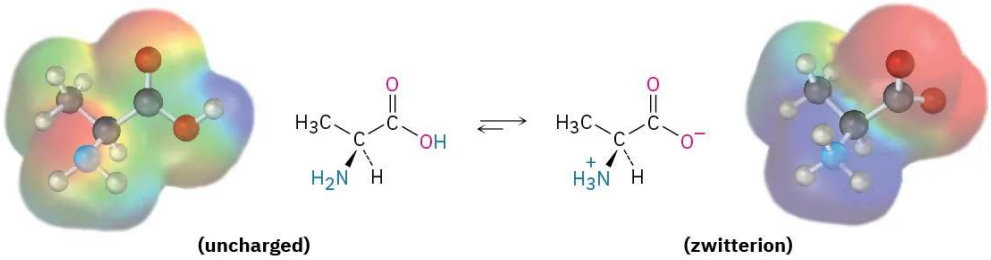
This is a good point at which to review some of the principles of stereochemistry presented in Chapter 5. Be sure to make full use of molecular models when any stereochemical issues arise.

You should recognize that a three-letter shorthand code is often used to represent individual amino acids. You need not memorize this code.

The distinction between essential and nonessential amino acids is not as clear-cut as one might suppose. For example, arginine is often regarded as being nonessential.

Amino Acids in Their Dipolar Ion Form

Amino acids exist in aqueous solution primarily in the form of a dipolar ion, or zwitterion (from the German *zwitter*, meaning "hybrid"). We saw in Section 6.4 that a carboxyl group is deprotonated and exists as the carboxylate anion at a physiological pH of 7.3, whereas an amino group is protonated and exists as the ammonium cation. Thus,



(uncharged) (zwitterion)

Alanine

Amino acid zwitterions are internal salts and therefore have many of the physical properties associated with salts. They have large dipole moments, are relatively soluble in water but insoluble in hydrocarbons, and are crystalline with relatively high melting points. This is evident from a comparison of the physical properties listed in the following table. All four compounds in the table are roughly the same size, and all have moderate to excellent water solubility. The first two are simple carboxylic acids, and the third is an amino alcohol. All three compounds are soluble in organic solvents (e.g. ether) and have relatively low melting points. The

carboxylic acids have pK_a's near 4.5, and the conjugate acid of the amine has a pK_a of 10. The simple amino acid alanine is the last entry. By contrast, it is very high melting (with decomposition), insoluble in organic solvents, and a million times weaker as an acid than ordinary carboxylic acids.

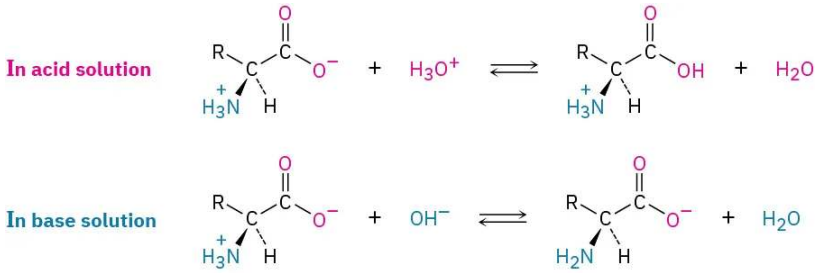
Physical Properties of Selected Acids and Amines

https://chem.libretexts.org/@go/page/500499

Compound	Formula	Mol.Wt.	Solubility in water
isobutyric acid	$(CH_3)_2CHCO_2H$	88	20 g/100 mL
lactic acid	$CH_3CH(OH)CO_2H$	90	completely miscible
3-amino-2-	$CH_3CH(NH_2)CH(OH)CH_3$	89	soluble

butanol		
alanine	$CH_3CH(NH_2)CO_2H$	89

Additionally, amino acids are **amphiprotic, meaning** they can react as either acids or bases, depending on the circumstances. In an aqueous acid solution, an amino acid zwitterion acts as a base, accepting a proton on its $–CO_2^-$ group to yield a cation. In aqueous base solution, the zwitterion is an acid that loses a proton from its $–NH_3^+$ group to form an anion.

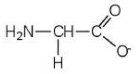


Example 12.1

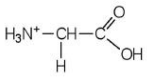
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

a.The base removes H^+ from the protonated amine group.

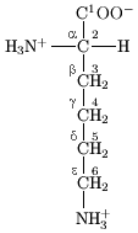


b. The acid adds H^+ to the carboxylate group.



Stereochemistry

The amino acids are all chiral, with the exception of glycine, whose side chain is H. As with lipids, biochemists use the L- and D- nomenclature. All naturally occurring proteins from all living organisms consist of L-amino acids. The configurations of the chiral amino acids are the same when written as a Fischer projection formula, as in the drawing on the right, and this was defined as the **L-configuration** by Fischer. The absolute stereochemistry is related to L-glyceraldehyde, as was the case for triacylglycerides and phospholipids.



Most naturally occurring chiral amino acids are S, with the exception of cysteine. As the diagram below shows, the absolute configuration of amino acids can be represented by the H atom pointing to the rear, the COOH groups pointing to the left, the R group to the right, and the NH_3 group pointing upwards. You can remember this with the anagram CORN.

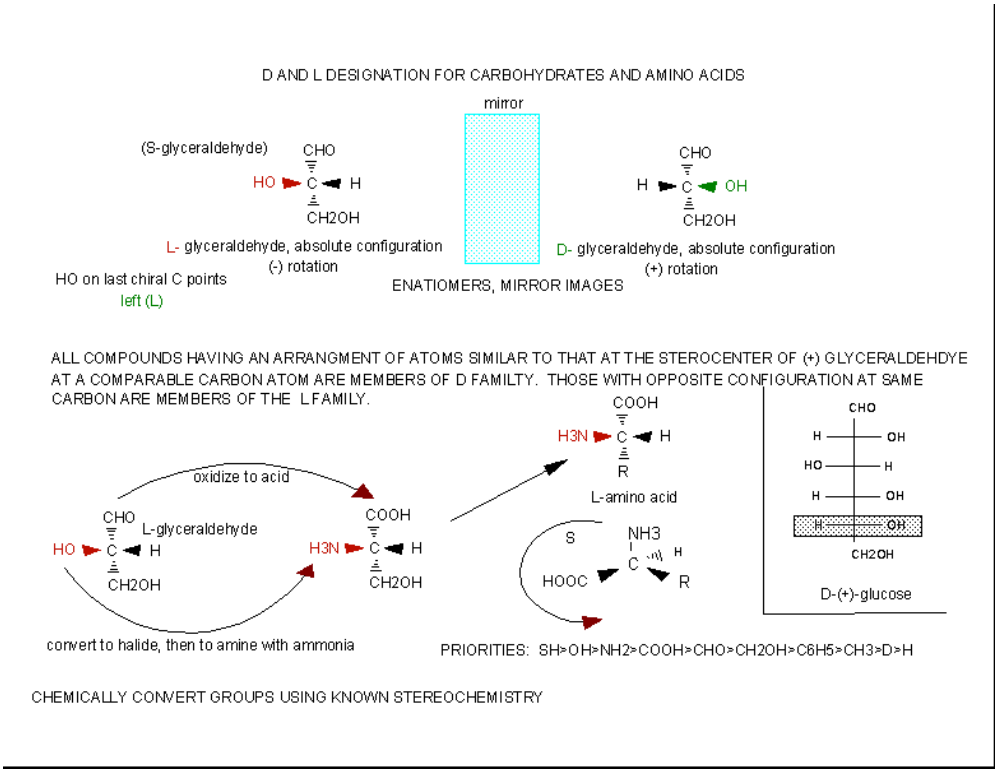


Figure 1: Stereochemistry of Amino Acids.

Why do biochemists still use D and L for sugars and amino acids? This explanation seems reasonable.

"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied to biochemical molecules. For example, as we have seen, all of the common amino acids are L, because they all have exactly the same structure, including the position of the R group if we just write the R group as R. However, they do not all have the same configuration in the (R,S) system: L-cysteine is also (R)-cysteine, but all the other L-amino acids are (S), which just reflects the human decision to give a sulfur atom higher priority than a carbon atom, and does not reflect a real difference in configuration. Worse problems can sometimes arise in substitution reactions: sometimes inversion of configuration can result in no change in the (R) or (S) prefix; and sometimes retention of configuration can result in a change of prefix.

It follows that it is not just conservatism or failure to understand the (R,S) system that causes biochemists to continue with D- and L-: it is just that the DL system fulfils their needs much better. As mentioned, chemists also use D and L when they are appropriate to their needs. The explanation given above of why the (R,S) system is little used in biochemistry is thus almost the exact opposite of reality. This system is actually the only practical way of unambiguously representing the stereochemistry of complicated molecules with several asymmetric centres, but it is inconvenient with regular series of molecules like amino acids and simple sugars. "

Natural α-Amino Acids

Hydrolysis of proteins by boiling aqueous acid or base yields an assortment of small molecules identified as α-aminocarboxylic acids. More than twenty such components have been isolated, and the most common of these are listed in the following table.

- Structure and Property of the Naturally-Occurring Amino Acids (Too large to include in text: print separately)

The structures, abbreviations (both three- and one-letter), and pK_a values of the 20 amino acids commonly found in proteins are shown in Table **12.1.1**. All are α-amino acids, meaning that the amino group in each is a substituent on the α carbon—the one next to the carbonyl group. Nineteen of the twenty amino acids are primary amines, RNH_2, and differ only in the nature of their side chain—the substituent attached to the α carbon. Proline is a secondary amine whose nitrogen and α carbon atoms are part of a five-membered pyrrolidine ring.

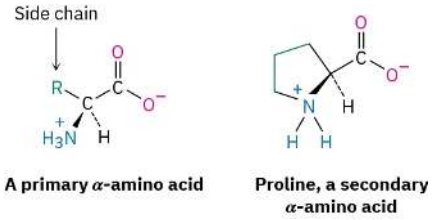
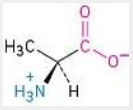
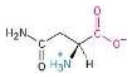
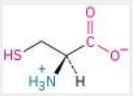
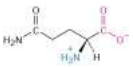
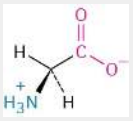
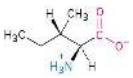
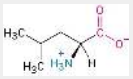
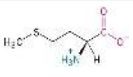
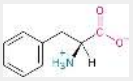
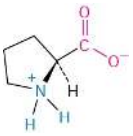
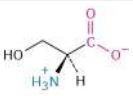
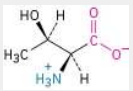
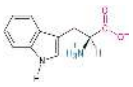
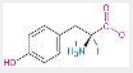
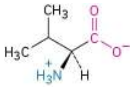
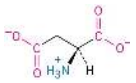
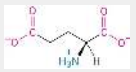
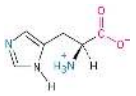
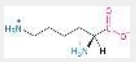
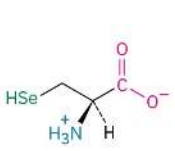


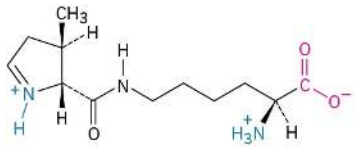
Table **12.1.1**: The 20 Common Amino Acids in Proteins

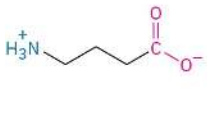
Name	Abbreviations		MW	Structure	pK_a α-CO_2H	pK_a α-NH_3^+	pK_a side chain	p*I*
Non-Polar Amino Acids								
Alanine	Ala	A	89		2.34	9.69	—	6.01
Asparagine	Asn	N	132		2.02	8.80	—	5.41
Cysteine	Cys	C	121		1.96	10.28	8.18	5.07
Glutamine	Gln	Q	146		2.17	9.13	—	5.65
Glycine	Gly	G	75		2.34	9.60	—	5.97
Isoleucine	Ile	I	131		2.36	9.60	—	6.02
Leucine	Leu	L	131		2.36	9.60	—	5.98
Methionine	Met	M	149		2.28	9.21	—	5.74
Phenylalanine	Phe	F	165		1.83	9.13	—	5.48
Proline	Pro	P	115		1.99	10.60	—	6.30
Polar-Neutral Amino Acids								
Serine	Ser	S	105		2.21	9.15	—	5.68
Threonine	Thr	T	119		2.09	9.10	—	5.60
Tryptophan	Trp	W	204		2.83	9.39	—	5.89
Tyrosine	Tyr	Y	181		2.20	9.11	10.07	5.66

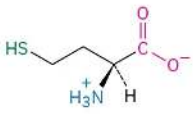
Name	Abbreviations		MW	Structure	pK_a α-CO_2H	pK_a α-NH_3^+	pK_a side chain	pI
Valine	Val	V	117		2.32	9.62	—	5.96
Polar Acidic Amino Acids								
Aspartic acid	Asp	D	133		1.88	9.60	3.65	2.77
Glutamic acid	Glu	E	147		2.19	9.67	4.25	3.22
Polar Basic Amino Acids								
Arginine	Arg	R	174		2.17	9.04	12.48	10.76
Histidine	His	H	155		1.82	9.17	6.00	7.59
Lysine	Lys	K	146		2.18	8.95	10.53	9.74

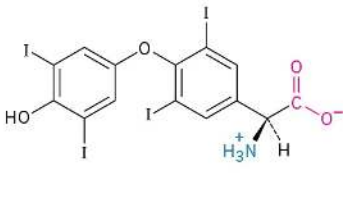
In addition to the 20 amino acids commonly found in proteins, 2 others—selenocysteine and pyrrolysine—are found in some organisms, and more than 700 nonprotein amino acids are also found in nature. γ-Aminobutyric acid (GABA), for instance, is found in the brain and acts as a neurotransmitter; homocysteine is found in blood and is linked to coronary heart disease; and thyroxine is found in the thyroid gland, where it acts as a hormone.



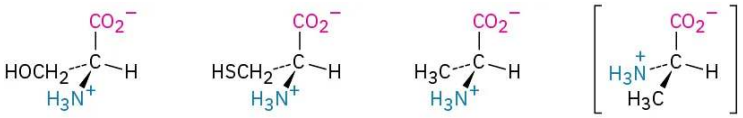








Except for glycine, $H_2NCH_2CO_2H$, the α carbons of amino acids are chiral centers. Two enantiomers of each are therefore possible, but nature uses only one to build proteins. In Fischer projections, naturally occurring amino acids are represented by placing the $-CO_2^-$ group at the top and pointing the side chain downwards, as if drawing a carbohydrate (Section 11.3) and then placing the $-NH_3^+$ group on the left. Because of their stereochemical similarity to L sugars (Section 11.4), the naturally occurring α-amino acids are often referred to as L amino acids. The non-naturally occurring enantiomers are called D amino acids.



L-Serine
(*S*)-Serine

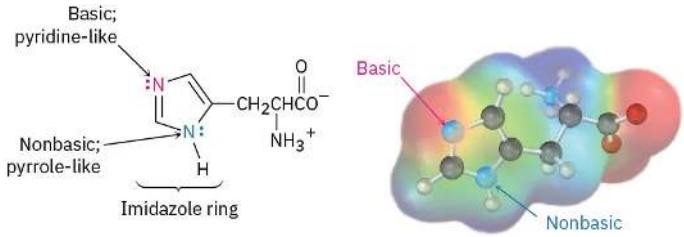
L-Cysteine
(*R*)-Cysteine

L-Alanine
(*S*)-Alanine

D-Alanine
(*R*)-Alanine

The 20 common amino acids can be further classified as neutral, acidic, or basic, depending on the structure of their side chains. Fifteen of the twenty have neutral side chains, two (aspartic acid and glutamic acid) have an extra carboxylic acid function in their side chains, and three (lysine, arginine, and histidine) have basic amino groups in their side chains. Note that both cysteine (a thiol) and tyrosine (a phenol), although usually classified as neutral amino acids, nevertheless have weakly acidic side chains that can be deprotonated in a sufficiently basic solution.

At the physiological pH of 7.3, the side-chain carboxyl groups of aspartic acid and glutamic acid are deprotonated, and the basic side-chain nitrogens of lysine and arginine are protonated. Histidine, however, which contains a heterocyclic imidazole ring in its side chain, is not quite basic enough to be protonated at pH 7.3. Note that only the pyridine-like, doubly bonded nitrogen in histidine is basic. The pyrrole-like singly bonded nitrogen is nonbasic because its lone pair of electrons is part of the six-π-electron aromatic imidazole ring (Section 10.10).



Histidine

Humans are able to biosynthesize only 11 of the 20 protein amino acids, called nonessential amino acids. The other 9, called essential amino acids, are biosynthesized only in plants and microorganisms and must be obtained in our diet. The division between essential and nonessential amino acids is not clear-cut, however. Tyrosine, for instance, is sometimes considered nonessential because humans can produce it from phenylalanine, but phenylalanine itself is essential and must be obtained in the diet. Arginine can be synthesized by humans, but much of the arginine we need also comes from our diet.

? Exercise 12.1.1

How many of the α-amino acids shown in Table 12.1 contain aromatic rings? How many contain sulfur? How many contain alcohol groups? How many contain hydrocarbon side chains?

Answer

Aromatic: Phe, Tyr, Trp, His; sulfur-containing: Cys, Met; alcohols: Ser, Thr; hydrocarbon side chains: Ala, Ile, Leu, Val, Phe

? Exercise 12.1.2

Of the 19 L amino acids, 18 have the *S* configuration at the α carbon. Cysteine is the only L amino acid that has an *R* configuration. Explain.

Answer

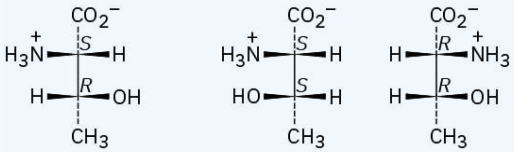
The sulfur atom in the $-CH_2SH$ group of cysteine makes the side chain higher in ranking than the $-CO_2H$ group.

Exercise 12.1.3

The amino acid threonine, (2*S*,3*R*)-2-amino-3-hydroxybutanoic acid, has two chirality centers.

a. Draw threonine, using normal, wedged, and dashed lines to show dimensionality.
b. Draw a diastereomer of threonine, and label its chiral centers as *R* or *S*.

Answer



L-Threonine Diastereomers of L-threonine

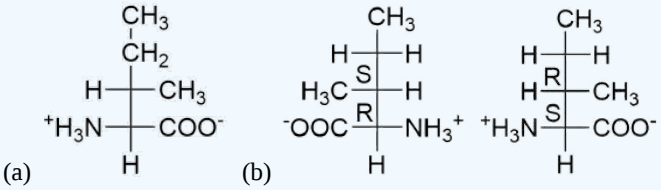
Exercise 12.1.4

Isoleucine has two stereogenic centers.

(a) Draw a Fischer projection of isoleucine.

(b) Draw a Fischer projection of an isoleucine diastereomer, and label each stereocenter as R or S.

Answer



(a) (b)

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12.2: Amino Acids and Isoelectric Points

Objectives

After completing this section, you should be able to

1. draw the predominant form of a given amino acid in a solution of known pH, given the isoelectric point of the amino acid.
2. describe, briefly, how a mixture of amino acids may be separated by paper electrophoresis.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- electrophoresis
- isoelectric point

Since amino acids, as well as peptides and proteins, incorporate both acidic and basic functional groups, the predominant molecular species present in an aqueous solution will depend on the pH of the solution. In order to determine the nature of the molecular and ionic species that are present in aqueous solutions at different pH's, we make use of the **Henderson-Hasselbalch Equation**, written below.

Definition: Henderson–Hasselbalch equation

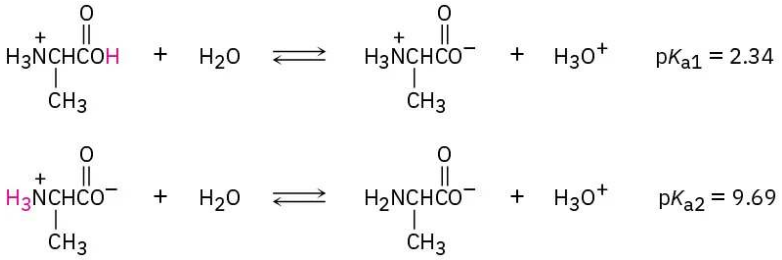
According to the Henderson–Hasselbalch equation, if we know both the pH of a solution and the pK_a of an acid HA, we can calculate the ratio of $[A^-]$ to [HA] in the solution. Furthermore, when pH = pK_a, the two forms A^- and HA are present in equal amounts because log 1 = 0.

$$\mathrm{pH} = \mathrm{p}K_a + \log \frac{[\mathrm{A}^-]}{[\mathrm{HA}]} \tag{12.2.1}$$

or

$$\log \frac{[\mathrm{A}^-]}{[\mathrm{HA}]} = \mathrm{pH} - \mathrm{p}K_a$$

To apply the Henderson–Hasselbalch equation to an amino acid, let's find out what species are present in a 1.00 M solution of alanine at pH = 9.00. According to Table 26.1, protonated alanine [$^+H_3NCH(CH_3)CO_2H$] has pK_{a1} = 2.34 and neutral zwitterionic alanine [$^+H_3NCH(CH_3)CO_2^-$] has pK_{a2} = 9.69:



Because the pH of the solution is much closer to pK_{a2} than to pK_{a1}, we need to use pK_{a2} for the calculation. From the Henderson–Hasselbalch expression (Equation 12.2.1), we have:

$$\log \frac{[\mathrm{A}^-]}{[\mathrm{HA}]} = \mathrm{pH} - \mathrm{p}K_a = 9.00 - 9.69 = -0.69$$

So

$$\frac{[\mathrm{A}^-]}{[\mathrm{HA}]} = \text{antilog}(-0.69) = 0.20$$

and

$$[A^-] = 0.20[HA]$$

In addition, we know that the solution is a 1.00 M alanine

$$[A^-] + [HA] = 1.00M$$

Solving the two simultaneous equations gives [HA] = 0.83 and [A^-] = 0.17. In other words, at pH = 9.00, 83% of alanine molecules in a 1.00 M solution are neutral (zwitterionic) and 17% are deprotonated. Similar calculations can be done at other pH values and the results plotted to give the titration curve shown in Figure **12.2.1**.

Titration curves

The titration curve for alanine, shown in Figure **12.2.2**, demonstrates this relationship. At a pH lower than 2, both the carboxylate and amine functions are protonated, so the alanine molecule has a net positive charge. At a pH greater than 10, the amine exists as a neutral base and the carboxyl as its conjugate base, so the alanine molecule has a net negative charge. At intermediate pH's the zwitterion concentration increases, and at a characteristic pH, called the **isoelectric point** (**pI**), the negatively and positively charged molecular species are present in equal concentrations. This behavior is general for simple (difunctional) amino acids. Starting from a fully protonated state, the pK_a's of the acidic functions range from 1.8 to 2.4 for -CO_2H, and 8.8 to 9.7 for -$NH_3^{(+)}$. The isoelectric points range from 5.5 to 6.2. Titration curves show the neutralization of these acids by added base, and the change in pH during the titration.

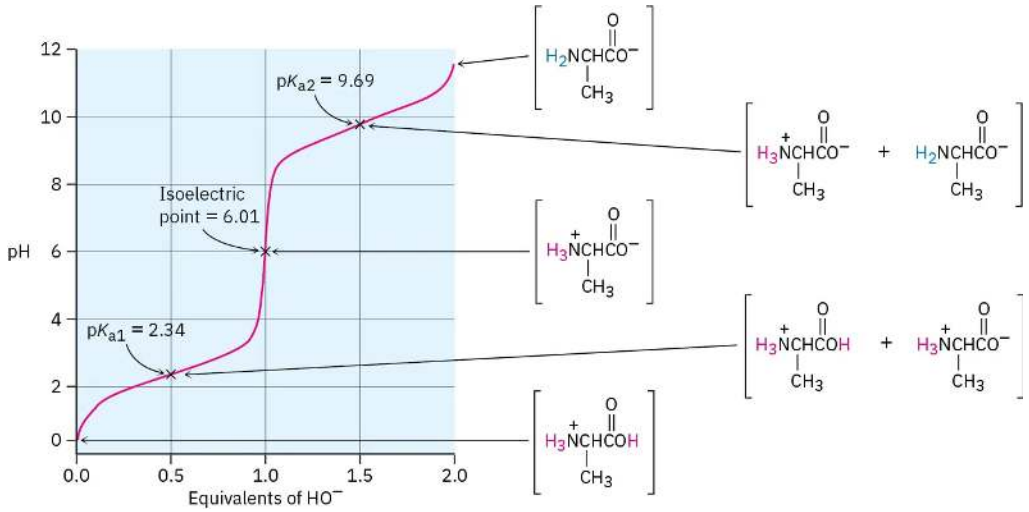


Figure **12.2.1**: A titration curve for alanine, plotted using the Henderson–Hasselbalch equation. Each of the two legs is plotted separately. At pH < 1, alanine is entirely protonated; at pH = 2.34, alanine is a 50 : 50 mix of protonated and neutral forms; at pH = 6.01, alanine is entirely neutral; at pH = 9.69, alanine is a 50 : 50 mix of neutral and deprotonated forms; at pH > 11.5, alanine is entirely deprotonated.

Some amino acids have additional acidic or basic functions in their side chains. These compounds are listed in Table **12.2.1**. A third pK_a, representing the acidity or basicity of the extra function, is listed in the fourth column of the table. The pI's of these amino acids (last column) are often very different from those noted above for the simpler members.

Table **12.2.1**: pKa Values of Polyfunctional Amino Acids

Amino Acid	α-CO_2H pK_a^1	α-NH_3 pK_a^2	Side Chain pK_a^3	pI
Arginine	2.1	9.0	12.5	10.8
Aspartic Acid	2.1	9.8	3.9	3.0
Cysteine	1.7	10.4	8.3	5.0
Glutamic Acid	2.2	9.7	4.3	3.2
Histidine	1.8	9.2	6.0	7.6
Lysine	2.2	9.0	10.5	9.8
Tyrosine	2.2	9.1	10.1	5.7

As expected, such compounds display three inflection points in their titration curves, illustrated by the titrations of aspartic acid (Figure\ (\PageIndex{2}\)) and arginine (Figure\ (\PageIndex{3}\)). For each of these compounds four possible charged species are possible, one of which has no overall charge. Formulas for these species are written to the right of the titration curves, together with the pH at which each is expected to predominate. The very high pH required to remove the last acidic proton from arginine reflects the exceptionally high basicity of the guanidine moiety at the end of the side chain.

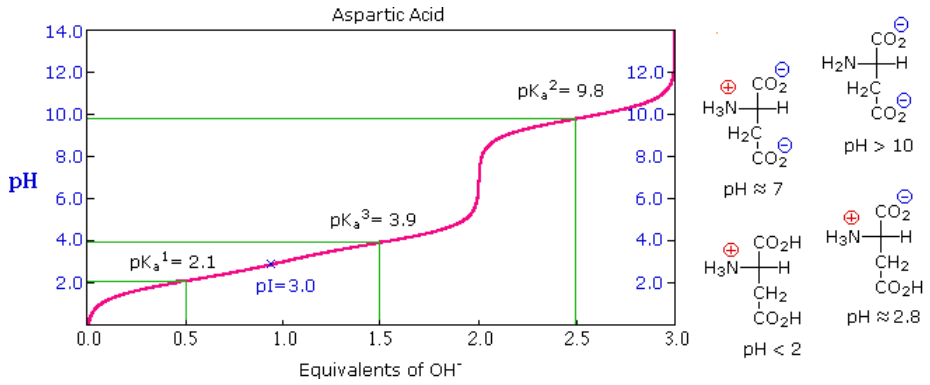


Figure **12.2.2**: A titration curve for Aspartic Acid, plotted using the Henderson–Hasselbalch equation. At pH < 1, Aspartic Acid is entirely protonated; at pH = 2.1, Aspartic Acid is a 50 : 50 mix of entirely protonated and neutral forms; at pH = 3.00, Aspartic Acid is entirely neutral; at pH = 3.9, Aspartic Acid is a 50 : 50 mix of neutral and single negative charged forms; at pH = 6.85, Aspartic Acid is entirely single negative charged; at pH = 9.8, Aspartic Acid is a 50 : 50 mix of single negative charged and double negative charged forms; at pH > 11.8, Aspartic Acid is entirely deprotonated.

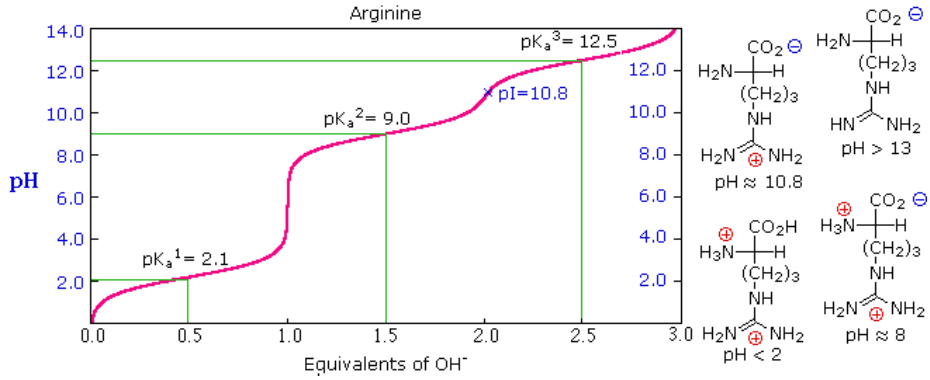
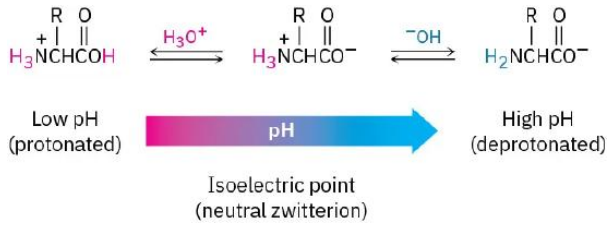


Figure **12.2.3**: A titration curve for Arginine, plotted using the Henderson–Hasselbalch equation. At pH < 1, Arginine is entirely protonated; at pH = 2.1, Arginine is a 50 : 50 mix of entirely protonated and single positive charged forms; at pH = 6.05, Arginine is entirely single positive charged; at pH = 9.0, Arginine is a 50 : 50 mix of single positive charged and neutral forms; at pH = 10.75, Arginine is entirely neutral; at pH = 12.5, Arginine is a 50 : 50 mix of neutral and deprotonated forms; at pH > 13.8, Arginine is entirely deprotonated.

The Isoelectric Point

Look carefully at the titration curve in Figure **12.2.1**. In an acid solution, the amino acid is protonated and exists primarily as a cation. In a basic solution, the amino acid is deprotonated and exists primarily as an anion. In between the two is an intermediate pH at which the amino acid is exactly balanced between anionic and cationic forms, existing primarily as the neutral, dipolar zwitterion. This pH is called the amino acid's **isoelectric point** (p*I*) and has a value of 6.01 for alanine.



The isoelectric point of an amino acid depends on its structure, with values for the 20 common amino acids given previously in Table 12.1.1. The 13 neutral amino acids have isoelectric points near neutrality, in the pH range 5.0 to 6.5. The isoelectric point, **pI**, is the pH of an aqueous solution of an amino acid (or peptide) at which the molecules on average have no net charge. In other words, the positively charged groups are exactly balanced by the negatively charged groups. For simple amino acids such as alanine, the pI is an average of the pK_a's of the carboxyl (2.34) and ammonium (9.69) groups. Thus, the pI for alanine is calculated to be: (2.34 + 9.69)/2 = 6.02, the experimentally determined value.

More specifically, the p*I* of any neutral amino acid is the average of the two acid-dissociation constants that involve the neutral zwitterion. For the 13 amino acids with a neutral side chain, p*I* is the average of pK_{a1} and pK_{a2}. For the 7 amino acids with either a strongly or weakly acidic side chain, p*I* is the average of the two lowest pK_a values. For the three amino acids with a basic side chain, p*I* is the average of the two highest pK_a values.

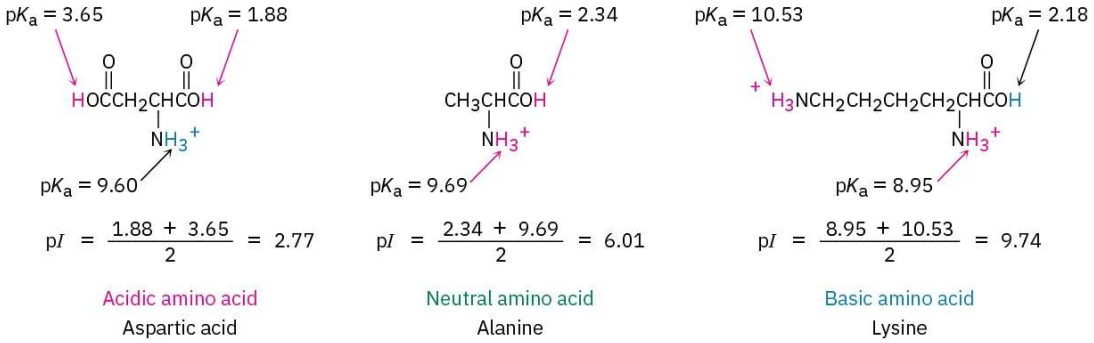


Figure \(\PageIndex{3}\): The representation of Aspartic acid, alanine and Lysine, are not at the pI point

If additional acidic or basic groups are present as side-chain functions, the pI is the average of the pK_a's of the two most similar acids. To assist in determining similarity we define two classes of acids. The first consists of acids that are neutral in their protonated form (e.g. CO_2H & SH). The second includes acids that are positively charged in their protonated state (e.g. $-NH_3^+$). In the case of aspartic acid, observe the titration curve in Figure **12.2.2**, the similar acids are the alpha-carboxyl function (pK_a = 2.1) and the side-chain carboxyl function (pK_a = 3.9), so pI = (2.1 + 3.9)/2 = 3.0. For arginine, observe the titration curve in Figure **12.2.3**, the similar acids are the guanidinium species on the side-chain (pK_a = 12.5) and the alpha-ammonium function (pK_a = 9.0), so the calculated pI = (12.5 + 9.0)/2 = 10.75

The acidic amino acids have isoelectric points at lower pH so that deprotonation of the side-chain $-CO_2H$ does not occur at their p*I*, and the three basic amino acids have isoelectric points at higher pH so that protonation of the side-chain amino group does not occur at their p*I*. As noted earlier, the titration curves of simple amino acids display two inflection points, one due to the strongly acidic carboxyl group (pK_a^1 = 1.8 to 2.4), and the other for the less acidic ammonium function (pK_a^2 = 8.8 to 9.7). For the 2°-amino acid proline, pK_a^2 is 10.6, reflecting the greater basicity of 2°-amines.

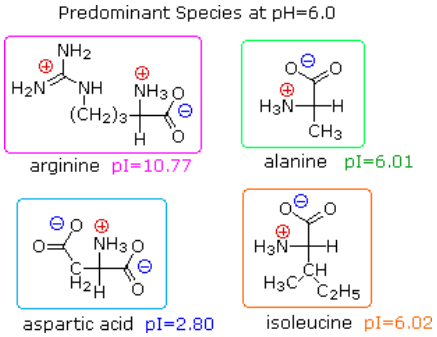
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Isoelectronic Point in Proteins

Just as individual amino acids have isoelectric points, proteins have an overall p*I* due to the cumulative effect of all the acidic or basic amino acids they may contain. The enzyme lysozyme, for instance, has a preponderance of basic amino acids and thus has a high isoelectric point (p*I* = 11.0). Pepsin, however, has a preponderance of acidic amino acids and a low isoelectric point (p*I* ~ 1.0). Not surprisingly, the solubilities and properties of proteins with different p*I*'s are strongly affected by the pH of the medium. Solubility in water is usually lowest at the isoelectric point, where the protein has no net charge, and is higher both above and below the p*I*, where the protein is charged.

Electrophoresis

At pH 6.00 alanine and isoleucine exist on average as neutral zwitterionic molecules, and are not influenced by the electric field. Arginine is a basic amino acid. Both base functions exist as "onium" conjugate acids in the pH 6.00 matrix. The solute molecules of arginine therefore carry an excess positive charge, and they move toward the cathode. The two carboxyl functions in aspartic acid are both ionized at pH 6.00, and the negatively charged solute molecules move toward the anode in the electric field. Structures for all these species are shown to the right of the display.



The distribution of charged species in a sample can be shown experimentally by observing the movement of solute molecules in an electric field, using the technique of **electrophoresis** (Figure **12.2.4**). For such experiments an ionic buffer solution is incorporated in a solid matrix layer, composed of paper or a crosslinked gelatin-like substance. A small amount of the amino acid, peptide or protein sample is placed near the center of the matrix strip and an electric potential is applied at the ends of the strip, as shown in the following diagram. The solid structure of the matrix retards the diffusion of the solute molecules, which will remain where they are inserted, unless acted upon by the electrostatic potential.

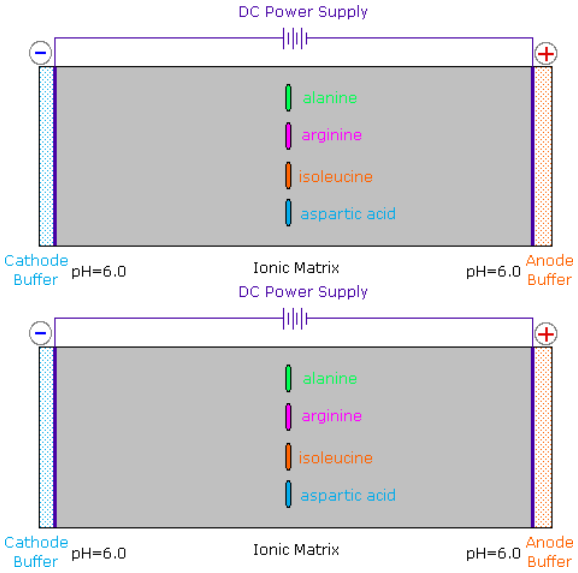


Figure **12.2.4**: In the example shown here, four different amino acids are examined simultaneously in a pH 6.00 buffered medium. To see the result of this experiment, click on the illustration. Note that the colors in the display are only a convenient reference, since these amino acids are colorless.

It should be clear that the result of this experiment is critically dependent on the pH of the matrix buffer. If we were to repeat the electrophoresis of these compounds at a pH of 3.80, the aspartic acid would remain at its point of origin, and the other amino acids would move toward the cathode. Ignoring differences in molecular size and shape, the arginine would move twice as fast as the alanine and isoleucine because its solute molecules, on average, would carry a double positive charge.

Different proteins migrate at different rates, depending on their isoelectric points and on the pH of the aqueous buffer, thereby effecting a separation of the mixture into its components. Figure **12.2.5** illustrates this process for a mixture containing basic, neutral, and acidic components.

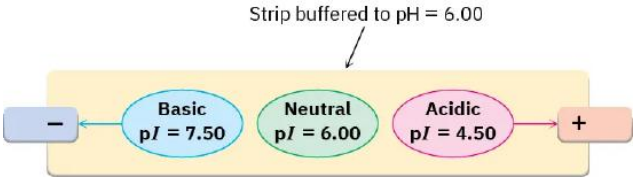


Figure **12.2.5**: Separation of a protein mixture by electrophoresis. At pH = 6.00, a neutral protein does not migrate, a basic protein is protonated and migrates toward the negative electrode, and an acidic protein is deprotonated and migrates toward the positive electrode.

? Exercise 12.2.1

Hemoglobin has p*I* = 6.8. Does hemoglobin have a net negative charge or a net positive charge at pH = 5.3? At pH = 7.3?

Answer

Net positive at pH = 5.3; net negative at pH = 7.3

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12.3: Synthesis of Amino Acids

Objectives

After completing this section, you should be able to

1. outline, by means of equations, how a racemic mixture of given amino acid can be prepared from a carboxylic acid using reactions you studied earlier in the course.
2. a. outline, by means of equations, the preparation of a given amino acid by the amidomalonate synthesis.
   b. identify the amino acid formed from using a given alkyl halide in an amidomalonate synthesis.
   c. identify the alkyl halide needed to produce a given amino acid by the amidomalonate synthesis.
3. describe, by means of equations, how an α-keto acid can be transformed to an amino acid by reductive amination.
4. a. describe a general method for resolving a racemic mixture of a given amino acid.
   b. provide a brief example of how a biological method may be employed to resolve a racemic mixture of a given amino acid.
   c. show the enantioselective preparation of an amino acid from the corresponding *Z* enamido acid.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

Bio-synthesis of α-Amino Acids

De novo synthesis of amino acids in human beings from intermediates of the citric acid cycle or glycolysis: ribose-5-phosphate, pyruvate, erythrose-4-phosphate, oxaloacetate, and α-ketoglutarate.

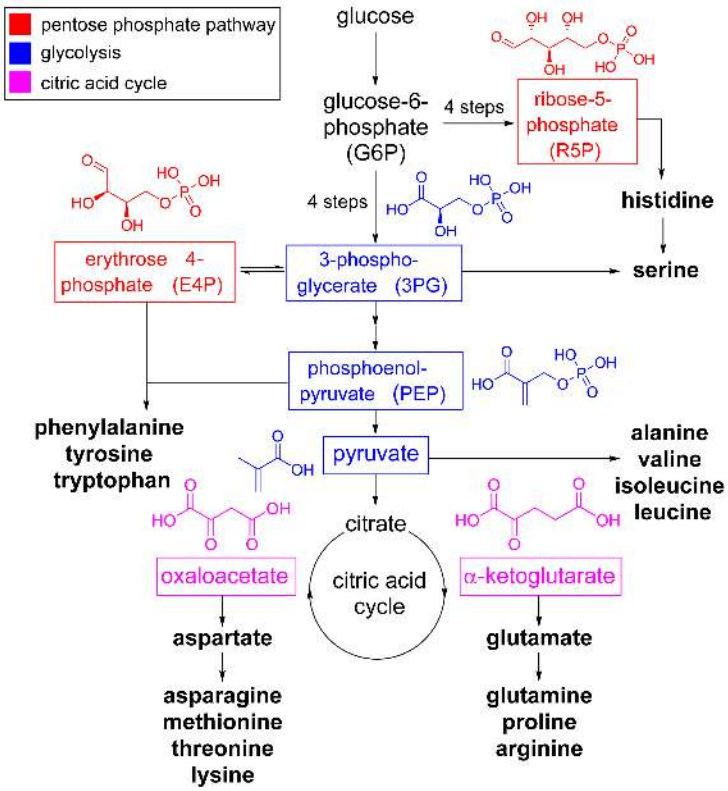


Figure 12.3.1: General Metabolism Diagram.

The nitrogen needed for amino acid biosynthesis ultimately comes from atmospheric nitrogen gas (N_2). However, the triple bond that holds a molecule of nitrogen gas together is very stable and resists alteration. Only certain microorganisms, including "nitrogen-fixing" bacteria and blue-green algae, have the capability to reduce atmospheric nitrogen. In an energy-consuming process, these organisms are able to convert N_2 into ammonium ions (NH_4^+).

In higher organisms, including human beings, NH_4^+ can be used by the enzyme glutamate dehydrogenase to synthesize the amino acid l-glutamate from α-ketoglutarate, a citric acid cycle intermediate. A second ammonium ion can then be incorporated by glutamine synthetase to form l-glutamine (Fig. 2). The amino groups ($-NH_2$) of the other amino acids are then derived from those of l-glutamate or l-glutamine by transamination, as in the synthesis of alanine from pyruvate. As is true for glutamate, glutamine, and alanine, the carbon-rich "backbones" of the other amino acids are also derived from intermediates of major metabolic pathways, such as the citric acid cycle, glycolysis, and the pentose phosphate pathway.

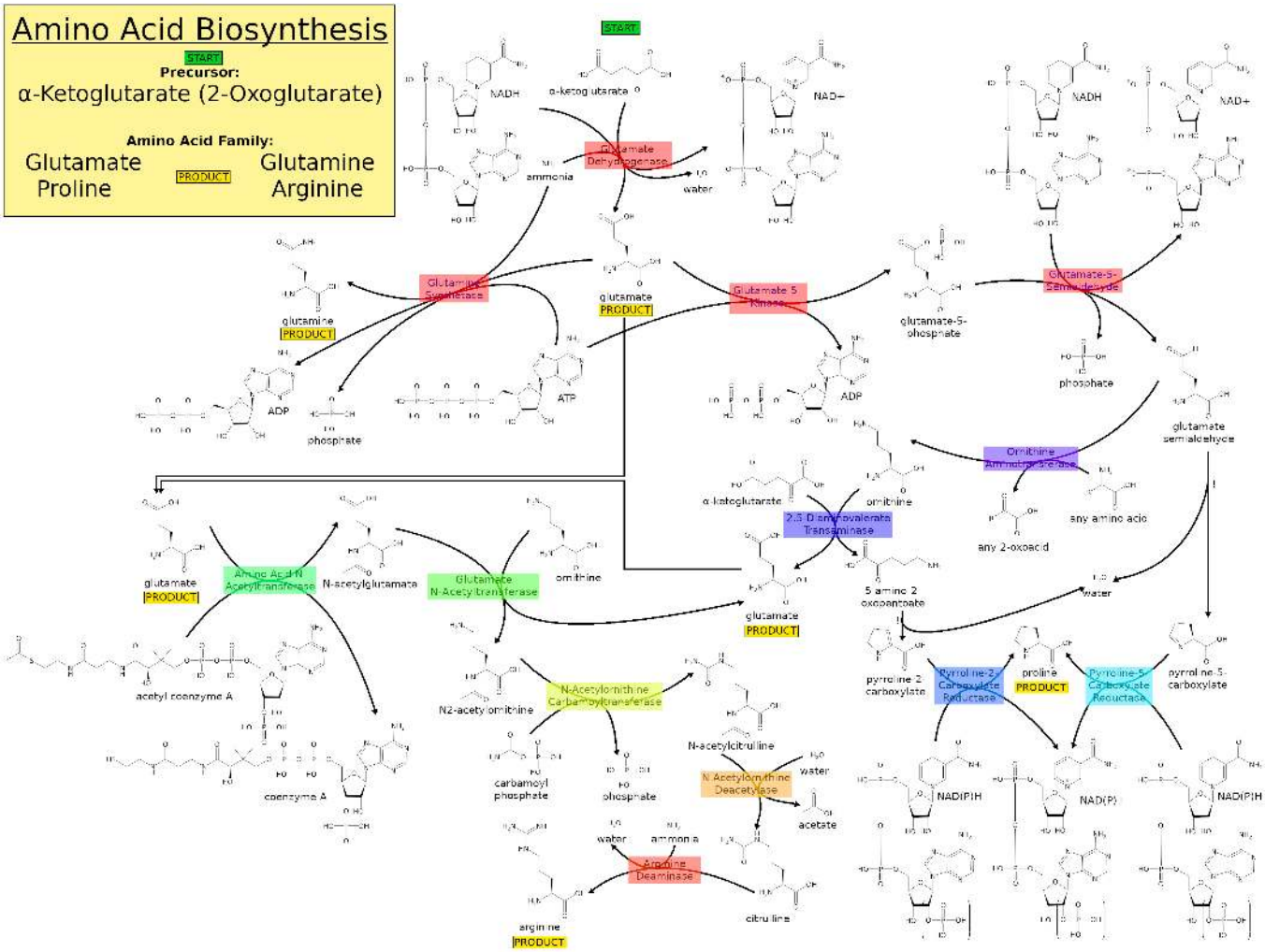


Figure **12.3.2**: *α*-ketoglutarate, a citric acid cycle intermediate, is the precursor for the synthesis of l-glutamate, l-glutamine, l-proline, and l-arginine.

The enzymatic reactions used by human beings to synthesize most of the nonessential amino acids are similar to those used by plants and microorganisms (Fig. 3). However, we use alternative pathways to produce cysteine, tyrosine, and arginine. We make these from other amino acids: cysteine from methionine, tyrosine from phenylalanine, and arginine from proline (via conversion of proline to ornithine). In lower organisms, histidine is synthesized from ribose 5-phosphate, a product of the pentose phosphate pathway. The extent and route of histidine biosynthesis in human beings are unclear.

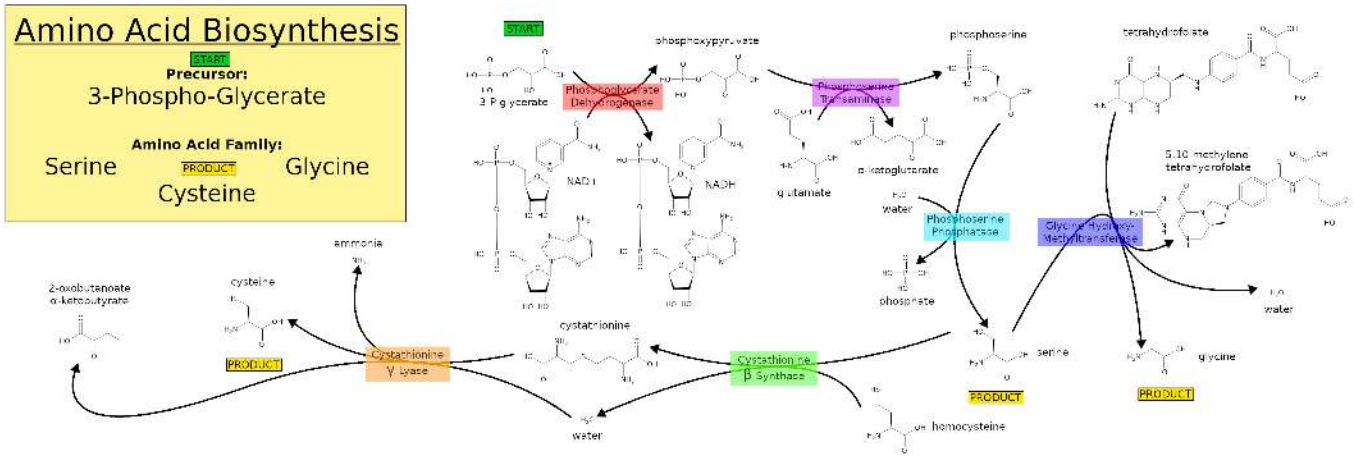


Figure **12.3.3**: 3-phospho-glycerate, is the precursor for the synthesis of l-serine, l-cysteine, and l-glycine.

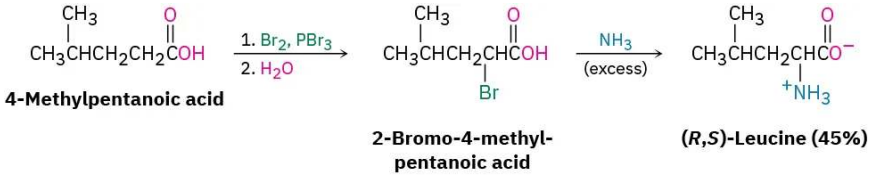
Phenylalanine, tyrosine, and tryptophan are produced from erythrose 4-phosphate and phosphoenolpyruvate,

Synthesis of α-Amino Acids

1-Amination of alpha-bromocarboxylic acids

Amination of alpha-bromocarboxylic acids, illustrated by the following equation, provides a straightforward method for preparing alpha-aminocarboxylic acids.

The bromoacid is conveniently prepared from carboxylic acids by treatment with Br_2 and PBr_3 (the Hell–Volhard–Zelinskii reaction; Section 22.4). The S_N2 substitution of the α-bromo acid with ammonia then yields an α-amino acid. Although this direct approach gave mediocre results when used to prepare simple amines from alkyl halides, it is more effective for making amino acids, thanks to the reduced nucleophilicity of the nitrogen atom in the product.



? Exercise 12.3.1

Show how you could prepare the following α-amino acids from the appropriate carboxylic acids:

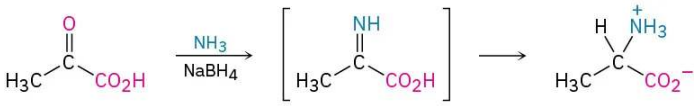
a. Phenylalanine
b. Valine

Answer

a. Start with 3-phenylpropanoic acid: 1. Br_2, PBr_3; 2. NH_3
b. Start with 3-methylbutanoic acid: 1. Br_2, PBr_3; 2. NH_3

2-Reductive Amination of α-Keto Acids

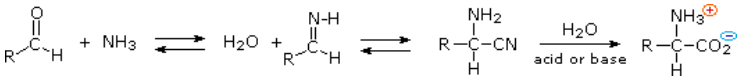
Yet another method for the synthesis of α-amino acids is by reductive amination of an α-keto acid with ammonia and a reducing agent. Alanine, for instance, is prepared by treatment of pyruvic acid with ammonia in the presence of $NaBH_4$. As described in Section 10.6, the reaction proceeds through formation of an intermediate imine which is then reduced.



Pyruvic acid **Imine intermediate** **(*R*,*S*)-Alanine**

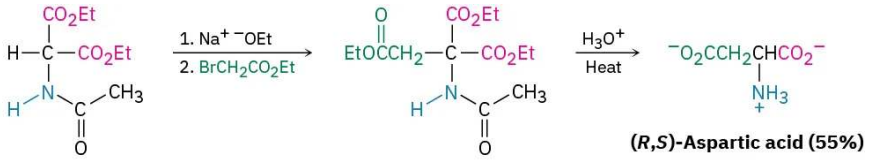
3-Strecker synthesis

An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this way can then be hydrolyzed to an amino acid by either acid- or base-catalysis.



4-The Amidomalonate Synthesis

A more general method for the preparation of α-amino acids is the amidomalonate synthesis, a straightforward extension of the malonic ester synthesis (Section 8.7). The reaction begins with the conversion of diethyl acetamidomalonate into an enolate ion by treatment with base, followed by S_N2 alkylation with a primary alkyl halide. Hydrolysis of both the amide protecting group and the esters occurs when the alkylated product is warmed with aqueous acid, and decarboxylation then takes place to yield an α-amino acid. For example, aspartic acid can be prepared from ethyl bromoacetate, $BrCH_2CO_2Et$:



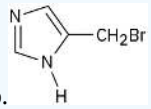
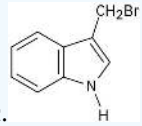
Diethyl acetamidomalonate **(*R*,*S*)-Aspartic acid (55%)**

? Exercise 12.3.2

What alkyl halides would you use to prepare the following *α*-amino acids by the amidomalonate method?

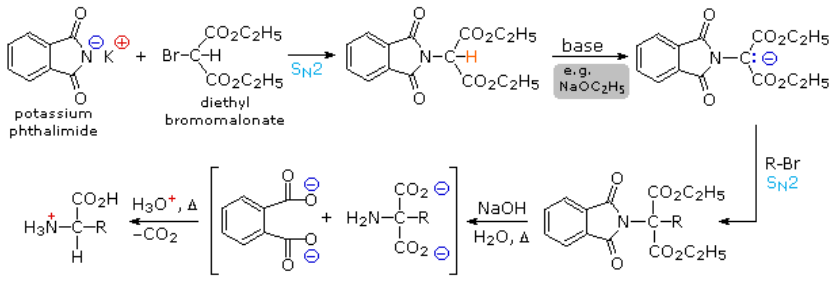
a. Leucine
b. Histidine
c. Tryptophan
d. Methionine

Answer

a. $(CH_3)_2CHCH_2Br$ b.  c.  d. $CH_3SCH_2CH_2Br$

5-Gabriel Synthesis

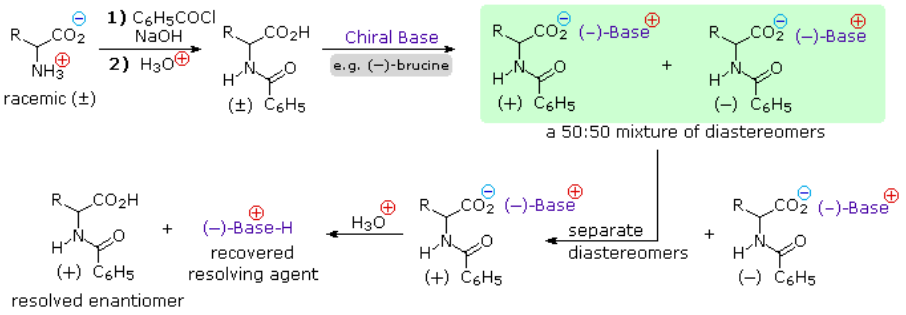
By modifying the nitrogen as a phthalimide salt, the propensity of amines to undergo multiple substitutions is removed, and a single clean substitution reaction of 1º- and many 2º-alkylhalides takes place. This procedure, known as the Gabriel synthesis, can be used to advantage in aminating bromomalonic esters, as shown in the upper equation of the following scheme. Since the phthalimide substituted malonic ester has an acidic hydrogen (colored orange), activated by the two ester groups, this intermediate may be converted to an ambident anion and alkylated. Finally, base catalyzed hydrolysis of the phthalimide moiety and the esters, followed by acidification and thermal decarboxylation, produces an amino acid and phthalic acid (not shown).



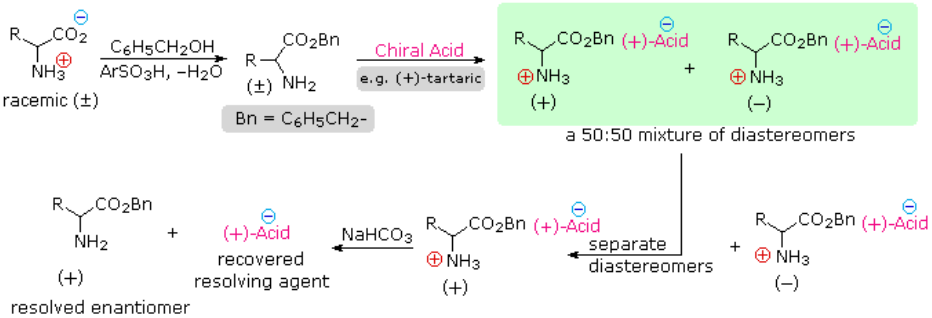
Resolution of Racemic Mixtures

The five synthetic procedures described above, as well as many others that can be conceived, yield racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation with a pure chiral acid or base. This is illustrated for a generic amino acid in the following diagram. Be careful to distinguish charge symbols, shown in colored circles, from optical rotation signs, shown in parenthesis.

In the initial display, the carboxylic acid function contributes to the formation of diastereomeric salts. The racemic amino acid is first converted to a benzamide derivative to remove the basic character of the amino group. Next, an ammonium salt is formed by combining the carboxylic acid with an optically pure amine, such as brucine (a relative of strychnine). The structure of this amine is not shown, because it is not a critical factor in the logical progression of steps. Since the amino acid moiety is racemic and the base is a single enantiomer (levorotatory in this example), an equimolar mixture of diastereomeric salts is formed (drawn in the green shaded box). Diastereomers may be separated by crystallization, chromatography or other physical manipulation, and in this way one of the isomers may be isolated for further treatment, in this illustration it is the (+):(-) diastereomer. Finally the salt is broken by acid treatment, giving the resolved (+)-amino acid derivative together with the recovered resolving agent (the optically active amine). Of course, the same procedure could be used to obtain the (-)-enantiomer of the amino acid.



Since amino acids are amphoteric, resolution could also be achieved by using the basic character of the amine function. For this approach we would need an enantiomerically pure chiral acid such as tartaric acid to use as the resolving agent. This alternative resolution strategy will be illustrated. Note that the carboxylic acid function is first esterified, so that it will not compete with the resolving acid.

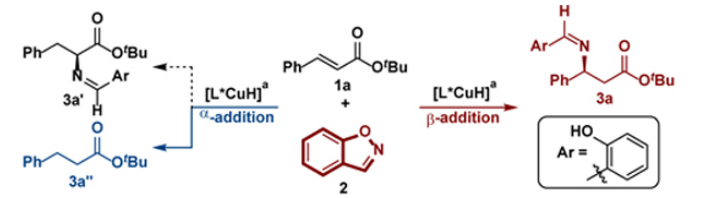


Resolution of amino acid derivatives may also be achieved by enzymatic discrimination in the hydrolysis of amides. For example, an aminoacylase enzyme from pig kidneys cleaves an amide derivative of a natural L-amino acid much faster than it does the D-enantiomer. If the racemic mixture of amides shown in the green shaded box above is treated with this enzyme, the L-enantiomer

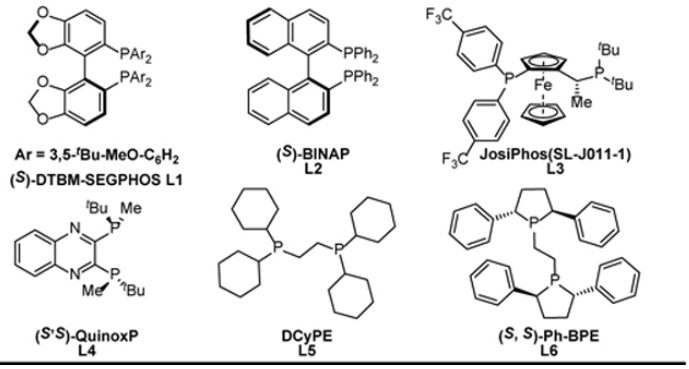
(whatever its rotation) will be rapidly converted to its free zwitterionic form, whereas the D-enantiomer will remain largely unchanged. Here, the diastereomeric species are transition states rather than isolable intermediates. This separation of enantiomers, based on very different rates of reaction, is called **kinetic resolution**.

Enantioselective Synthesis

To date, all the synthetic routes to α-amino acids we have discussed yield racemic mixtures. Once produced, one could resolve the mixture to obtain pure **L** or **D** enantiomers. However, enantioselective synthetic methods to produce pure compounds are being developed in the presence of an appropriate chiral ligands. For instance, several catalysts are now available for reduction of C=C to expose enantiopure beta amino acids.



Entry	Ligand	3a (%)	3a' (%)	3a'' (%)	β-addition/α-addition	er (3a)
1	L1	4	0	92	1 : 23	-
2	L2	0	0	99	0	-
3	L3	21	0	80	1 : 4	>99:1
4	L4	37	0	63	1 : 2	3:97
5	L5	70	0	23	3 : 1	-
6	L6	87	0	13	7 : 1	>99:1
7[b]	L6	87	0	13	7 : 1	>99:1
8[c]	L6	85	0	15	6 : 1	>99:1



Source:
https://pmc.ncbi.nlm.nih.gov/articles/PMC8038868/

A good example is the industrial synthesis of L-DOPA, a drug used in the treatment of Parkinson's disease. W.S. Knowles shared the 2001 Nobel Price with R. Noyori and K.B. Sharpless for their contributions in the area of asymmetric catalytic reductions**.** Knowles developed several chiral phosphine–metal catalysts for asymmetric reductions. The rhodium(I) catalyst shown, which is complexed by large organic ligands, facilitates the production of almost pure L-DOPA.

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12.4: Peptides and Proteins

Objectives

After completing this section, you should be able to

1. a. show, by means of a diagram, how two different amino acid residues can be combined to give two different dipeptides.
   b. draw the structure of a relatively simple peptide, given its full or abbreviated name and the structures of the appropriate amino acids.
   c. draw, or name, the six possible isomeric tripeptides that can be formed by combining three different amino acid residues (amino acid units) of given structure.
2. account for the fact that there is restricted rotation about the C(O)-N bonds in peptides.
3. illustrate the formation of a disulfide linkage between two cysteine residues, and show how such bonds can link together two separate peptide chains or can provide a bridge between two cysteine residues present in a single peptide molecule.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- C-terminal amino acid
- N-terminal amino acid
- peptides
- residues

The general term peptide refers to an amino acid chain of unspecified length. However, chains of approximately 50 amino acids or more are typically referred to as proteins or polypeptides. In its physiologically active form, a protein may be composed of one or more polypeptide chains. A chain consisting of only two amino acid units is called a dipeptide; a chain consisting of three is a tripeptide. By convention, pept ide and protein structures are depicted with the amino acid whose amino group is free (the N-terminal end) on the left and the amino acid with a free carboxyl group (the C-terminal end) to the right

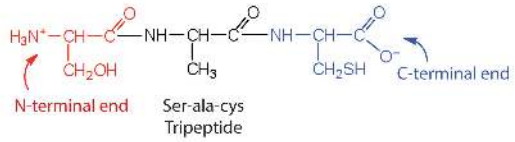


Figure 1: Structure of a tripeptide formed with serine, alanine, and cysteine.

Exercise 12.4.1

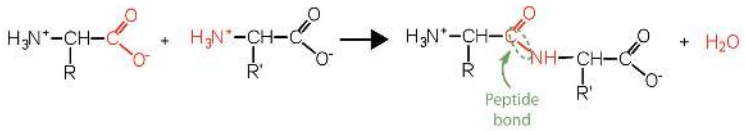
Identify the C- and N-terminal amino acids for the peptide lys-val-phe-gly-arg-cys.

Solution

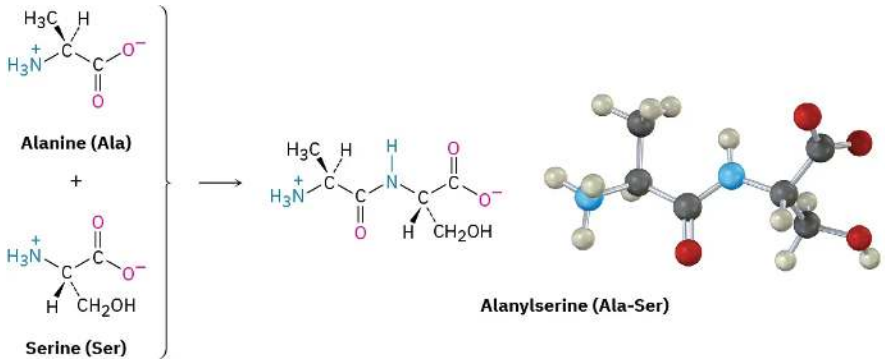
C-terminal amino acid: cysteine (cys or C); N-terminal amino acid: lysine (lys or K)

Peptide Bond Formation or Amide Synthesis

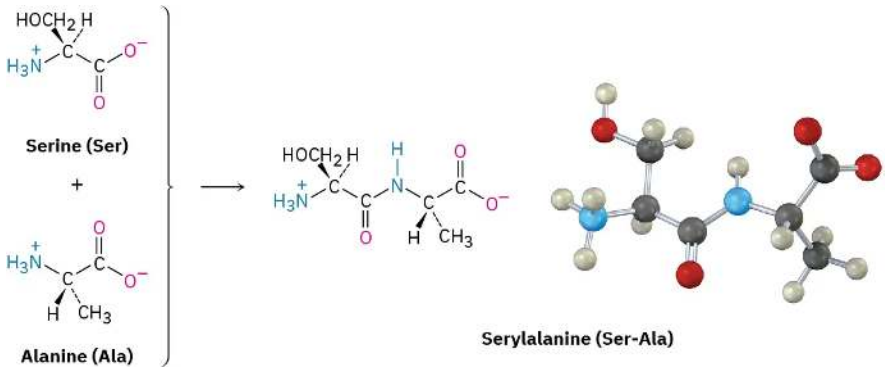
The formation of peptides is nothing more than the application of the **amide synthesis reaction**. By convention, the amide bond in the peptides should be made in the order that the amino acids are written. The amine end (N terminal) of an amino acid is always on the left, while the acid end (C terminal) is on the right.



For example, alanylserine is the dipeptide that results when an amide bond forms between the alanine carboxyl and the serine amino group.



Note that two dipeptides can result from reaction between alanine and serine, depending on which carboxyl group reacts with which amino group. If the alanine amino group reacts with the serine carboxyl, serylalanine results.



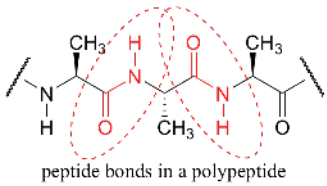
? Exercise 12.4.2

Write the reactions for:

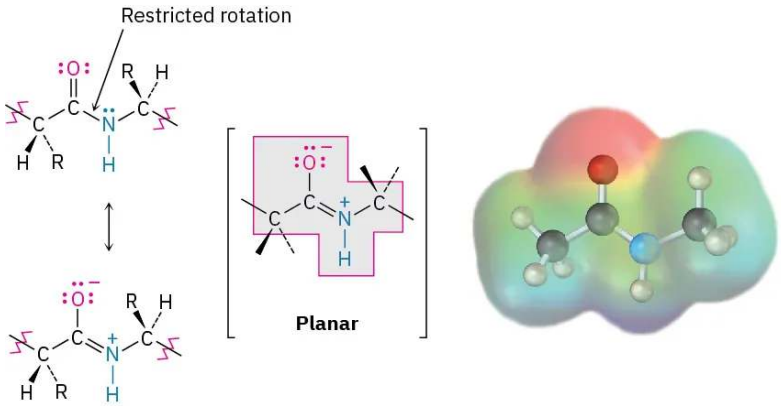
a. ala + gly ---> ▯ Answer graphic
b. phe + ser ----> ▯ Answer graphic

Resonance Contributors for the Peptide Bonds

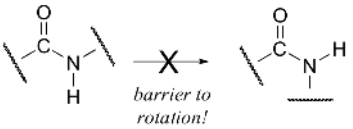
A consideration of resonance contributors is crucial to any discussion of the amide functional group. One of the most important examples of amide groups in nature is the 'peptide bond' that links amino acids to form polypeptides and proteins.



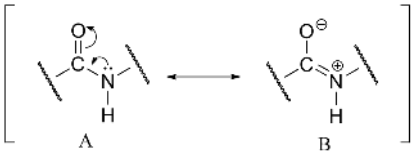
The amide bond that links amino acids together in peptides is no different from any other amide bond (Section 10.4). An amide nitrogen is nonbasic because its unshared electron pair is delocalized by resonance with the carbonyl group.



This overlap of the nitrogen *p* orbital with the *p* orbitals of the carbonyl group imparts a **certain amount of double-bond character** to the C–N bond and **restricts rotation** around it. The amide bond is therefore planar, and the N–H is oriented 180° to the C═O.

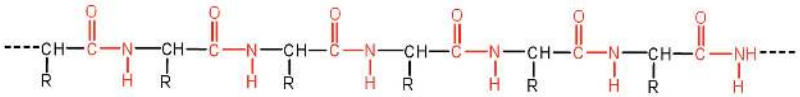


This, along with the observation that the bonding around the peptide nitrogen has trigonal planar geometry, strongly suggests that **the nitrogen is sp^2-hybridized**. An important resonance contributor has a C=N double bond and a C-O single bond, with a separation of charge between the oxygen and the nitrogen. Although B is a minor contributor due to the separation of charges, it remains highly relevant in terms of peptide and protein structure – our proteins would not fold properly if there were free rotation about the peptide C-N bond.



Backbone Peptide or Protein Structure

The structure of a peptide can be written fairly easily without showing the complete amide synthesis reaction by learning the structure of the "backbone" for peptides and proteins.



After the backbone is written, go back and write the specific structure for the side chains as represented by the "R" as ser-ala-cys for this example. The amine end (N terminal) of an amino acid is always on the left (ser), while the acid end (C terminal) is on the right (cys).

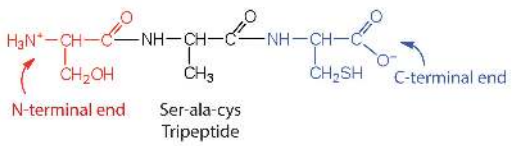


Figure 1: Structure of a tripeptide ser-ala-cys formed with serine, alanine, and cysteine.

Exercise 12.4.3

Write the structure for the following tripeptides. First, write the "backbone" and then add the specific side chains.

a. val-ser-cys b. glu-cys-gly c. phe-tyr-asn

Solution

a. Answer graphic b. Answer graphic c. Answer graphic

Exercise 12.4.4

Six isomeric tripeptides contain valine, tyrosine, and glycine. Name them using both three- and one-letter abbreviations.

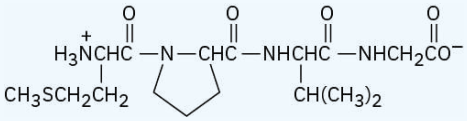
Answer

Val-Tyr-Gly (VYG), Tyr-Gly-Val (YGV), Gly-Val-Tyr (GVY), Val-Gly-Tyr (VGY), Tyr-Val-Gly (YVG), Gly-Tyr-Val (GYV)

Exercise 12.4.5

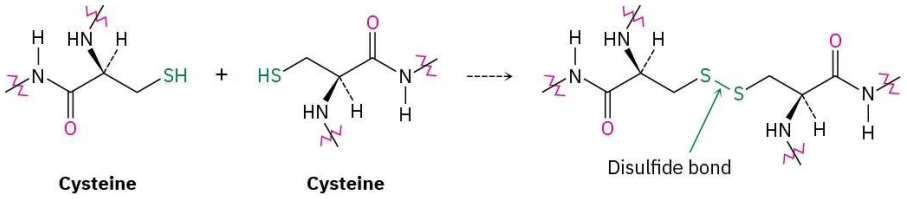
Draw the structure of M-P-V-G, and indicate its amide bonds.

Answer

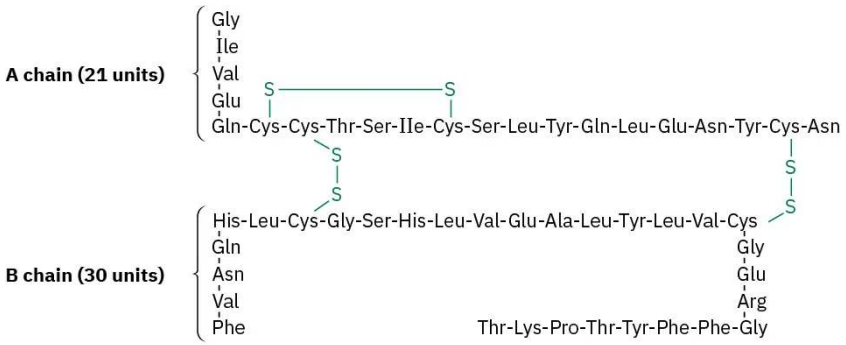


Disulfide Bridge

The amino acid cysteine undergoes oxidation and reduction reactions involving the -SH (sulfhydryl group). The oxidation of two sulfhydryl groups results in the formation of a **disulfide bond** by the removal of two hydrogen atoms. The **oxidation** of two cysteine amino acids is shown in the graphic. An unspecified oxidizing agent (O) provides oxygen, which reacts with the hydrogen (green) on the -SH group to form water. The sulfurs (green) join to make the **disulfide bridge**. This is an important bond to recognize in the tertiary structure of proteins. As we saw in Section 4.8, a disulfide is formed by mild oxidation of a thiol, RSH, and is cleaved by mild reduction. The reduction of a disulfide bond is the opposite reaction, which again leads to two separate cysteine molecules.



Cysteine residues in the peptide chain can form a loop by forming the disulfide bond (—S—S—), while cysteine residues in different peptide chains can actually link what were otherwise separate chains. Insulin was the first protein whose amino acid sequence was determined. This pioneering work, completed in 1953 after some 10 years of effort, earned a Nobel Prize for British biochemist Frederick Sanger (born 1918). He found that the primary structure consisted of two chains, totaling 51 amino acids, linked by two cysteine disulfide bridges. Also, note that the first peptide chain possesses an internal loop.



Insulin

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12.5: Peptide Synthesis- Solution-Phase

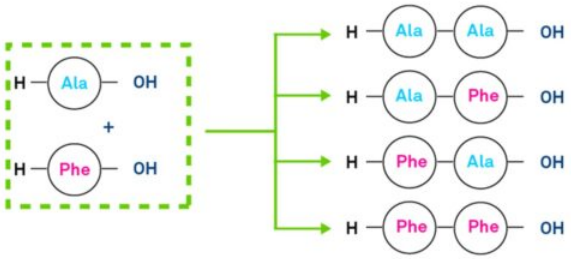
Objectives

After completing this section, you should be able to

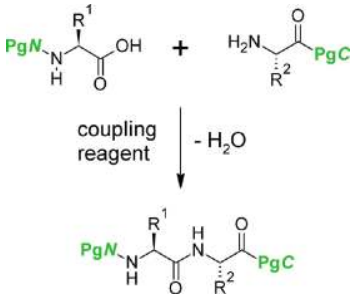
1. describe why it is necessary to protect certain amino and carboxyl groups during the synthesis of a peptide.
2. describe, using appropriate equations, how carboxyl groups are protected by ester formation and amino groups are protected by the formation of their *tert*-butoxycarbonyl amide derivatives.
3. describe, using appropriate equations, the formation of a peptide link between an amino acid with a protected amino group and an amino acid with a protected carboxyl group using dicyclohexylcarbodiimide.
4. outline the five steps required to form a dipeptide from two given amino acids.

Solution-phase synthesis was the first developed and the only method for peptide synthesis until the introduction of solid-phase peptide synthesis (SPPS) by Merrifield revolutionized the way peptides and their analogues are prepared today. However, some peptides, due to their chemical structure, cannot be synthesized by SPPS, and the “old school” technique remains favorable for making them.

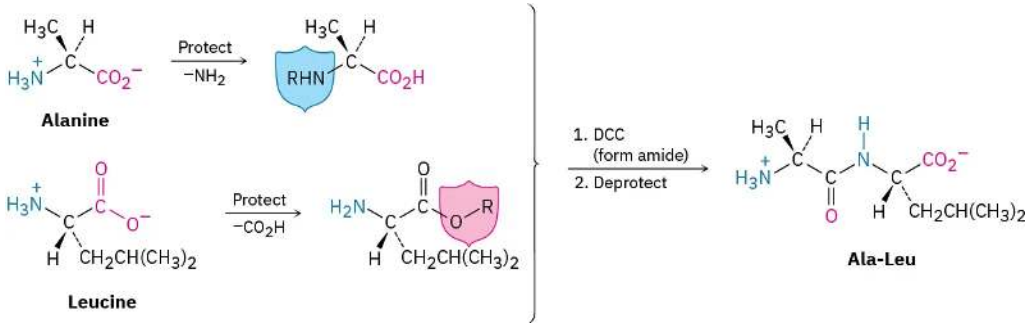
Once the structure of a peptide is known, its synthesis can be undertaken—perhaps to obtain a larger amount for biological evaluation. A simple amide might be formed by treating an amine and a carboxylic acid with a carbodiimide (either DCC or EDC; Section 7.4), but in solution, peptide synthesis is a more difficult problem because many different amide bonds must be formed in a specific order, rather than at random.



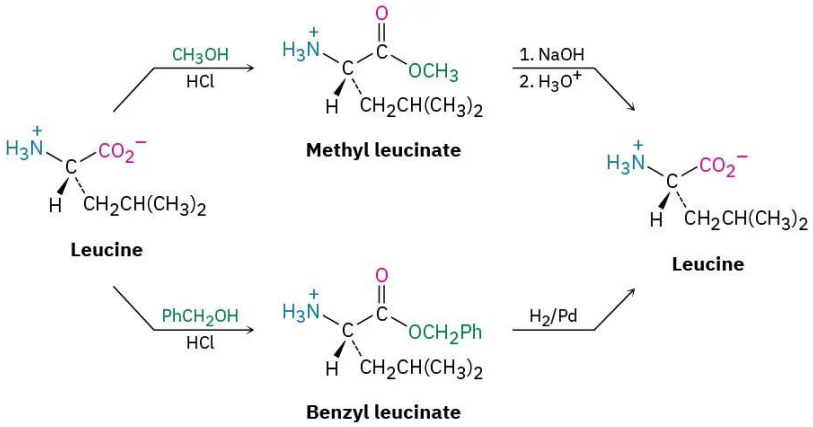
The solution to the specificity problem is the use of protecting groups. The protective groups should be specific for amines (PgN) or carboxylic acids (PgC) and should be easy to remove under mild conditions.



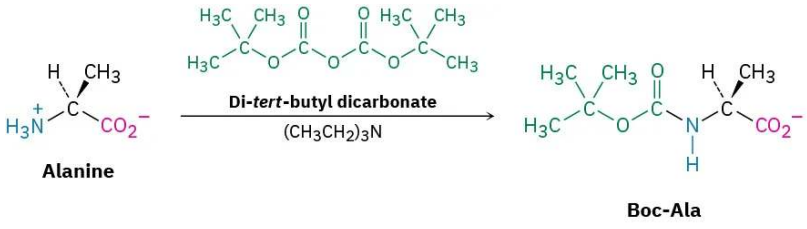
If we want to couple alanine with leucine to synthesize Ala-Leu, for instance, we could protect the $–NH_2$ group of alanine and the $–CO_2H$ group of leucine to shield them from reacting, then form the desired Ala-Leu amide bond by reaction with EDC or DCC, and then remove the protecting groups.

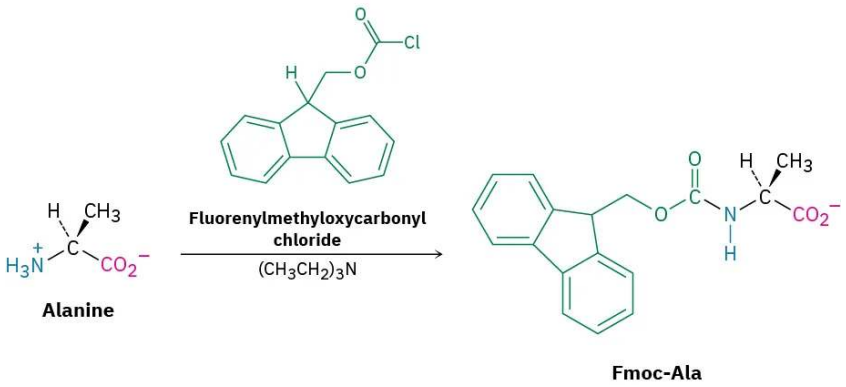


A number of different amino- and carboxyl-protecting groups have been devised, but only a few are used in peptide synthesis. Carboxyl groups are often protected simply by converting them into methyl or benzyl esters. Both groups are easily introduced by standard methods of ester formation (Section 7.7) and are easily removed by mild hydrolysis with aqueous NaOH. Benzyl esters can also be cleaved by catalytic *hydrogenolysis* of the weak benzylic C–O bond ($\mathbf{RCO_2{-}CH_2Ph^+H_2 \longrightarrow RCO_2H^+PhCH_3}$).

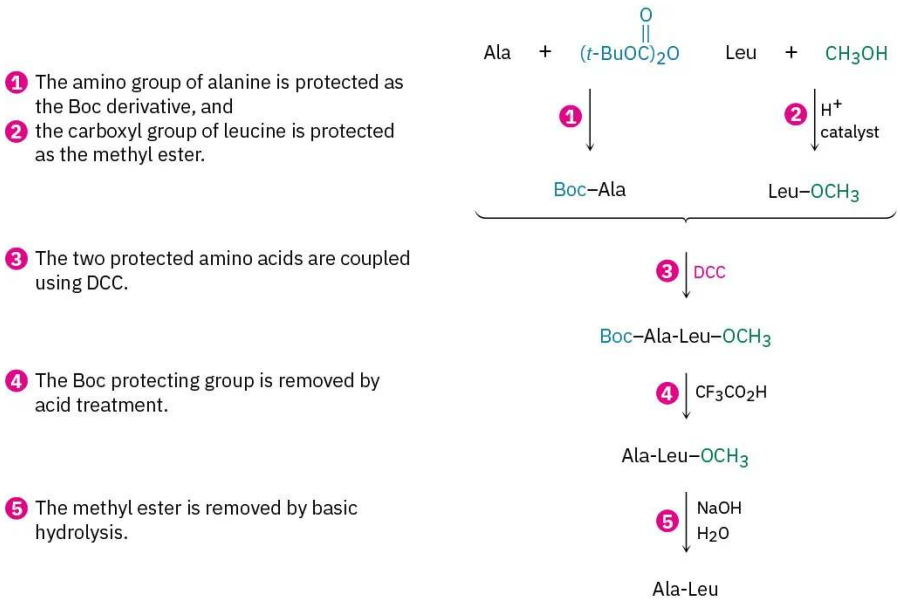


Amino groups are sometimes protected as their *tert*-butyloxycarbonyl amide (Boc) or, more commonly, as their fluorenylmethyloxycarbonyl amide (Fmoc). The Boc protecting group is introduced by reaction of the amino acid with di-*tert*-butyl dicarbonate in a nucleophilic acyl substitution reaction and is removed by brief treatment with a strong acid such as trifluoroacetic acid, CF_3CO_2H. The Fmoc protecting group is introduced by reaction with fluorenylmethyloxycarbonyl chloride and is removed by treatment with a 20% solution of the amine piperidine in dimethylformamide as solvent.





Thus, five steps are needed to synthesize a dipeptide such as Ala-Leu:



These steps can be repeated to add one amino acid at a time to the growing chain or to link two peptide chains together. Many remarkable achievements in peptide synthesis have been reported, including a complete synthesis of human insulin. Insulin is composed of two chains totaling 51 amino acids linked by two disulfide bridges. The three-dimensional structure of insulin, shown previously, was determined by Dorothy Crowfoot Hodgkin, a British chemist who received the 1964 Nobel Prize in Chemistry for her work on this and other complex biological molecules.

? Exercise 12.5.1

Show the mechanism of the formation of a Boc derivative by reaction of an amino acid with di-*tert*-butyl dicarbonate.

Answer

This is a typical nucleophilic acyl substitution reaction, with the amine of the amino acid as the nucleophile and *tert*-butyl carbonate as the leaving group. The *tert*-butyl carbonate then loses CO_2, giving *tert*-butoxide, which is subsequently protonated.

? Exercise 12.5.2

Write all five steps required for the synthesis of Leu-Ala from alanine and leucine.

Answer

1. Protect the amino group of leucine.
2. Protect the carboxylic acid group of alanine.
3. Couple the protected amino acids with DCC.
4. Remove the leucine protecting group.
5. Remove the alanine protecting group.

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12.6: Automated Peptide Synthesis - Solid-Phase Technique

Objectives

After completing this section, you should be able to describe, briefly, the Merrifield solid-phase technique for the synthesis of polypeptides.

Key Terms

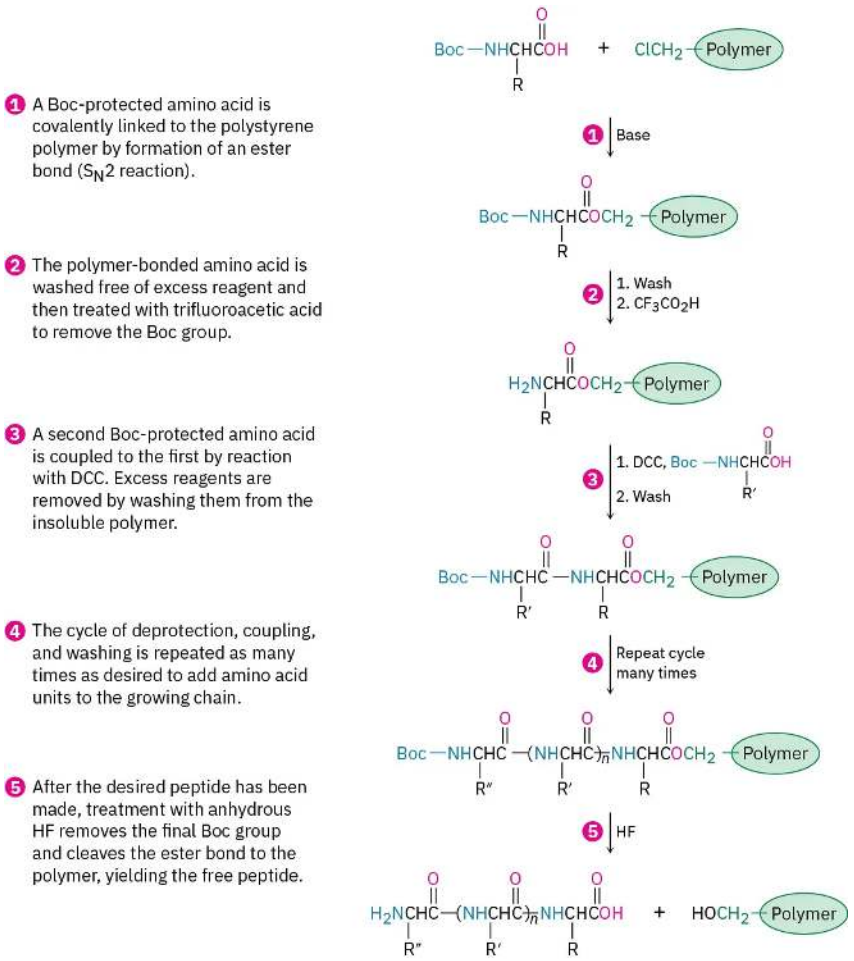
Make certain that you can define, and use in context, the key term below.

- solid-phase method (solid-phase synthesis)

The Merrifield Peptide Synthesis

The solution-phase synthesis of a peptide of significant length (e.g. ten residues) requires many steps, and the product must be carefully purified after each step to prevent unwanted cross-reactions. To facilitate the tedious and time-consuming purifications and reduce the material losses that occur in handling, the introduction of solid-phase peptide synthesis (SPPS) by Merrifield revolutionized the way peptides and their analogues are prepared today

This procedure involves attaching the C-terminus of the peptide chain to a polymeric solid, usually in the form of very small beads. Separation and purification are accomplished by filtering and washing the beads with appropriate solvents. The reagents for the next peptide bond addition are then added, and the purification steps are repeated. The entire process can be automated, and peptide synthesis machines based on the Merrifield approach are commercially available. A series of equations illustrating the Merrifield synthesis is presented below. The final step, in which the completed peptide is released from the polymer support, is a simple benzyl ester cleavage.



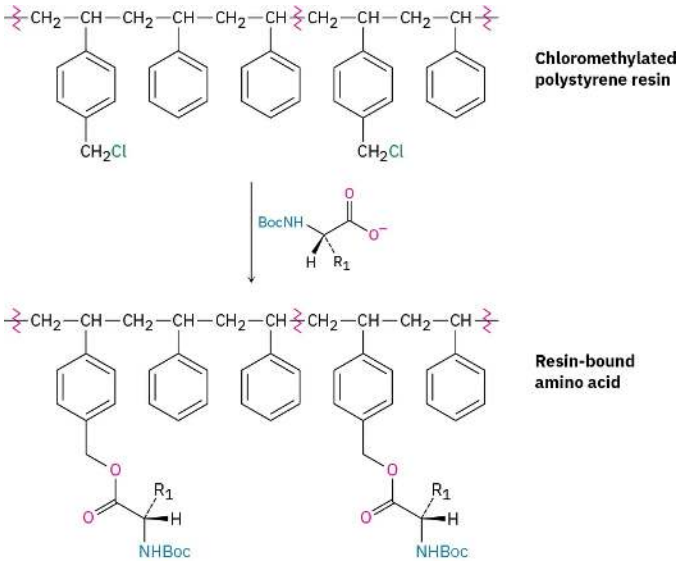
Robotic peptide synthesizers are now used to automatically repeat the coupling, washing, and deprotection steps with different amino acids. Each step occurs in high yield, and mechanical losses are minimized because the peptide intermediates are never removed from the insoluble polymer until the final step. Peptides with 20 amino acids can be routinely prepared in a few hours.

Notes

For his work on the synthesis of peptides, Bruce Merrifield was awarded the 1984 Nobel Prize in Chemistry using the Merrifield solid-phase method.

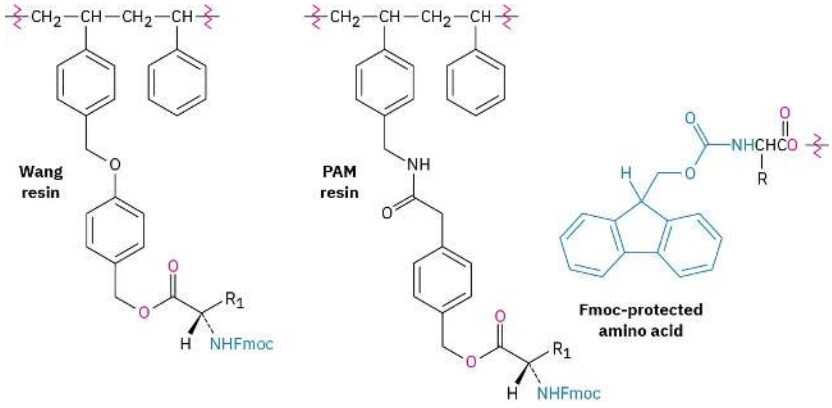
Polymer: The Solid-Phase

In the original procedure, polystyrene resin was used, prepared so that one of every hundred or so benzene rings contained a chloromethyl ($-CH_2Cl$) group. A Boc-protected C-terminal amino acid was then attached to the resin through an ester bond formed by S_N2 reaction.



With the first amino acid bonded to the resin, a repeating series of four steps is then carried out to build a peptide.

The steps in the solid-phase procedure have been improved substantially over the years, but the fundamental idea remains the same. A common procedure is use of the Wang resin, developed by Su-Sun Wang, with the Fmoc protecting group. Less common is using the PAM (phenylacetamidomethyl) resin with Boc as the N-protecting group.



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12.7: Protein Structure

Objectives

After completing this section, you should be able to

1. discuss, with reference to a suitable example (either given or of your own choice), the structure of proteins, paying particular attention to distinguishing between the primary, secondary, tertiary and quaternary structure.
2. describe the α-helical secondary structure displayed by many proteins.
3. describe the β-pleated-sheet structure displayed by many proteins.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- α helix, β pleated sheet, primary structure, secondary structure, tertiary structure, quaternary structure

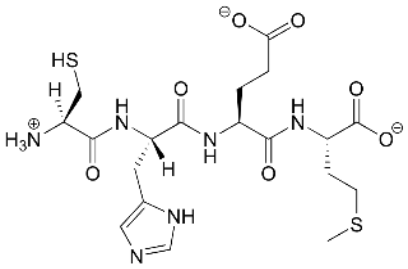
Proteins are compounds of high molar mass consisting largely or entirely of chains of amino acids. Because of their great complexity, protein molecules cannot be classified on the basis of specific structural similarities, as carbohydrates and lipids are categorized. The two major structural classifications of proteins are based on far more general qualities: whether the protein is (1) fiberlike and insoluble or (2) globular and soluble. Some proteins, such as those that compose hair, skin, muscles, and connective tissue, are fiberlike. These fibrous proteins are insoluble in water and usually serve structural, connective, and protective functions. Examples of fibrous proteins are keratins, collagens, myosins, and elastins. Hair and the outer layer of skin are composed of keratin. Connective tissues contain collagen. Myosins are muscle proteins and are capable of contraction and extension. Elastins are found in ligaments and the elastic tissue of artery walls.

Globular proteins, the other major class, are soluble in aqueous media. In these proteins, the chains are folded so that the molecule as a whole is roughly spherical. Familiar examples include egg albumin from egg whites and serum albumin in blood. Serum albumin plays a major role in transporting fatty acids and maintaining proper osmotic pressure in the body. Hemoglobin and myoglobin, which are important for binding oxygen, are also globular proteins.

The Four Levels of Protein Structure

Primary Structure

Protein structure can be discussed at four distinct levels. A protein's **primary structure** is two-dimensional - simply the sequence of amino acids in the peptide chain. Below is a Lewis structure of a short segment of a protein with the sequence CHEM (cysteine - histidine - glutamate - methionine)



The primary structure of insulin, composed of 51 amino acids, is shown in Figure **12.7.1**.

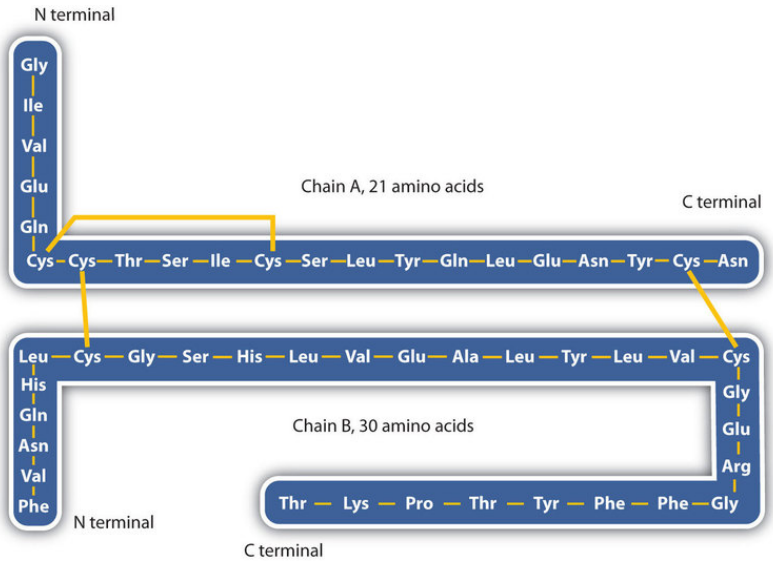


Figure \(\
PageIndex
{1}\): Primary Structure of Human Insulin. Human insulin, whose amino acid sequence is shown here, is a hormone that is required for the proper metabolism of glucose.

Secondary Structure

Secondary structure refers to the shape of a folding protein due exclusively to hydrogen bonding between its backbone amide and carbonyl groups. Secondary structure does not include bonding between the R-groups of amino acids, hydrophobic interactions, or other interactions associated with tertiary structure. The two most commonly encountered secondary structures of a polypeptide chain are α-helices and beta-pleated sheets. These structures are the first major steps in the folding of a polypeptide chain, and they establish important topological motifs that dictate subsequent tertiary structure and the ultimate function of the protein.

α-Helices

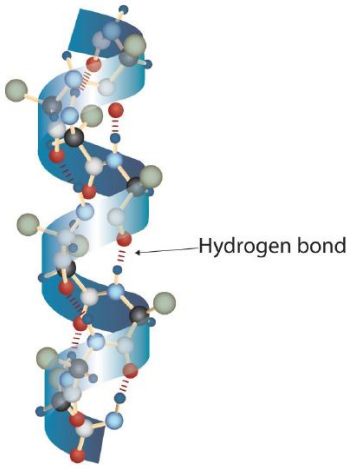
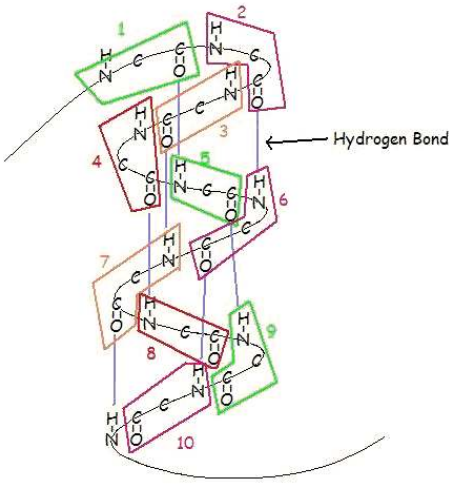


Figure **12.7.2** A Ball-and-Stick Model of an α-Helix. This ball-and-stick model shows the intrachain hydrogen bonding between carbonyl oxygen atoms and amide hydrogen atoms. Each turn of the helix spans 3.6 amino acids. Note that the side chains (represented as green spheres) point out from the helix.

An α-helix is a right-handed coil of amino-acid residues on a polypeptide chain, typically ranging between 4 and 40 residues. This coil is held together by hydrogen bonds between the oxygen of C=O on the top coil and the hydrogen of N-H on the bottom coil. Such a hydrogen bond is formed exactly every 4 amino acid residues, and every complete turn of the helix is only 3.6 amino acid

residues. This regular pattern gives the α-helix very definite features with regards to the thickness of the coil and the length of each complete turn along the helix axis.



The structural integrity of an α-helix is in part dependent on correct steric configuration. Amino acids whose R-groups are too large (tryptophan, tyrosine) or too small (glycine) destabilize α-helices. Proline also destabilizes α-helices because of its irregular geometry; its R-group bonds back to the nitrogen of the amide group, which causes steric hindrance. In addition, the lack of a hydrogen on Proline's nitrogen prevents it from participating in hydrogen bonding.

Another factor affecting α-helix stability is the total dipole moment of the helix, arising from the individual dipoles of the C=O groups involved in hydrogen bonding. Stable α-helices typically end with a charged amino acid to neutralize the dipole moment.

Study Notes

Note that in a diagram of the *α*-helical structure of a protein, the C-terminal of the protein is at the bottom of the diagram, and the N-terminal is at the top. In an *α* helix, such as the one shown in Figure 2, the bulky R groups are all found on the outside of the helix, where they have the most room.

BETA-PLEATED SHEETS

Another common type of secondary structure, known as the *β-pleated sheet conformation*, is a sheet-like arrangement in which two or more extended polypeptide chains (or separate regions on the same chain) are aligned side by side. The aligned segments can run either parallel or antiparallel—that is, the N-terminals can face in the same direction on adjacent chains or in different directions—and are connected by *interchain* hydrogen bonding (Figure **12.7.3**). The β-pleated sheet is particularly important in structural proteins, such as silk fibroin. It is also seen in portions of many enzymes, such as carboxypeptidase A and lysozyme.

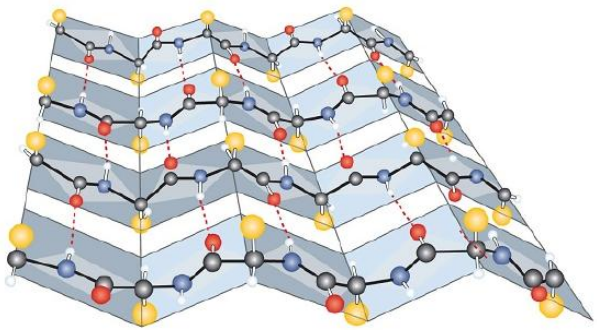
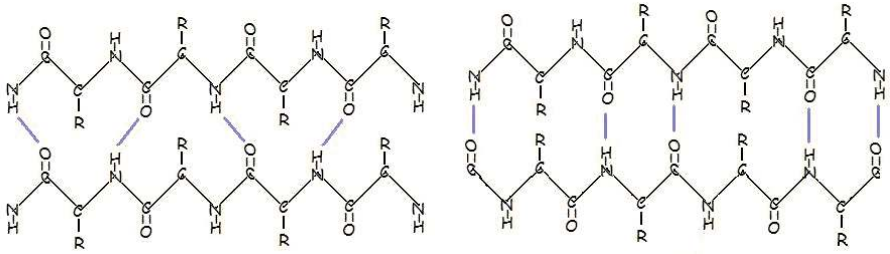


Figure **12.7.3**: A Ball-and-Stick Model of the β-Pleated Sheet Structure in Proteins. The side chains extend above or below the sheet and alternate along the chain. The protein chains are held together by interchain hydrogen bonding.

This can happen in a parallel or in anti-parallel arrangement:



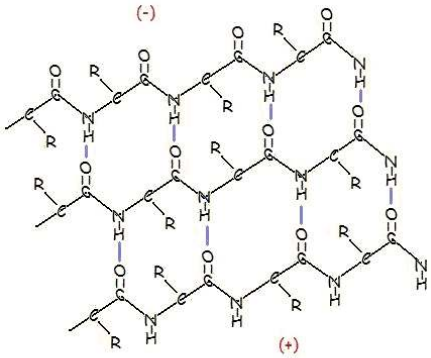
Parallel and anti-parallel arrangement is the direct consequence of the directionality of the polypeptide chain. In anti-parallel arrangement, the C-terminus end of one segment is on the same side as the N-terminus end of the other segment. In parallel arrangement, the C-terminus end and the N-terminus end are on the same sides for both segments. The "pleat" occurs because of the alternating planes of the peptide bonds between amino acids; the aligned amino and carbonyl group of each opposite segment alternate their orientation from facing towards each other to facing opposite directions.

The parallel arrangement is less stable because the geometry of the individual amino acid molecules forces the hydrogen bonds to occur at an angle, making them longer and thus weaker. Contrarily, in the anti-parallel arrangement the hydrogen bonds are aligned directly opposite each other, making for stronger and more stable bonds.

Commonly, an anti-parallel beta-pleated sheet forms when a polypeptide chain sharply reverses direction. This can occur in the presence of two consecutive proline residues, which create an angled kink in the polypeptide chain and bend it back upon itself. This is not necessary for distant segments of a polypeptide chain to form beta-pleated sheets, but for proximal segments it is a definite requirement. For short distances, the two segments of a beta-pleated sheet are separated by 4+2n amino acid residues, with 4 being the minimum number of residues.

α-PLEATED SHEETS

A similar structure to the beta-pleated sheet is the α-pleated sheet. This structure is energetically less favorable than the beta-pleated sheet, and is fairly uncommon in proteins. An α-pleated sheet is characterized by the alignment of its carbonyl and amino groups; the carbonyl groups are all aligned in one direction, while all the N-H groups are aligned in the opposite direction. The polarization of the amino and carbonyl groups results in a net dipole moment on the α-pleated sheet. The carbonyl side acquires a net negative charge, and the amino side acquires a net positive charge.



Alpha-Pleated Sheet

Tertiary Structure

A protein's **tertiary structure** is the shape in which the entire protein chain folds together in three-dimensional space, which results from the folding and bending of the protein backbone. The tertiary structure is intimately tied to the proper biochemical functioning of the protein. Figure **12.7.4** shows a depiction of the three-dimensional structure of insulin.

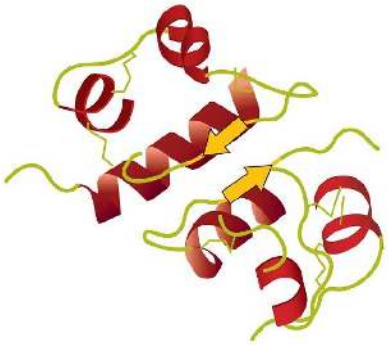


Figure **12.7.4**: A Ribbon Model of the Three-Dimensional Structure of Insulin. The spiral regions represent sections of the polypeptide chain that have an α-helical structure, while the broad arrows represent β-pleated sheet structures.

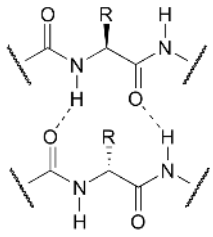
The Forces that Hold Proteins Together

The question of exactly how a protein 'finds' its specific folded structure out of the vast number of possible folding patterns is still an active area of research. What *is* known, however, is that the forces that cause a protein to fold properly and to remain folded are the basic non-covalent forces: ion-ion, ion-dipole, hydrogen bonding, dipole-dipole, and hydrophobic (London dispersion) interactions, and one covalent bond: disulfide linkages.

Four major types of attractive interactions determine the shape and stability of the tertiary structure of proteins. You studied several of them previously.

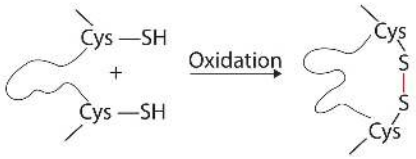
1. Ionic bonding. Ionic bonds result from electrostatic attractions between positively and negatively charged side chains of amino acids. For example, the mutual attraction between an aspartic acid carboxylate ion and a lysine ammonium ion helps to maintain a particular folded area of a protein (part (a) of Figure **12.7.5**).
2. Hydrogen bonding. Hydrogen bonding forms between a highly electronegative oxygen atom or a nitrogen atom and a hydrogen atom attached to another oxygen atom or a nitrogen atom, such as those found in polar amino acid side chains. Hydrogen bonding (as well as ionic attractions) is extremely important in both the intra- and intermolecular interactions of proteins (part (b) of Figure **12.7.5**).

   Both helix and the beta-sheet structures are held together by very specific hydrogen-bonding interactions between the amide nitrogen on one amino acid and the carbonyl oxygen on another. The hydrogen bonding pattern in a section of a beta-strand is shown below.



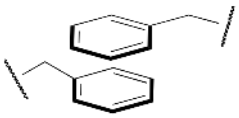
hydrogen bonding in a β-strand

3. Disulfide linkages. Two cysteine amino acid units may be brought close together as the protein molecule folds. Subsequent oxidation and linkage of the sulfur atoms in the highly reactive sulfhydryl (SH) groups leads to the formation of cystine (part (c) of Figure **12.7.5**). Intrachain disulfide linkages are found in many proteins, including insulin (yellow bars in Figure **12.7.1**) and have a strong stabilizing effect on the tertiary structure.



4. Dispersion forces. Dispersion forces arise when a normally nonpolar atom becomes momentarily polar due to an uneven distribution of electrons, leading to an instantaneous dipole that induces a shift of electrons in a neighboring nonpolar atom. Dispersion forces are weak but can be important when other types of interactions are either missing or minimal (part (d) of Figure **12.7.5**). This is the case with fibroin, the major protein in silk, in which a high proportion of amino acids in the protein have nonpolar side chains. The term *hydrophobic interaction* is often misused as a synonym for dispersion forces.

One interesting type of hydrophobic interaction is called 'aromatic stacking', and occurs when two or more planar aromatic rings on the side chains of phenylalanine, tryptophan, or tyrosine stack together like plates, thus maximizing surface area contact.



Hydrophobic interactions arise because water molecules engage in hydrogen bonding with other water molecules (or groups in proteins capable of hydrogen bonding). Because nonpolar groups cannot engage in hydrogen bonding, the protein folds in such a way that these groups are buried in the interior part of the protein structure, minimizing their contact with water.

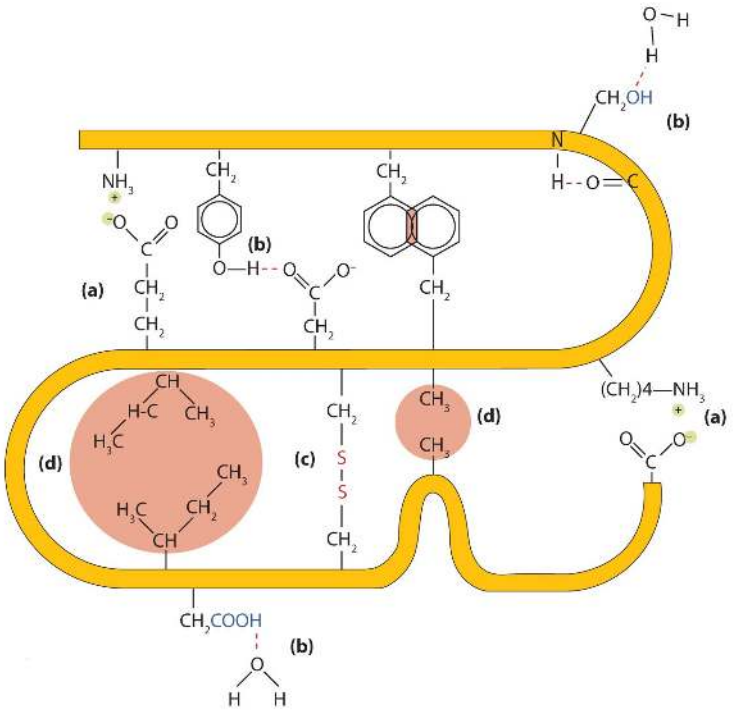
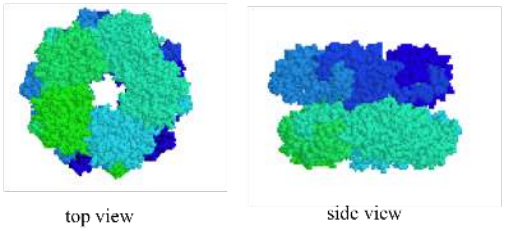


Figure **12.7.5**: Tertiary Protein Structure Interactions. Four interactions stabilize the tertiary structure of a protein: (a) ionic bonding, (b) hydrogen bonding, (c) disulfide linkages, and (d) dispersion forces.

Quaternary Structure

When a protein contains more than one polypeptide chain, each chain is called a *subunit*. Many other proteins consist of two identical subunits (these are called homodimers) or two non-identical subunits (these are called heterodimers). The arrangement of multiple subunits represents a fourth level of structure, the quaternary structure of a protein.

Quaternary structures can be quite elaborate: below we see a protein whose quaternary structure is defined by ten identical subunits arranged in two five-membered rings, forming what can be visualized as a 'double donut' shape (this is fructose 1,6-bisphosphate aldolase):



Hemoglobin, with four polypeptide chains or subunits, is the most frequently cited example of a protein having quaternary structure (Figure **12.7.6**). The quaternary structure of a protein is produced and stabilized by the same kinds of interactions that produce and maintain the tertiary structure. A schematic representation of the four levels of protein structure is in Figure **12.7.7**.



Figure **12.7.6** The Quaternary Structure of Hemoglobin. Hemoglobin is a protein that transports oxygen throughout the body.

Source: Image from the RCSB PDB (www.pdb.org(opens in new window)) of PDB ID 1I3D (R.D. Kidd, H.M. Baker, A.J. Mathews, T. Brittain, E.N. Baker (2001) Oligomerization and ligand binding in a homotetrameric hemoglobin: two high-resolution crystal structures of hemoglobin Bart's (gamma(4)), a marker for alpha-thalassemia. Protein Sci. 1739–1749).

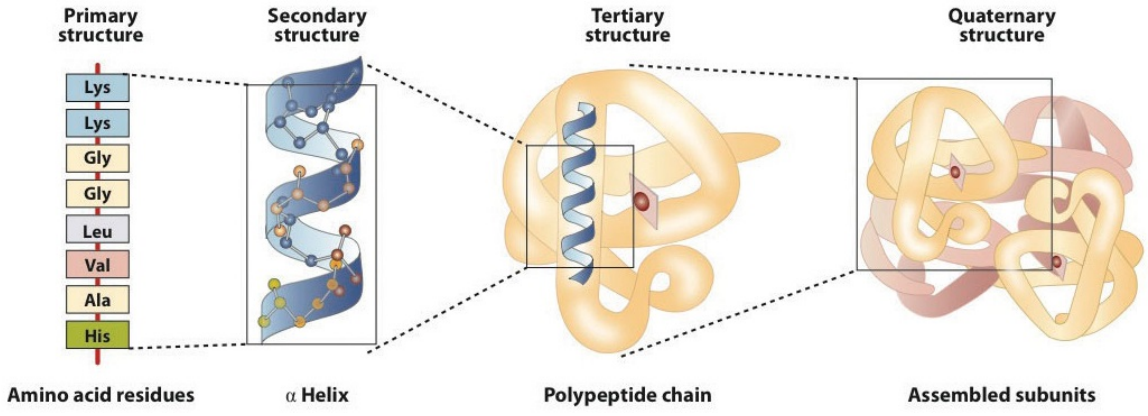


Figure **12.7.7**: Levels of Structure in Proteins

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12.8: Protein Misfolding and Denaturation

Learning Objectives

- Understand the misfolding of proteins and the medical problems associated with it.
- Understand the denaturation of proteins and the factors that cause it.

Protein Misfolding and Associated Diseases

Newly synthesized proteins fold in a specific way, i.e., into secondary, tertiary, and quaternary structures, to be able to perform their function, as illustrated in Figure **12.8.1**. Some proteins can fold in only one way, but others can fold in multiple ways. There are proteins in the cell, called chaperones, that help newly formed proteins to fold in the way needed for their function.

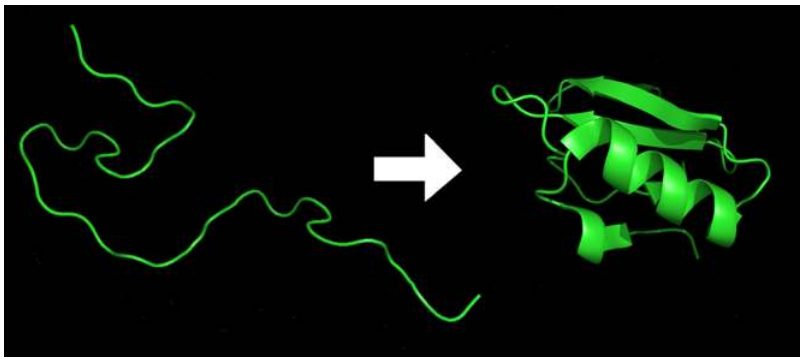


Figure **12.8.1**: Illustration of the protein folding process. Chymotrypsin inhibitor 2 from pdb file 1LW6. (Copyright; DrKjaergaard, Public domain, via Wikimedia Commons)

Sometimes normal proteins misfold and become pathological. Often, these proteins are in soluble α helix forms that re-assembles into β-pleated sheet forms that are sticky and aggregate into plaques or amyloid structures, as illustrated in Figure **12.8.2**, with the example of plaque formation in Alzheimer's affected brain.

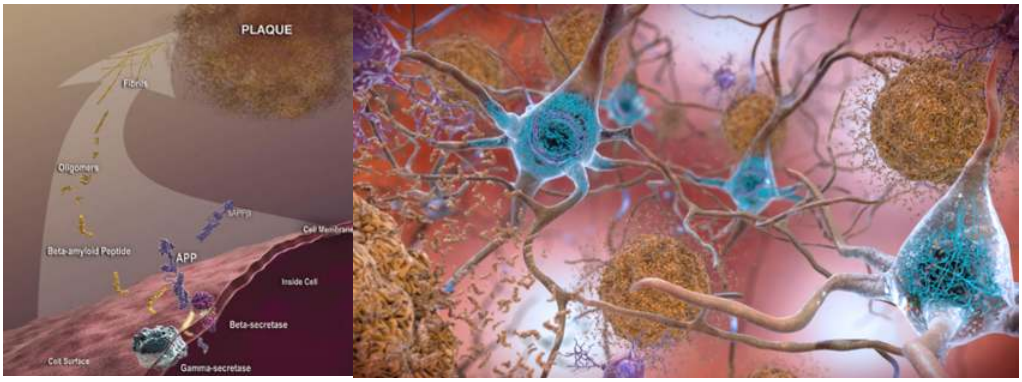


Figure **12.8.2**: Illustration of plaque formation when β-amyloid changes confirmation from α-helix to β-pleated sheets that aggregate to form the plaque (left) and abnormal levels of β-amyloid proteins aggregated to form plaques (shown in brown color) that collect between neurons. (Copyright; Left: National Institute on Aging, Public domain, via Wikimedia Commons, Right: NIH Image Gallery from Bethesda, Maryland, USA, Public domain, via Wikimedia Commons)

Prions are small proteins found in nerve tissue. Their exact functions are unknown, but when they misfold, they can cause more normal proteins to misfold. This protein misfolding is related to diseases such as mad cow disease in cows, Creutzfeldt–Jakob disease in humans, Alzheimer's disease, and familial amyloid cardiomyopathy or polyneuropathy, as well as intracellular aggregation diseases such as Huntington's and Parkinson's disease.

Denaturation of Proteins

The highly organized structures of proteins are truly masterworks of chemical architecture. But highly organized structures tend to have a certain delicacy, and this is true of proteins. Denaturation is the term used for any change in the three-dimensional structure

of a protein that renders it incapable of performing its assigned function.

One of the most important ideas to understand regarding tertiary structure is that *a protein, when properly folded, is polar on the surface and nonpolar in the interior*. It is the protein's surface that is in contact with water, and therefore the surface must be hydrophilic in order for the whole structure to be soluble. If you examine a three-dimensional protein structure, you will see many charged side chains (e.g. lysine, arginine, aspartate, glutamate) and hydrogen-bonding side chains (e.g. serine, threonine, glutamine, asparagine) exposed on the surface, in direct contact with water. Inside the protein, out of contact with the surrounding water, there tend to be many more hydrophobic residues such as alanine, valine, phenylalanine, etc. If a protein chain is induced to unfold (through exposure to heat, for example, or extremes of pH), it will usually lose its solubility and form solid precipitates, as hydrophobic residues from the interior come into contact with water. You can see this phenomenon for yourself if you pour a little bit of vinegar (acetic acid) into milk. The solid clumps that form in the milk are proteins that have come unfolded due to the sudden acidification, and precipitated out of solution.

A denatured protein cannot do its job. (Sometimes denaturation is equated with the precipitation or coagulation of a protein; our definition is a bit broader.) A wide variety of reagents and conditions, such as heat, organic compounds, pH changes, and heavy metal ions can cause protein denaturation (Figure **12.8.3**).

Figure **12.8.1**: Protein Denaturation Methods

Method	Effect on Protein Structure
Heating: Heat above 50°C or ultraviolet (UV) radiation	Heat or UV radiation supplies kinetic energy to protein molecules, causing their atoms to vibrate more rapidly and disrupting relatively weak hydrogen bonding and dispersion forces (hydrophobic interactions), causing protein denaturation. Example: sterilizing surgical instruments by autoclave treatment. In laser surgery, laser, i.e., the light of a single wavelength, is focused on a spot, causing heat that denatures proteins. Heating by laser cauterizes incisions, i.e., burns the site or the wound. It helps prevent blood loss.
Organic compounds: Such as ethyl alcohol	These compounds are capable of engaging in intermolecular hydrogen bonding with protein molecules, disrupting intramolecular hydrogen bonding within the protein.
Heavy metal ions: Such as mercury, silver, and lead	These ions form strong bonds with the carboxylate anions of the acidic amino acids or SH groups of cysteine, disrupting ionic bonds and disulfide linkages. Pb^{2+} and Hg^{2+} attack $-SH$ groups making salt bridges, like $-S^{-}Pb^{2+}\ ^{-}S-$. Egg white or milk is an antidote to heavy metal poisoning as they precipitate the metal ions in the stomach, based on the salt bridge forming reaction. Vomiting is induced to remove the metal before the precipitate is dissolved, releasing the metal in the later parts of the digestive system.
Acids and bases: Alkaloid reagents, such as tannic acid (used in tanning leather)	Disrupt hydrogen bonding and salt bridges, e.g., by neutralizing some ions involved in the salt bridges, when these reagents combine with positively charged amino groups in proteins to disrupt ionic bonds.
Agitation	physically disrupts hydrogen bonding and hydrophobic interactions. Example: Whipped cream and whipped egg whites are prepared based on the agitation process.

Anyone who has fried an egg has observed denaturation. With the exposure to heat, the clear egg white turns opaque as the albumin denatures and coagulates. No one has yet reversed that process (Figure **12.8.3**).

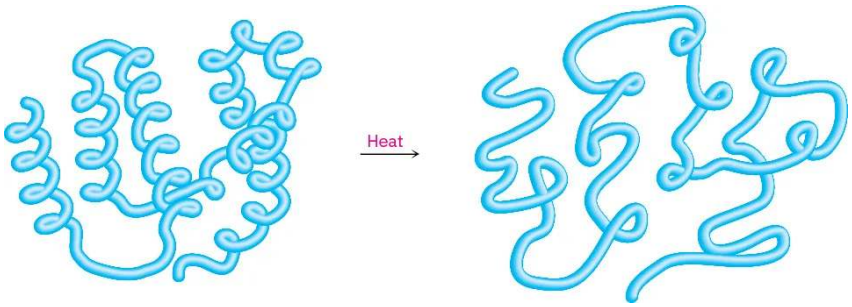


Figure 12.8.3: A representation of protein denaturation. A globular protein loses its specific three-dimensional shape and becomes randomly looped.

However, it is hypothesized that given the proper circumstances and enough time, a protein that has unfolded under sufficiently gentle conditions can refold and MAY again exhibit biological activity (Figure 12.8.4). Such evidence suggests that, at least for these proteins, the primary structure determines the secondary and tertiary structure. A given sequence of amino acids seems to adopt its particular three-dimensional arrangement naturally if conditions are right.

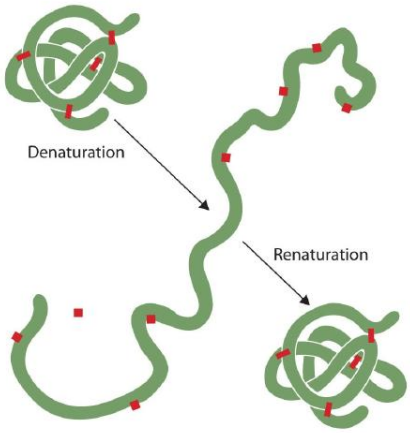


Figure 12.8.4: Denaturation and Renaturation of a Protein. The denaturation (unfolding) and renaturation (refolding) of a protein are depicted. The red boxes represent stabilizing interactions, such as disulfide linkages, hydrogen bonding, and/or ionic bonds.

The primary structures of proteins are quite sturdy. Generally, fairly vigorous conditions are required to hydrolyze peptide bonds. At the secondary through quaternary levels, however, proteins are quite vulnerable to attack, though their susceptibility to denaturation varies. The delicately folded globular proteins are much easier to denature than are the tough, fibrous proteins of hair and skin.

Denaturation

Loss of the secondary, tertiary, and quaternary structures of proteins by a physical process or a chemical agent, while maintaining the primary structure almost intact, is called **protein denaturation**.

In recent years, scientists have become increasingly interested in the proteins of so-called ‘thermophilic’ (heat-loving) microorganisms that thrive in hot water environments such as geothermal hot springs. While the proteins in most organisms (including humans) will rapidly unfold and precipitate out of solution when put in hot water, the proteins of thermophilic microbes remain completely stable, sometimes even in water that is just below the boiling point. In fact, these proteins typically only gain full biological activity when in appropriately hot water - at room temperature, they act as if they are ‘frozen’. Is the chemical structure of these thermostable proteins somehow unique and exotic? As it turns out, the answer to this question is ‘no’: the overall three-dimensional structures of thermostable proteins look very much like those of ‘normal’ proteins. The critical difference seems to be simply that thermostable proteins have more extensive networks of noncovalent interactions, particularly ion-ion interactions on their surface, that provides them with a greater stability to heat. Interestingly, the proteins of ‘psychrophilic’ (cold-loving)

microbes isolated from pockets of water in arctic ice show the opposite characteristic: they have far fewer ion-ion interactions, which gives them greater flexibility in cold temperatures but leads to their rapid unfolding in room temperature water.

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12.9: Enzymes and Coenzymes

Objectives

After completing this section, you should be able to

1. describe the catalytic role of an enzyme in a biochemical reaction.
2. Distinguish between the lock-and-key model and induced-fit model of enzyme action.
3. give an example of one fat-soluble and one water-soluble vitamin.

Key Terms

Make certain that you can define, and use in context, the key term below.

- coenzyme; cofactor; enzyme; substrate; vitamin

A **catalyst** is any substance that increases the *rate* or speed of a chemical reaction without being changed or consumed in the reaction. **Enzymes** are biological catalysts, and nearly all of them are proteins. Like all catalysts, an enzyme doesn't affect the equilibrium constant of a reaction and can't bring about a chemical change that is otherwise unfavorable.

Enzyme-catalyzed reactions occur in at least two steps. In the first step, an enzyme molecule (E) and the substrate molecule or molecules (S) collide and react to form an intermediate compound called the *enzyme-substrate* (E–S) *complex* (Equation 12.9.1). This step is reversible because the complex can break apart into the original substrate or substrates and the free enzyme. Once the E–S complex forms, the enzyme is able to catalyze the formation of product (P), which is then released from the enzyme surface (Equation 12.9.2):

$$S + E \rightleftharpoons E\text{–}S \tag{12.9.1}$$

$$E\text{–}S \rightarrow P + E \tag{12.9.2}$$

The extraordinary rate accelerations achieved by enzymes are due to a combination of several factors. One important factor is simple geometry: an enzyme will adjust its shape to hold the substrate, other reactants, and various catalytic sites on acidic or basic residues in the precise geometry needed for reaction. In addition, the wrapping of the enzyme around the substrate can create specialized microenvironments that protect the substrate from the aqueous medium and can dramatically change the behavior of acid–base catalytic residues in the active site. But perhaps most important is that the enzyme stabilizes and thus lowers the energy of the rate-limiting transition state for reaction. That is, it's not the ability of the enzyme to bind the *substrate* that matters but rather its ability to bind and stabilize the *transition state*. Often, in fact, the enzyme binds the transition structure as much as 10^{12} times more tightly than it binds the substrate or products. An energy diagram for an enzyme-catalyzed process might resemble that in Figure 12.9.1.

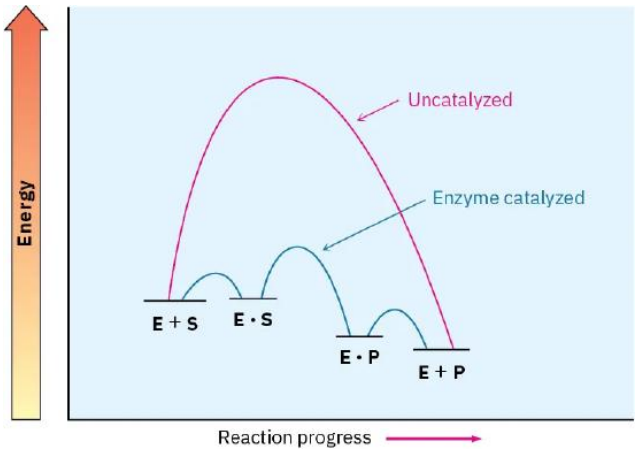


Figure **12.9.1**: Energy diagrams for **uncatalyzed** and **enzyme-catalyzed** processes. The enzyme makes available an alternative, lower-energy pathway. Rate enhancement is due to the ability of the enzyme to bind to the transition state for product formation, thereby lowering its energy.

Classification of Enzymes

In addition, enzymes are highly specific in their action; that is, each enzyme catalyzes only one type of reaction in only one compound or a group of structurally related compounds. The compound or compounds on which an enzyme acts are known as its **substrates**. Enzymes are classified by reaction type into six categories show in Table **12.9.1**.

Table **12.9.1**: ***Classes of Enzymes***

Class	Type of Reaction Catalyzed	Examples
oxidoreductases	oxidation-reduction reactions	Dehydrogenases catalyze oxidation-reduction reactions involving hydrogen and reductases catalyze reactions in which a substrate is reduced.
transferases	transfer reactions of groups, such as methyl, amino, and acetyl	Transaminases catalyze the transfer of amino group, and kinases catalyze the transfer of a phosphate group.
hydrolases	hydrolysis reactions	Lipases catalyze the hydrolysis of lipids, and proteases catalyze the hydrolysis of proteins
lyases	Reactions in which groups are removed without hydrolysis or addition of groups to a double bond	Decarboxylases catalyze the removal of carboxyl groups.
i	Reactions in which a compound is converted to its isomer	Isomerases may catalyze the conversion of an aldose to a ketose,

Class	Type of Reaction Catalyzed	Examples
somerases		and mutases catalyze reactions in which a functional group is transferred from one atom in a substrate to another.
ligases	Reactions in which new bonds are formed between carbon and another atom; energy is required	Synthetases catalyze reactions in which two smaller molecules are linked to form a larger one.

Enzyme-Substrate Interaction

Hydrogen bonding and other electrostatic interactions hold the enzyme and substrate together in the complex. The structural features or functional groups on the enzyme that participate in these interactions are located in a cleft or pocket on the enzyme surface. This pocket, where the enzyme combines with the substrate and transforms the substrate to product, is called the active site of the enzyme (Figure **12.9.2**).

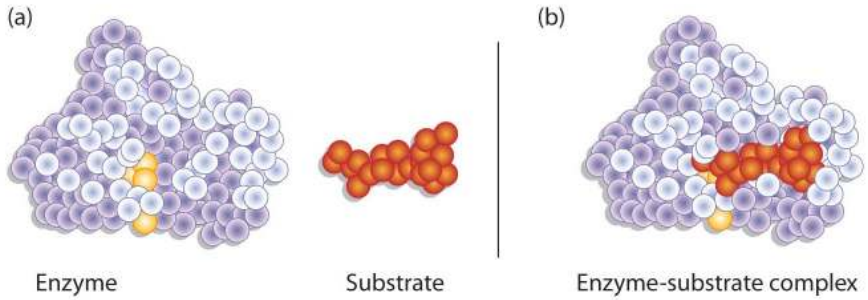


Figure **12.9.2**: Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.

Lock-and-Key Model

The active site possesses a unique conformation (including correctly positioned bonding groups) that is complementary to the structure of the substrate, so that the enzyme and substrate molecules fit together in much the same manner as a key fits into a tumbler lock. In fact, an early model describing the formation of the enzyme-substrate complex was called the lock-and-key model (Figure **12.9.3**). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

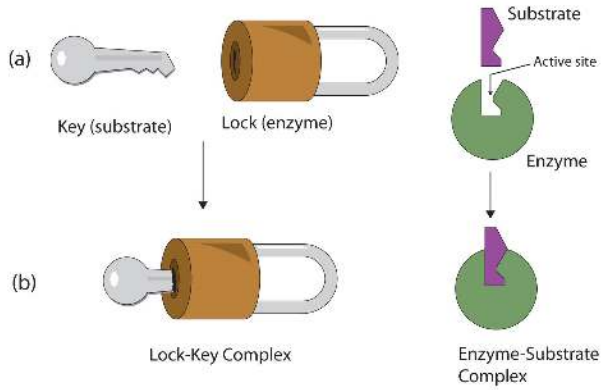


Figure **12.9.3**: The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate complex.

Induced-Fit Model

Working out the precise three-dimensional structures of numerous enzymes has enabled chemists to refine the original lock-and-key model of enzyme actions. They discovered that the binding of a substrate often leads to a large conformational change in the enzyme, as well as to changes in the structure of the substrate or substrates. The current theory, known as the induced-fit model, says that enzymes can undergo a change in conformation when they bind substrate molecules, and the active site has a shape complementary to that of the substrate only after the substrate is bound, as shown for hexokinase in Figure **12.9.4**. After catalysis, the enzyme resumes its original structure.

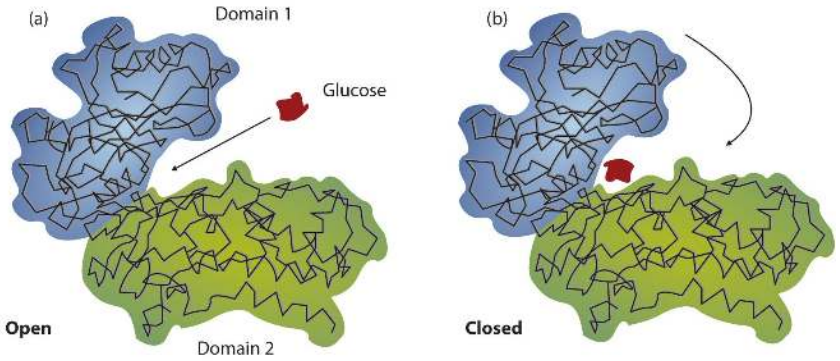


Figure **12.9.4**: The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and glucose.

The structural changes that occur when an enzyme and a substrate join together bring specific parts of a substrate into alignment with specific parts of the enzyme's active site. Amino acid side chains in or near the binding site can then act as acid or base catalysts, provide binding sites for the transfer of functional groups from one substrate to another or aid in the rearrangement of a substrate. The participating amino acids, which are usually widely separated in the primary sequence of the protein, are brought close together in the active site as a result of the folding and bending of the polypeptide chain or chains when the protein acquires its tertiary and quaternary structure. Binding to enzymes brings reactants close to each other and aligns them properly, which has the same effect as increasing the concentration of the reacting compounds.

✔ Example 12.9.1

a. What type of interaction would occur between an OH group present on a substrate molecule and a functional group in the active site of an enzyme?
b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

Solution

a. An OH group would most likely engage in hydrogen bonding with an appropriate functional group present in the active site of an enzyme.

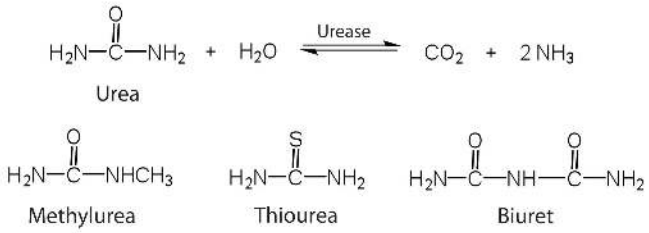
b. Several amino acid side chains would be able to engage in hydrogen bonding with an OH group. One example would be asparagine, which has an amide functional group.

? Exercise 12.9.1

a. What type of interaction would occur between an COO^- group present on a substrate molecule and a functional group in the active site of an enzyme?

b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

One characteristic that distinguishes an enzyme from all other types of catalysts is its *substrate specificity*. An inorganic acid such as sulfuric acid can be used to increase the reaction rates of many different reactions, such as the hydrolysis of disaccharides, polysaccharides, lipids, and proteins, with complete impartiality. In contrast, enzymes are much more specific. Some enzymes act on a single substrate, while other enzymes act on any of a group of related molecules containing a similar functional group or chemical bond. Some enzymes even distinguish between D- and L-stereoisomers, binding one stereoisomer but not the other. Urease, for example, is an enzyme that catalyzes the hydrolysis of a single substrate—urea—but not the closely related compounds methyl urea, thiourea, or biuret. The enzyme carboxypeptidase, on the other hand, is far less specific. It catalyzes the removal of nearly any amino acid from the carboxyl end of any peptide or protein.



Enzyme specificity results from the uniqueness of the active site in each different enzyme because of the identity, charge, and spatial orientation of the functional groups located there. It regulates cell chemistry so that the proper reactions occur in the proper place at the proper time. Clearly, it is crucial to the proper functioning of the living cell.

Takeaways

- A substrate binds to a specific region on an enzyme known as the active site, where the substrate can be converted to product.
- The substrate binds to the enzyme primarily through hydrogen bonding and other electrostatic interactions.
- The induced-fit model says that an enzyme can undergo a conformational change when binding a substrate.
- Enzymes exhibit varying degrees of substrate specificity.

Exercises

? Exercise 12.9.1

Distinguish between the lock-and-key model and the induced-fit model of enzyme action.

Answer

The lock-and-key model portrays an enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site. The induced fit model portrays the enzyme structure as more flexible and is complementary to the substrate only after the substrate is bound.

Exercise 12.9.2

What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?

a. COOH
b. NH_3^+
c. OH
d. $CH(CH_3)_2$

Answer

a. hydrogen bonding b. ionic bonding c. hydrogen bonding d. dispersion forces

Exercise 12.9.3

What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?

a. SH b. NH_2 c. C_6H_5 d. COO^-

Answer

a. disulfide bond b. hydrogen bonding c. dispersion forces d. ionic bonding

Exercise 12.9.4

For each functional group in Exercise 2, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.

Answer

a. The amino acid has a polar side chain capable of engaging in hydrogen bonding; serine (answers will vary).
b. The amino acid has a negatively charged side chain; aspartic acid (answers will vary).
c. The amino acid has a polar side chain capable of engaging in hydrogen bonding; asparagine (answers will vary).
d. The amino acid has a nonpolar side chain; isoleucine (answers will vary).

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12.10: Regulation of Enzyme Activity

Optimal Conditions for Enzymes

The single most important property of enzymes is the ability to increase the rates of reactions occurring in living organisms, a property known as *catalytic activity*. Because most enzymes are proteins, their activity is affected by factors that disrupt protein structure, as well as by factors that affect catalysts in general. Factors that disrupt protein structure include temperature and pH; factors that affect catalysts in general include reactant or substrate concentration and catalyst or enzyme concentration. The activity of an enzyme can be measured by monitoring either the rate at which a substrate disappears or the rate at which a product forms.

One way that enzymes act is to bring reactants (substrates) together so they don't have to expend energy moving about until they collide at random. Enzymes bind both reactant molecules (substrates), tightly and specifically, at a site on the enzyme's active site. Enzymes can also bring molecules to the active site to break them apart. For example, sucrase is the enzyme for the breakdown of sucrose which enters the active site of the enzyme and helps weaken the interactions between the fructose and glucose that make up sucrose. Sucrase is specific to the breakdown of sucrose as are most enzymes. The active site is specific for the reactants of the biochemical reaction the enzyme catalyzes. Similar to puzzle pieces fitting together, the active site can only bind certain substrates. The activities of enzymes also depend on the temperature, concentration, and the pH of the surroudings.

Concentration

As with most reactions, the concentration of the reactant(s) affects the reaction rate. This is also true in enzyme concentration. When either substrate or enzyme concentration is low, the rate of the reaction will be slower than where there are higher concentrations. The two species must interact for a reaction to occur and higher concentrations of one or both will result in more effective interactions between the two.

Concentration of substrate

In the presence of a given amount of enzyme, the rate of an enzymatic reaction increases as the substrate concentration increases until a limiting rate is reached, after which further increase in the substrate concentration produces no significant change in the reaction rate (part (a) of Figure **12.10.1**). At this point, so much substrate is present that essentially all of the enzyme active sites have substrate bound to them. In other words, the enzyme molecules are saturated with substrate. The excess substrate molecules cannot react until the substrate already bound to the enzymes has reacted and been released (or been released without reacting).

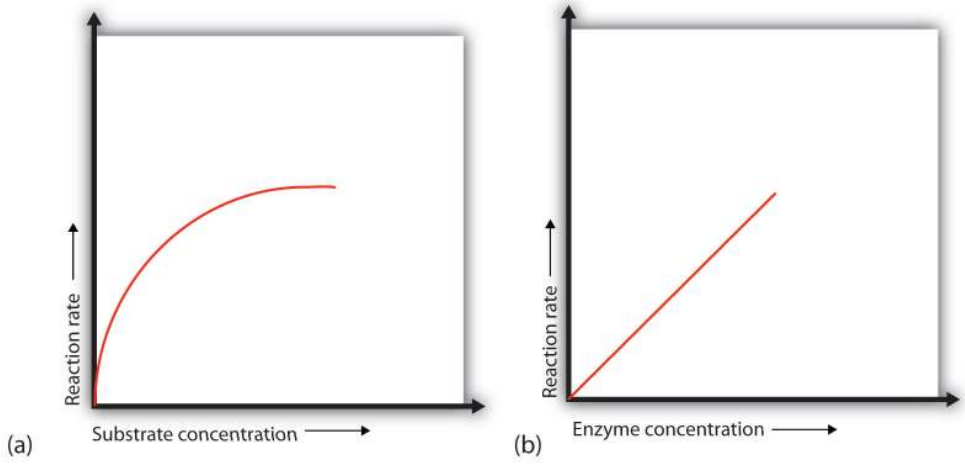


Figure **12.10.1**: Concentration versus Reaction Rate. (a) This graph shows the effect of substrate concentration on the rate of a reaction that is catalyzed by a fixed amount of enzyme. (b) This graph shows the effect of enzyme concentration on the reaction rate at a constant level of substrate.

Let’s consider an analogy. Ten taxis (enzyme molecules) are waiting at a taxi stand to take people (substrate) on a 10-minute trip to a concert hall, one passenger at a time. If only 5 people are present at the stand, the rate of their arrival at the concert hall is 5 people in 10 minutes. If the number of people at the stand is increased to 10, the rate increases to 10 arrivals in 10 minutes. With 20 people at the stand, the rate would still be 10 arrivals in 10 minutes. The taxis have been “saturated.” If the taxis could carry 2 or 3

passengers each, the same principle would apply. The rate would simply be higher (20 or 30 people in 10 minutes) before it leveled off.

Concentration of Enzyme

When the concentration of the enzyme is significantly lower than the concentration of the substrate (as when the number of taxis is far lower than the number of waiting passengers), the rate of an enzyme-catalyzed reaction is directly dependent on the enzyme concentration (part (b) of Figure 12.10.1). This is true for any catalyst; the reaction rate increases as the concentration of the catalyst is increased.

pH

The activity of enzymes is greatly influenced by both pH and temperature, as expected from the discussion of protein structure. Activity profiles of most enzymes show a peak of activity that tails off on either side, whether it is pH or temperature. Some enzymes work best at acidic pHs, while others work best in neutral environments. This is an innate characteristic of the enzyme. At very high or very low pH values, changes in the ionization of amino acid side chains can alter interactions with the substrate or lead to changes in tertiary structure, resulting in denaturation.

For example, digestive enzymes secreted in the acidic environment (low pH) of the stomach help break down proteins into smaller molecules. The main digestive enzyme in the stomach is pepsin, which works best at a pH of about 2. These enzymes would not work optimally at other pHs. As shown in the figure below, the blue line, the enzyme achieves a maximum reaction rate at low pH. Notice that the reaction will continue at higher pH values because the enzyme will still function at other pH values, but above pH > 5 is not effective.

Trypsin is another enzyme in the digestive system, which breaks protein chains in food into smaller particles. Trypsin, which is secreted into the duodenum, works in the small intestine, where the pH is ~8, does not work in acidic environments. Trypsin's optimum pH is about 8. Different reactions and different enzymes will achieve their maximum rate at certain pH values.

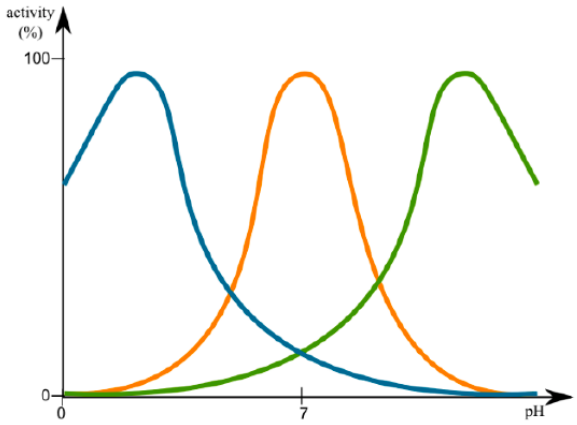


Figure 12.10.1: pH dependence of enzymatic activity. This graph depicts three hypothetical enzymes with acidic, neutral, and basic pH optima.

Temperature

As with pH, reactions also have an ideal temperature where the enzyme functions most effectively. For many biological reactions, the ideal temperature is at physiological conditions, which is approximately 37 °C, corresponding to the normal body temperature; while an enzyme from bacteria that live in deep-sea volcanic vents (e.g. *Thermophilus aquaticus*) might have temperature optima over 90°C.

Many enzymes lose function at lower and higher temperatures. This is one of the reasons that refrigeration can slow down the growth of microorganisms (which obviously have no ability to regulate their own temperature), and why most microorganisms are killed (enzymes are permanently denatured) when placed in sustained high-temperature environments. At higher temperatures, an enzyme's shape deteriorates. The increased energy can lead to the breaking of hydrogen bonds within the enzyme's structure, resulting in changes that inactivate its catalytic ability or prevent it from binding the substrate with sufficient affinity.

Interestingly, the DNA polymerase from the *T. aquaticus* bacteria, also commonly called Taq polymerase, is used in a rapid DNA-amplifying lab technique known as PCR (polymerase chain reaction, see Methods chapter) in which samples are repeatedly heated to high temperatures to separate DNA strands in preparation for making copies of them. DNA polymerases from most prokaryotic or eukaryotic species would be denatured and inactivated by high heat, but Taq has evolved (with respect to its tertiary structure) to exhibit extraordinary structural stability even in extreme heat.

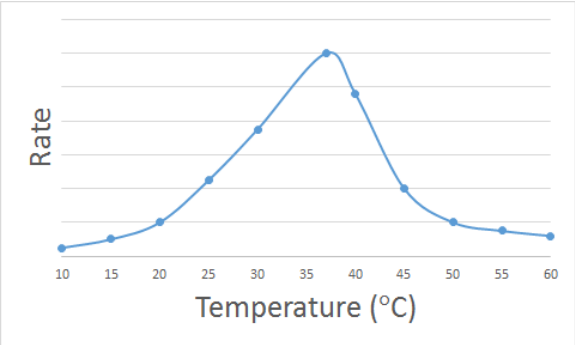


Figure **12.10.2**: Relationship between temperature and rate of a human enzyme.

Cofactors and Coenzymes

Finally, many enzymes that function properly require a molecular partner that has no catalytic activity of its own but, like a catalyst, is not permanently altered by the chemical reaction. These molecules are ***cofactors***. Some are simple: elemental, in fact, including metal ions such as Zn^{2+} or Ca^{2+} called ***inorganic cofactors***. Others are slightly more complex: small organic cofactors are called ***coenzyme***, (Figure **12.10.3**) and accomplish the same thing, acting as a required partner to the enzyme in catalyzing a reaction. Most **coenzymes** are vitamins or are derived from vitamins.

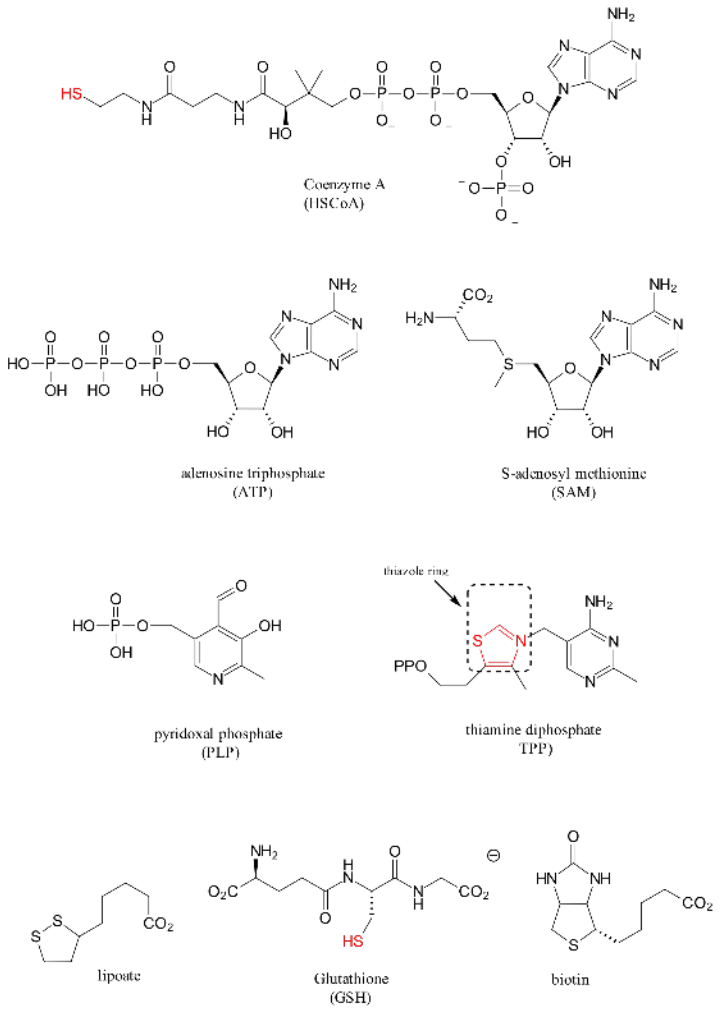


Figure **12.10.3**: Structures of Some Common Coenzymes

Because organisms differ in their synthetic abilities, a substance that is a vitamin for one species may not be so for another. Over the past 100 years, scientists have identified and isolated 13 vitamins required in the human diet and have divided them into two broad categories: the *fat-soluble vitamins* (Table **12.10.1**), which include vitamins A, D, E, and K, and the *water-soluble vitamins*, which are the B complex vitamins and vitamin C (Table **12.10.2**). All fat-soluble vitamins contain a high proportion of hydrocarbon structural components. There are one or two oxygen atoms present, but the compounds as a whole are nonpolar. In contrast, water-soluble vitamins contain large numbers of electronegative oxygen and nitrogen atoms, which can engage in hydrogen bonding with water. Most water-soluble vitamins act as coenzymes or are required for the synthesis of coenzymes. The fat-soluble vitamins are important for a variety of physiological functions.

Table **12.10.1**: Fat-Soluble Vitamins and Physiological Functions

Vitamin	Physiological Function	Effect of Deficiency
vitamin A (retinol)	formation of vision pigments; differentiation of epithelial cells	night blindness; continued deficiency leads to total blindness
vitamin D (cholecalciferol)	increases the body's ability to absorb calcium and phosphorus	osteomalacia (softening of the bones); known as rickets in children
vitamin E (tocopherol)	fat-soluble antioxidant	damage to cell membranes
vitamin K (phylloquinone)	formation of prothrombin, a key enzyme in the blood-clotting process	increases the time required for blood to clot

The interaction of coenzymes with the enzyme itself varies and may be only transient, as in NAD+/NADH, which are coenzymes used in redox reactions, or permanently bound to the enzyme by a covalent bond, like the heme group of hemoglobin. Often, the function of a coenzyme is to provide an active group that facilitates the catalyzed reaction. Coenzyme A, in metabolic pathways such as glycolysis and the tricarboxylic acid cycle, can bind to a substrate to form a stable product that then serves as an intermediate. The Co-A is released from the molecule as it undergoes the next step in a series of reactions in the metabolic pathway.

Table **12.10.2**: *Water-Soluble Vitamins and Physiological Functions*

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
vitamin B_1 (thiamine)	thiamine pyrophosphate	decarboxylation reactions	beri-beri
vitamin B_2 (riboflavin)	flavin mononucleotide or flavin adenine dinucleotide	oxidation-reduction reactions involving two hydrogen atoms	—
vit	nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate	oxidation-reduction reactions involving the hydride ion (H^-)	pellagra

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
amin B_3 (niacin)			
vitamin B_6 (pyridoxine)	pyridoxal phosphate	variety of reactions including the transfer of amino groups	—
vitamin B_1	methylcobalamin or deoxyadenoxylcobalamin	intramolecular rearrangement reactions	pernicious anemia

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
B_{12} (cyanocobalamin)			
biotin	biotin	carboxylation reactions	—
folic acid	tetrahydrofolate	carrier of one-carbon units such as the formyl group	anemia
pantothenic	coenzyme A	carrier of acyl groups	—

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
Acid			
vitamin C (ascorbic acid)	none	antioxidant; formation of collagen, a protein found in tendons, ligaments, and bone	scurvy

Inhibitors

Figure 12.10.3 illustrates the effects of two different types of inhibition on the different components of enzyme kinetics. Enzymes can be slowed down or even prevented from catalyzing reactions in many ways, including by preventing the substrate from entering the active site or by preventing the enzyme from altering its conformation to catalyze the reaction. The inhibitors that do this can do so either reversibly or irreversibly. The irreversible inhibitors are also called **inactivators**, and either bind to the enzyme with such high affinity that they are virtually irreversible, or form covalent bonds with the enzyme. Reversible inhibitors are generally grouped into two basic types: competitive and non-competitive.

> Finasteride (trade names include Propecia and Proscar) is an irreversible inhibitor that binds very tightly to the enzyme 5-a-reductase, used in converting testosterone to dihydrotestosterone. It is used in the treatment of male pattern baldness, benign prostatic hyperplasia, and prostate cancer.
>
> Aspirin is an example of an irreversible inhibitor that actually forms a covalent bond with the enzyme. Aspirin (acetylsalicylic acid) transfers its acetyl group to a serine residue on cyclooxygenase-2 (COX-2). This stops the production of inflammation-producing prostaglandins and thromboxanes by COX-2.

Methotrexate is a competitive inhibitor of dihydrofolate reductase (DHFR), an enzyme that synthesizes tetrahydrofolate, which is a precursor for purine synthesis, and therefore for DNA and RNA. It has a very similar molecular structure to folic acid, the natural substrate of DHFR. Methotrexate is used as an anticancer drug because it affects rapidly reproducing cells (which need to make DNA more quickly than other cells) more than noncancerous cells.

Competitive inhibition

Competitive inhibition is perhaps the simplest to understand. The inhibitor molecule competes directly with the substrate for the active site of an unbound enzyme. If an inhibitor binds to the active site, the substrate is unable to do so until the inhibitor has vacated the site. Thus, one could potentially overwhelm competitive inhibition with sufficiently larger concentrations of substrate so that the probability that the enzyme bumps into a substrate to bind becomes exceedingly large compared to the probability of bumping into an inhibitor. Normal, uninhibited V_{max} is then achieved despite the presence of the competitive inhibitor, which has affected only Km, that is, the concentration of substrate required to reach $V_{max}/2$. This is the kinetic signature of competitive inhibitors: with increasing inhibitor concentrations, K_M is increased, but V_{max} is unaffected.

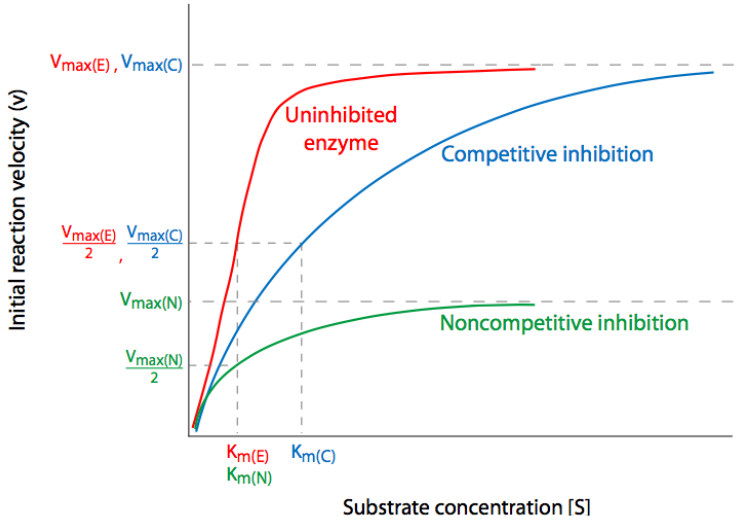


Figure **12.10.3**. Saturation curves for enzyme-catalyzed reactions without inhibitor (red) with competitive inhibitor (blue) at a constant concentration, and with noncompetitive inhibitor (green) at a constant concentration.

Non-competitive inhibition involves inhibiting the enzyme by altering its ability to complete the catalyzed reaction through binding of the enzyme at a position that is not the active site. When the inhibitor binds to the enzyme, it causes a change, usually conformational, that may either prevent the enzyme from binding the substrate, or prevent the enzyme from acting upon a bound substrate. In either case, increasing the availability of substrate will not ultimately overcome the inhibitory effect. Thus, V_{max} is reduced not because some proportion of the enzymes are no longer usable, but because the available enzymes have the same access to substrate as it would without inhibitor (that is, it is not in competition with an inhibitor), the K_m is not affected.

Non-competitive Regulation

Non-competitive regulation is one example of *allosteric regulation* of enzymes. Allosteric interactions occur when the binding of a ligand (not necessarily a substrate) to a protein influences the binding of another ligand to the protein at a separate binding site. These kinds of interactions can be either positive (activating) or negative (inhibitory), and either homotropic (both ligands are identical) or heterotropic (ligands are different). Interestingly, sometimes the regulator ligand may actually be a product of the catalyzed reaction. In this kind of feedback mechanism, the progress of a reaction is self-regulating.

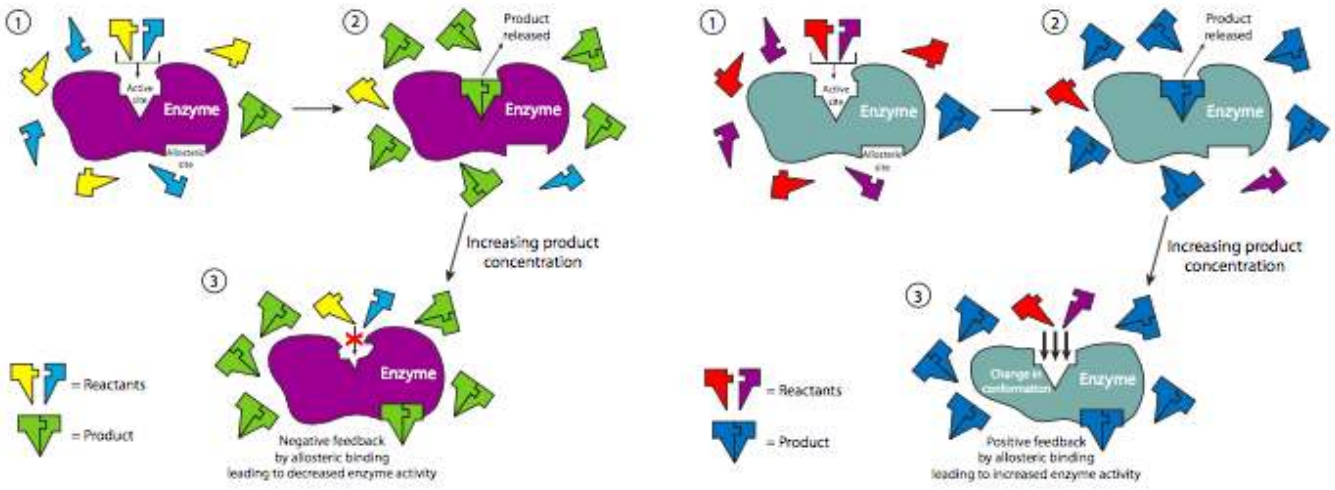


Figure **12.10.4**. Feedback control loops. (Left) Negative feedback is a common biological mechanism for self-regulating processes. The product of the reaction, either by itself or in conjunction with other molecules, acts as an allosteric inhibitor of the enzyme. (Right) Positive feedback is less common because it can lead to rapid expansion of the scope of a reaction, and requires an external (relative to the enzymatic reaction) mechanism for slowing or stopping the reaction.

Many of the enzymes in metabolic pathways are regulated by a naturally occurring non-competitive inhibitor. One example is phosphofructokinase (PFK), which is involved in glycolysis, which produces ATP for the cell. However, if there are high enough levels of ATP in the cell that other cellular processes aren't using, then it can bind to phosphofructokinase outside of its active site (it binds fructose-6-phosphate) and turn it off. This blocks glycolysis and production of excess ATP when the cell does not need it. As ATP is used up, there is less available to inhibit PFK, and glycolysis starts back up.

Modeling Allosteric Behavior

There are two models for such allosteric interactions.

- The **symmetry model**, also known as the concerted model, or MWC model (Monod, Wyman, and Changeux, 1965), proposes that the allosteric enzyme is an oligomer of several subunits, each of which are symmetrically related, and can be in either a "tensed" or "relaxed" state, but all of the subunits are in the same state and at equilibrium. When a ligand binds, it changes the state of the subunit(s) to which it binds, and to maintain equilibrium, that in turn causes the state of the other subunits to match, thus altering binding properties for a subsequent ligand.
- The **sequential model**, or the KNF model (Koshland, Nemethy, and Filmer, 1966), proposes something quite different: although it also supposes subunits in either tensed or relaxed states, it does not require all subunits to be connected in such a way as to mandate that all subunits be in the same state, and therefore conformational changes in one subunit need not be propagated to all. Instead, using an induced-fit model of ligand binding rather than the more rigid basic lock-and-key mechanism, it suggests that when a ligand binds to the enzyme, it induces a slight conformational change in the active site that increases the enzyme's affinity for the ligand. The conformational change may slightly alter the conformation of other subunits of the enzyme, but may not constitute a state change between relaxed and tensed, depending on how tightly the subunits are interacting. However, the change is enough to increase substrate affinity in adjacent subunits.

Advanced: Uncompetitive and Mixed inhibition

Most cell/molecular courses stop the discussion of enzyme inhibitors at competitive vs non-competitive based on their kinetic profiles. However, it should be noted that if you take a biochemistry course, you may encounter the terms *uncompetitive* inhibitor and *mixed* inhibitor. These terms are defined not just by the enzyme kinetics, but the mechanism of interaction:

- *Uncompetitive inhibitors* bind only to the enzyme-substrate (ES) complex, not to the enzyme before it encounters substrate. This leads to decreased V_{max} and decreased K_m.

- *Mixed inhibition* means that the inhibitor can bind to either the enzyme alone or the enzyme-substrate complex. Because the affinities of the inhibitor for the two forms of the enzyme are different, and because part of it depends on substrate concentration while the other kind of binding does not, generally, V_{max} decreases and K_m increases. Non-competitive inhibition is a special case of mixed inhibition in which the catalytic activity of the enzyme is diminished or abolished, but the ability to bind substrate is unaltered.

Other Mechanisms of Inhibition

While important, especially pharmaceutically, the use of enzyme inhibitors is not the only way to regulate enzymes. There are numerous examples of one type of enzyme activating or inhibiting another. The most common general example are the protein kinases. These enzymes phosphorylate (transfer a phosphate group to) other enzymes and thereby activate them. Kinases are generally fast and very specific, and this is an efficient method for activating large numbers of particular enzymes quickly. Conversely, protein phosphatases are enzymes (also quite fast, but much less specific than kinases) that remove the phosphate groups from phosphorylated proteins, thereby turning off those enzymes. Keep in mind that this is a generalization, and that not all phosphorylations are activating. In addition to enzymatic inhibition of enzymes, there is also inhibition by binding and sequestration of the substrates. In fact, the antibiotic vancomycin works just this way, binding to the substrate peptide for transpeptidase and preventing the enzyme from recognizing it. Transpeptidase normally helps stabilize the cell wall of certain bacteria by altering some of the proteins, and without its activity, the protection of the cell wall is compromised, and the bacteria may be more easily killed.

Well over half of the enzymes discovered so far do not act according to the simplistic Michaelis-Menten one-substrate-one-product mechanism, but rather operate with two substrates and two products, usually involving the transfer of an active group. These types of reactions are sometimes known as Bi Bi reactions. There are two major classes of these reactions: the *sequential reactions*, in which all substrates bind with the enzyme before the reaction proceeds, and the *ping pong reactions*, in which one or more products are created and released before all of the substrates have been bound. In fact, unlike sequential reactions, the two substrates do not interact with one another while bound to the enzyme.

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12.11: How do Enzymes Work? Citrate Synthase

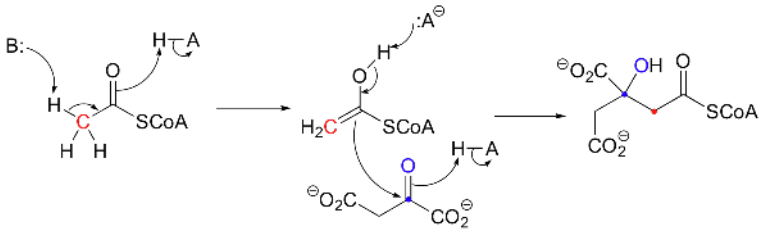
Objectives

After completing this section, you should be able to

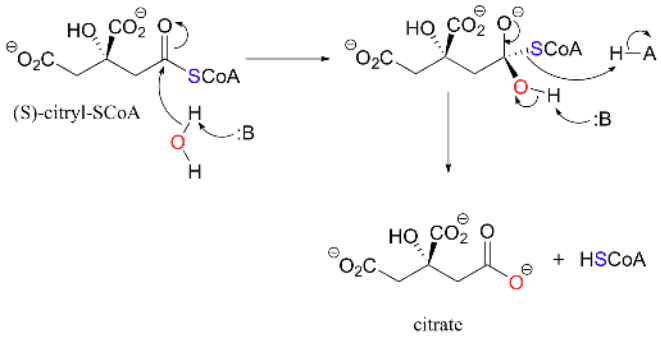
1. describe and explain the general function of an enzyme like citrate synthase in a reaction.
2. identify the structures of ten common coenzymes.

Oxaloacetate to Citrate Catalyzed by Citrate Synthase

Citrate synthase is a protein with 433 amino acids with various functional groups that can react with substrates. This enzyme catalyzes oxaloacetate to eventually produce citrate as part of the citric acid (Krebs) cycle. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA. The carboxylate group of an aspartic acid (B:) on citrate synthase removes the acidic alpha proton on acetyl CoA, while a histidine site (H-A) donates a proton to form the enol. Then a second histidine site (H-A) protonates the carbonyl oxygen of oxaloacetate, while the carbon of the carbonyl is attacked by the enol. Simultaeously, that first histidine ($:A^-$) deprotonates the acetyl CoA enol. (S)-citryl CoA is generated.



The acyl group of a thioester of (S)-citryl CoA can be transferred to a water molecule in a hydrolysis reaction to converting (S)-citryl CoA to citrate. Again histidine sites on citrate synthase are an integral part of the mechanism and assist with removal and addition of protons.



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12.12: Additional Problems

Visualizing Chemistry

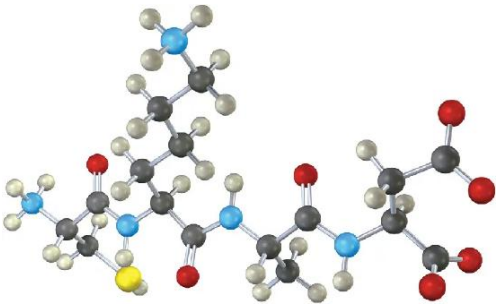
PROBLEM 12-19 Identify the following amino acids:


(a)

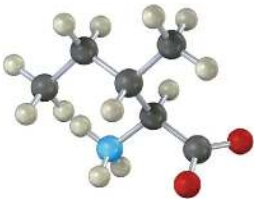

(b)


(c)

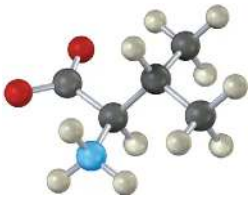
PROBLEM 12-20 Give the sequence of the following tetrapeptide (yellow = S):



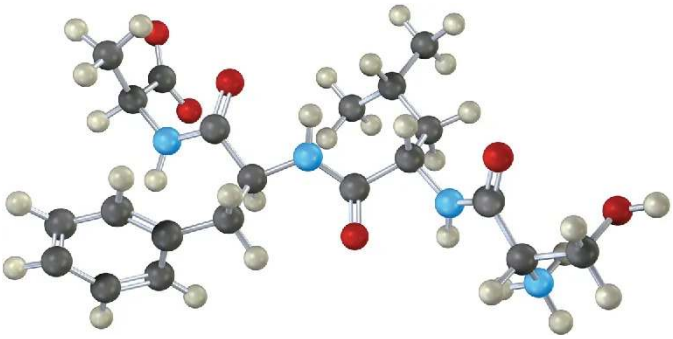
PROBLEM 12-21 Isoleucine and threonine are the only two amino acids with two chiral centers. Assign *R* or *S* configuration to the methyl-bearing carbon atom of isoleucine.



PROBLEM 12-22 Is the following structure a D- amino acid or an L- amino acid? Identify it.



PROBLEM 12-23 Give the sequence of the following tetrapeptide:



Amino Acid Structures and Chirality

PROBLEM 12-29 Except for cysteine, only *S* amino acids occur in proteins. Several *R* amino acids are also found in nature, however. (*R*)-Serine is found in earthworms, and (*R*)-alanine is found in insect larvae. Draw Fischer projections of (*R*)-serine and (*R*)-alanine. Are these D or L amino acids?

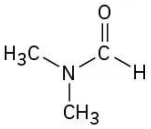
PROBLEM 12-30 Cysteine is the only amino acid that has L stereochemistry but an *R* configuration. Make up a structure for another L amino acid of your own creation that also has an *R* configuration.

PROBLEM 12-31 Draw a Fischer projection of (*S*)-proline.

PROBLEM 12-32 Show the structures of the following amino acids in their zwitterionic forms:

(a) Trp (b) Ile (c) Cys (d) His

PROBLEM 12-53 Evidence for restricted rotation around amide Math input error ^{1}H NMR spectrum of *N*,*N*-dimethylformamide shows three peaks: 2.9 δ (singlet, 3 H), 3.0 δ (singlet, 3 H), and 8.0 δ (singlet, 1 H). As the temperature is raised, however, the two singlets at 2.9 δ and 3.0 δ slowly merge. At 180 °C, the ^{1}H NMR spectrum shows only two peaks: 2.95 δ (singlet, 6 H) and 8.0 δ (singlet, 1 H). Explain this temperature-dependent behavior.



***N,N*-Dimethylformamide**

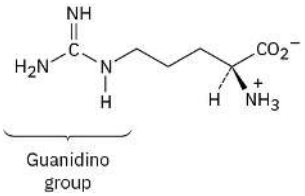
PROBLEM 12-33 Proline has pK_{a1} = 1.99 and pK_{a2} = 10.60. Use the Henderson–Hasselbalch equation to calculate the ratio of protonated and neutral forms at pH = 2.50. Calculate the ratio of neutral and deprotonated forms at pH = 9.70.

PROBLEM 12-34 Using both three- and one-letter codes for amino acids, write the structures of all possible peptides that contain the following amino acids:

(a) Val, Ser, Leu. (b) Ser, Leu_2, Pro

PROBLEM 12-35 Look at the side chains of the 20 amino acids in Table 12.1, and then think about what is *not* present. None of the 20 contains either an aldehyde or a ketone carbonyl group, for instance. Is this just one of nature's oversights, or is there a likely chemical reason? What complications might an aldehyde or ketone carbonyl group cause?

PROBLEM 12-51 Arginine, the most basic of the 20 common amino acids, contains a *guanidino* functional group in its side chain. Explain, using resonance structures to show how the protonated guanidino group is stabilized.



Arginine

Amino Acid Reactions

PROBLEM 12-41 Predict the product of the reaction of valine with the following reagents:

(a) CH_3CH_2OH, acid (b) KOH, H_2O (c) CH_3COCl, pyridine; then H_2O

Peptides and Enzymes

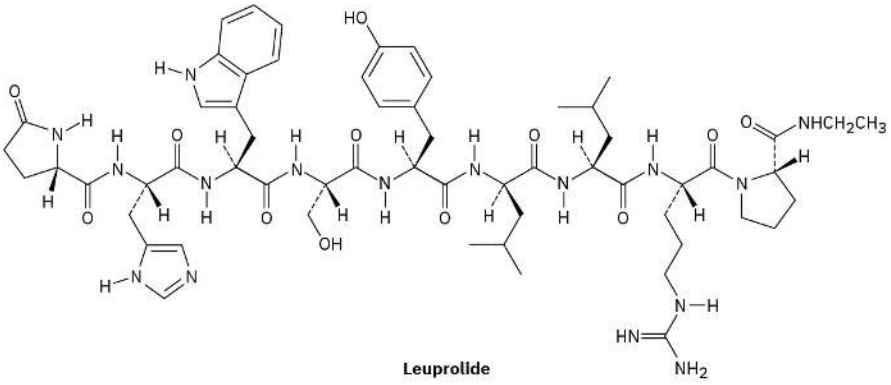
PROBLEM 12-42 Write full structures for the following peptides:

(a) C-H-E-M. (b) P-E-P-T-I-D-E

PROBLEM 12-48 Which of the following amino acids are more likely to be found on the exterior of a globular protein, and which on the interior? Explain.

(a) Valine (b) Aspartic acid (c) Phenylalanine (d) Lysine

PROBLEM 12-49 Leuprolide is a synthetic nonapeptide used to treat both endometriosis in women and prostate cancer in men.



Leuprolide

1. Both C-terminal and N-terminal amino acids in leuprolide have been structurally modified. Identify the modifications.
2. One of the nine amino acids in leuprolide has D stereochemistry rather than the usual L. Which one?
3. Write the structure of leuprolide using both one- and three-letter abbreviations.
4. What charge would you expect leuprolide to have at neutral pH?

PROBLEM 12-58 Aspartame, a non-nutritive sweetener marketed under such trade names as Equal, NutraSweet, and Canderel, is the methyl ester of a simple dipeptide, Asp-Phe-OCH_3.

1. Draw the structure of aspartame.
2. The isoelectric point of aspartame is 5.9. Draw the principal structure present in aqueous solution at this pH.
3. Draw the principal form of aspartame present at physiological pH = 7.3.

PROBLEM 12-54 Propose a structure for an octapeptide that shows the composition Asp, Gly_2, Leu, Phe, Pro_2, Val on amino acid analysis. Edman analysis shows a glycine N-terminal group, and leucine is the C-terminal group. Acidic hydrolysis gives the following fragments:

Val-Pro-Leu, Gly, Gly-Asp-Phe-Pro, Phe-Pro-Val

PROBLEM 12-57 Oxytocin, a nonapeptide hormone secreted by the pituitary gland, functions by stimulating uterine contraction and lactation during childbirth. Its sequence was determined from the following evidence:

1. Oxytocin is a cyclic compound containing a disulfide bridge between two cysteine residues.
2. When the disulfide bridge is reduced, oxytocin has the constitution Asn, Cys_2, Gln, Gly, Ile, Leu, Pro, Tyr.
3. Partial hydrolysis of reduced oxytocin yields seven fragments: Asp-Cys, Ile-Glu, Cys-Tyr, Leu-Gly, Tyr-Ile-Glu, Glu-Asp-Cys, and Cys-Pro-Leu.
4. Gly is the C-terminal group.

What is the primary structure of oxytocin?

Mechanism Problems (not required for our class)

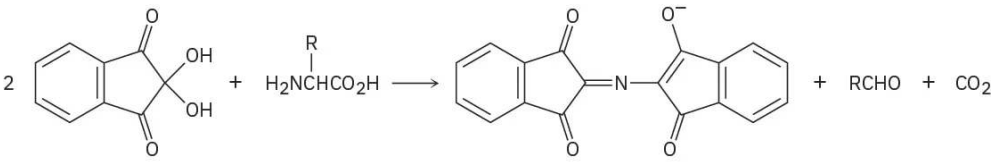
PROBLEM 12-24 The reaction of ninhydrin with an α-amino acid occurs in several steps.

(a) The first step is the formation of an imine by the reaction of the amino acid with ninhydrin. Show its structure and the mechanism of its formation.

(b) The second step is a decarboxylation. Show the structure of the product and the mechanism of the decarboxylation reaction.

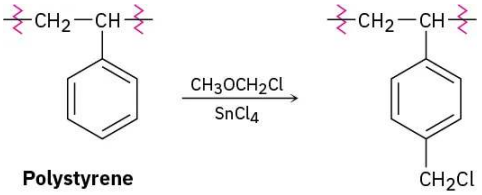
(c) The third step is hydrolysis of an imine to yield an amine and an aldehyde. Show the structures of both products and the mechanism of the hydrolysis reaction.

(d) The final step is the formation of the purple anion. Show the mechanism of the reaction.



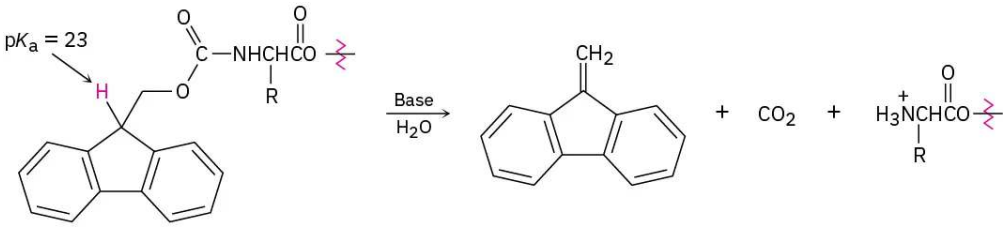
Ninhydrin

PROBLEM 12-25 The chloromethylated polystyrene resin originally used for Merrifield solid-phase peptide synthesis was prepared by treatment of polystyrene with chloromethyl methyl ether and a Lewis acid catalyst. Propose a mechanism for the reaction.



Polystyrene

PROBLEM 12-26 An Fmoc protecting group can be removed from an amino acid by treatment with the amine base piperidine. Propose a mechanism.



Fmoc-protected amino acid

PROBLEM 12-27 Proteins can be cleaved specifically at the amide bond on the carboxyl side of methionine residues by reaction with cyanogen bromide, BrC≡N.



The reaction occurs in several steps:

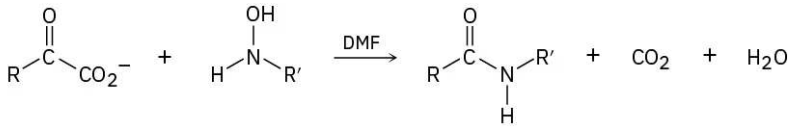
(a) The first step is a nucleophilic substitution reaction of the sulfur on the methionine side chain with BrCN to give a cyanosulfonium ion, $[R_2SCN]^+$. Show the structure of the product, and propose a mechanism for the reaction.

(b) The second step is an internal S_N2 reaction, with the carbonyl oxygen of the methionine residue displacing the positively charged sulfur leaving group and forming a five-membered ring product. Show the structure of the product and the mechanism of its formation.

(c) The third step is a hydrolysis reaction to split the peptide chain. The carboxyl group of the former methionine residue is now part of a lactone (cyclic ester) ring. Show the structure of the lactone product and the mechanism of its formation.

(d) The final step is a hydrolysis of the lactone to give the product shown. Show the mechanism of the reaction.

PROBLEM 12-28 A clever recent method of peptide synthesis involves the formation of an amide bond by the reaction of an α-keto acid with an *N*-alkylhydroxylamine:



An α-keto acid **A hydroxylamine** **An amide**

The reaction is thought to occur via nucleophilic addition of the *N*-alkylhydroxylamine to the keto acid, forming an oxime (Section 5.8), followed by decarboxylation and elimination of water. Show the mechanism.

Amino Acid Synthesis (not required for our class)

PROBLEM 12-36 Show how you could use the acetamidomalonate method to prepare the following amino acids:

(a) Leucine. (b) Tryptophan

PROBLEM 12-37 Show how you could prepare the following amino acids using a reductive amination:

(a) Methionine (b) Isoleucine

PROBLEM 12-38 Show how you could prepare the following amino acids enantioselectively:

(a) Pro. (b) Val

PROBLEM 12-39 Serine can be synthesized by a simple variation of the amidomalonate method using formaldehyde rather than an alkyl halide. How might this be done?

PROBLEM 12-42 Draw resonance forms for the purple anion obtained by reaction of ninhydrin with an α-amino acid (see Problem 12-24).

Peptides Synthesis and Reactions (not required for our class)

PROBLEM 12-43 Propose two structures for a tripeptide that gives Leu, Ala, and Phe on hydrolysis but does not react with phenyl isothiocyanate.

PROBLEM 12-44 Show the steps involved in a synthesis of Phe-Ala-Val using the Merrifield procedure.

PROBLEM 12-45 Draw the structure of the PTH derivative product you would obtain by Edman degradation of the following peptides:

(a) I-L-P-F. (b) D-T-S-G-A

PROBLEM 12-46 Which amide bonds in the following polypeptide are cleaved by trypsin? By chymotrypsin?

Phe-Leu-Met-Lys-Tyr-Asp-Gly-Gly-Arg-Val-Ile-Pro-Tyr

PROBLEM 12-47 What kinds of reactions do the following classes of enzymes catalyze?

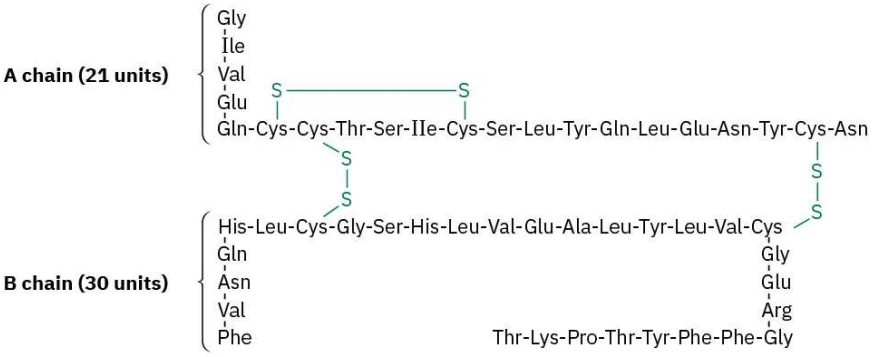
(a) Hydrolases (b) Lyases (c) Transferases

General Problems (not required for our class)

PROBLEM 12-50 The α-helical parts of myoglobin and other proteins stop whenever a proline residue is encountered in the chain. Why is proline never present in a protein α helix?

PROBLEM 12-52 Cytochrome *c* is an enzyme found in the cells of all aerobic organisms. Elemental analysis of cytochrome *c* shows that it contains 0.43% iron. What is the minimum molecular weight of this enzyme?

PROBLEM 12-55 Look at the structure of human insulin, and indicate where in each chain the molecule is cleaved by trypsin and chymotrypsin.



Insulin

PROBLEM 12-56 What is the structure of a nonapeptide that gives the following fragments when cleaved?

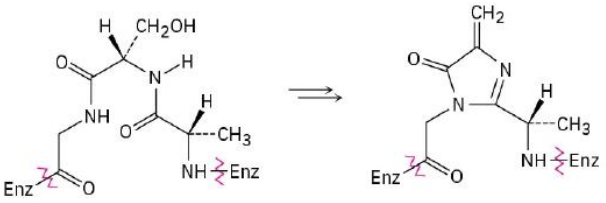
Trypsin cleavage: Val-Val-Pro-Tyr-Leu-Arg, Ser-Ile-Arg

Chymotrypsin cleavage: Leu-Arg, Ser-Ile-Arg-Val-Val-Pro-Tyr

PROBLEM 12-59 Refer to Figure 12.5 and propose a mechanism for the final step in Edman degradation—the acid-catalyzed rearrangement of the ATZ derivative to the PTH derivative.

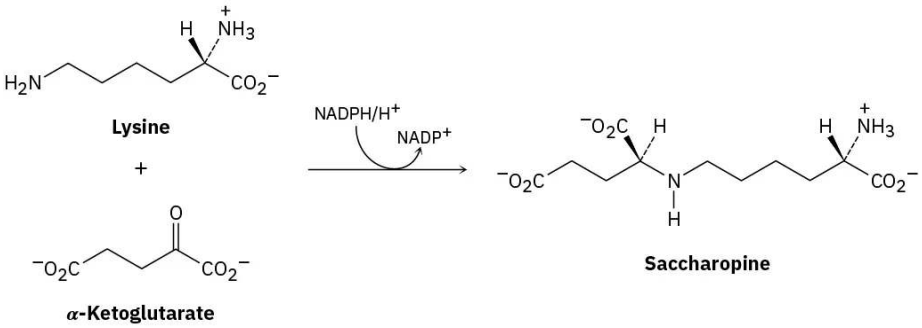
PROBLEM 12-60 Amino acids are metabolized by a transamination reaction in which the $-NH_2$ group of the amino acid changes places with the keto group of an α-keto acid. The products are a new amino acid and a new α-keto acid. Show the product from transamination of isoleucine.

PROBLEM 12-61 The first step in the biological degradation of histidine is the formation of a 4-methylidene-5-imidazolone (MIO) by cyclization of a segment of the peptide chain in the histidine ammonia lyase enzyme. Propose a mechanism.



4-Methylidene-5-imidazolone (MIO)

PROBLEM 12-62 The first step in the biological degradation of lysine is reductive amination with α-ketoglutarate to give saccharopine. Nicotinamide adenine dinucleotide phosphate (NADPH), a relative of NADH, is the reducing agent. Show the mechanism.



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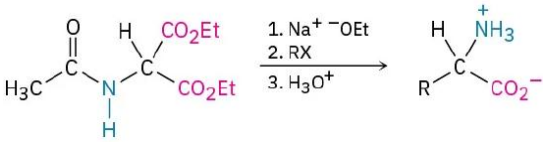
12.S: Biomolecules - Amino Acids (Summary)

1. Amino acid synthesis (Section 12.4)

   a. From α-bromo acids



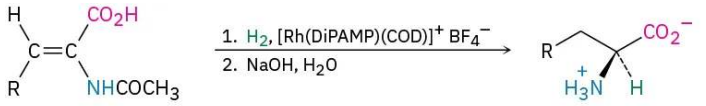
   b. Diethyl acetamidomalonate synthesis



   c. Reductive amination of an α-keto acid



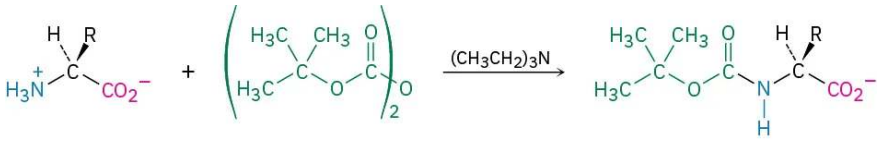
   d. Enantioselective synthesis



A (*Z*) enamido acid **An (*S*)-amino acid**

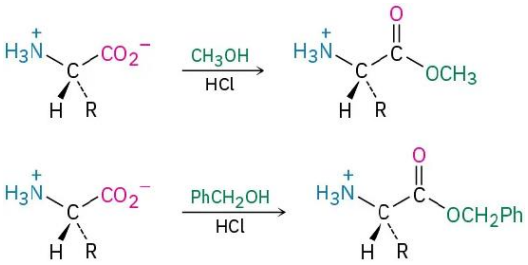
2. Peptide synthesis (Section 12.6)

   a. Amine protection



Boc-protected amino acid

   b. Carboxyl protection



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CHAPTER OVERVIEW

13: Biomolecules - Nucleic Acids

Learning Objectives

When you have completed Chapter 14, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. draw the structure of a given nucleotide.
3. discuss the structure of DNA and RNA.
4. describe the processes involved in DNA replication, transcription, translation, and protein synthesis.
5. define, and use in context, the key terms introduced in this chapter.

Two types of nucleic acids are found in cells—deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). These highly complex substances are built up from a number of simpler units, called nucleotides. Each nucleotide consists of three parts: a phosphoric acid residue, a sugar and a nitrogen-containing heterocyclic base. Thus, in order to understand the biochemistry of the nucleic acids, you must first study the chemistry of the sugars (see Chapter 11) and simple heterocyclic systems. We have already discussed certain aspects of the structure of heterocyclic ring systems during our study of aromaticity (Sections 3.5–3.6). You may find it helpful to review this chapter.

Chapter 14 examines the structure and replication of DNA and then describes the structure and synthesis of RNA. The chapter closes with a brief study of RNA's role in protein biosynthesis.

13.0: Why This Chapter?
13.1: Nucleotides and Nucleic Acids
13.2: Base Pairing in DNA - The Watson-Crick Model
13.3: Transcription of DNA
13.4: Translation of RNA - Protein Biosynthesis
13.5: Drugs and Infectious Diseases
13.6: Chemicals Against Cancer
13.7: Chemistry Matters—DNA Fingerprinting
13.8: Additional Problems
13.S: Biomolecules - Nucleic Acids (Summary)

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14.0: Why This Chapter?

Nucleic acids are the last of the four major classes of biomolecules we'll consider. So much has been written and spoken about DNA in the media that the basics of DNA replication and transcription are probably known to you. Thus, we'll move fairly quickly through the fundamentals and then look more closely at the chemical details of DNA sequencing, synthesis, and metabolism. This field is moving rapidly, and there's a lot you may not be familiar with.



Figure **14.0.1**: If these Afghan hounds look similar, that's because they're identical—all cloned from somatic cells of the same donor. (credit: modification of work "Figure 1" in "Birth of clones of the world's first cloned dog" by Kim, M.J., Oh, H.J., Kim, G.A. et al./*Sci Rep* 7, 15235 (2017), CC BY 4.0)

The nucleic acids, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), are the chemical carriers of a cell's genetic information. Coded in a cell's DNA is the information that determines the nature of the cell, controls its growth and division, and directs biosynthesis of the enzymes and other proteins required for cellular functions.

In addition to nucleic acids themselves, nucleic acid derivatives such as ATP are involved as phosphorylating agents in many biochemical pathways, and several important coenzymes, including NAD^+, FAD, and coenzyme A, have nucleic acid components.

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14.3: Nucleotides and Nucleic Acids

Objectives

The Learning Objective of this Module is to identify the different molecules that combine to form nucleotides.

After completing this section, you should be able to

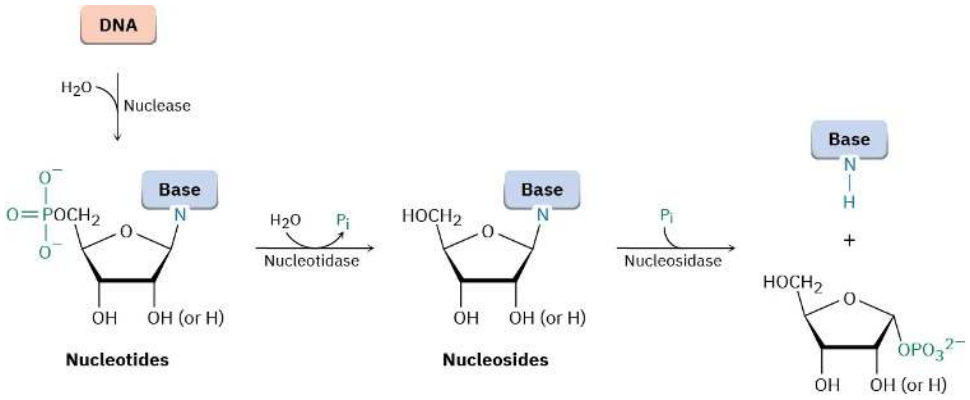
- outline the relationship between nucleic acids, nucleotides and nucleosides.
- identify, in general terms, the enzymatic hydrolysis products of nucleosides.
- explain the structural difference between the sugar components of DNA and RNA.
- identify by name the four heterocyclic amine bases found in deoxyribonucleotides.
- identify by name the four heterocyclic amine bases found in ribonucleotides.
- draw the general structure of a nucleotide and a nucleoside.
- indicate the nitrogen atom by which a given purine or pyrimidine base attaches to the sugar component in nucleotides and nucleosides.
- sketch a section of nucleic acid to show how the nucleotide units are joined together.

Key Terms

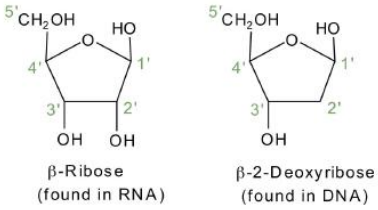
Make certain that you can define, and use in context, the key terms below.

- deoxyribonucleic acid (DNA)
- nucleosides nucleotides
- ribonucleic acid (RNA)

The repeating, or monomer, units that are linked together to form **nucleic acids** are known as **nucleotides**. The deoxyribonucleic acid (DNA) of a typical mammalian cell contains about 3×10^9 nucleotides. Nucleotides can be further broken down to a phosphate group (PO_4^{-3}) and a nucleoside which is composed of a aldopentose sugar (a sugar with five carbon atoms), and a heterocyclic purine or pyrimidine base (a base containing nitrogen atoms).



If the pentose sugar is ribose, the nucleotide is more specifically referred to as a *ribonucleotide*, and the resulting nucleosides are used in ribonucleic acid (RNA). If the sugar is 2-deoxyribose, the nucleotide is a *deoxyribonucleotide*, and the nucleoside are used in deoxyribonucleic acid (DNA). The prefix -deoxy implies that there is an oxygen missing from the 2' position of ribose.



The nitrogenous bases found in nucleotides are classified as pyrimidines or purines. Pyrimidines are heterocyclic amines with two nitrogen atoms in a six-member ring and include uracil, thymine, and cytosine. Purines are heterocyclic amines consisting of a pyrimidine ring fused to a five-member ring with two nitrogen atoms. Adenine and guanine are the major purines found in nucleic acids (Figure **14.3.1**). The numbering convention is that primed numbers designate the atoms of the pentose ring, and unprimed numbers designate the atoms of the purine or pyrimidine ring.

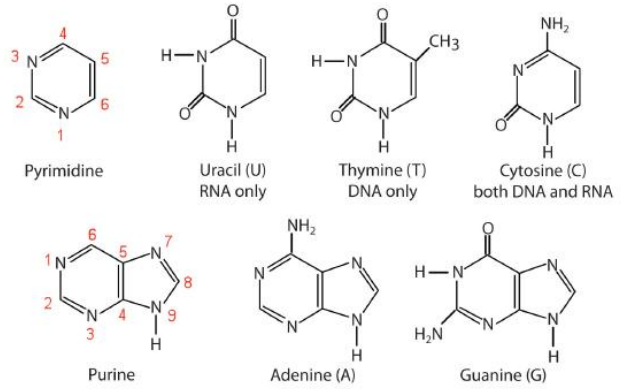


Figure **14.3.1**: The Nitrogenous Bases Found in DNA and RNA

Nucleosides vs Nucleotides

Nucleosides are formed by a bond between the anomeric C1′ of the pentose sugar and N1 position of the pyrimidine base or the N9 position of the purine base. The addition of a phospate groups at the 5' position of a nucleoside creates a corresponding nucleotide. DNA is made from four deoxyribonucleotides (Cytosine, Thymine, Adenine, Guanine) and RNA is made from four ribonucleotides Cytosine, Uracil, Adenine, Guanine. The names and structures of the major ribonucleotides and deoxyribonucleotides are given in Figure **14.3.2**.

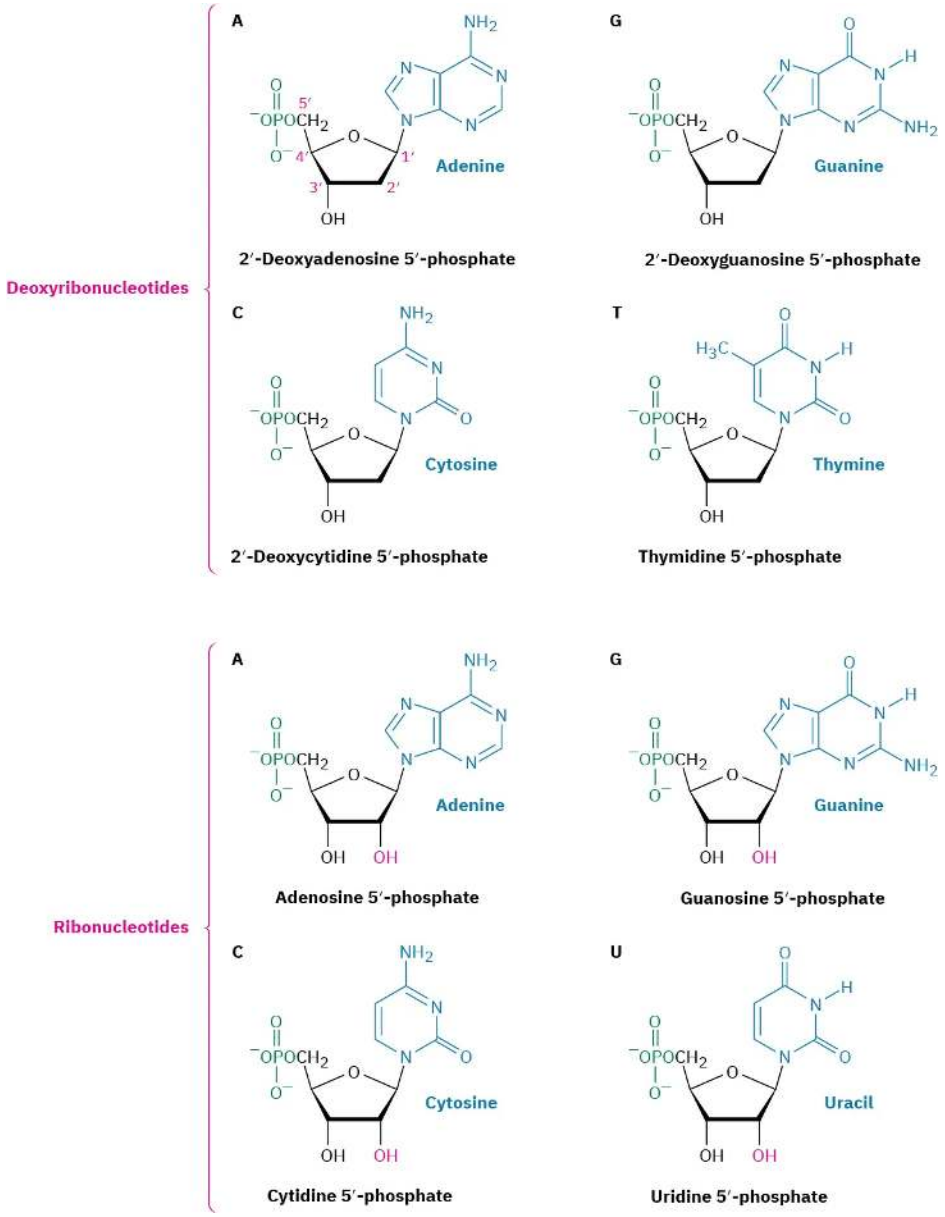


Figure **14.3.2**: Structures of the four deoxyribonucleotides and the four ribonucleotides.

Apart from being the monomer units of DNA and RNA, the nucleotides and some of their derivatives have other functions as well. Adenosine diphosphate (ADP) and adenosine triphosphate (ATP), shown in Figure **14.3.3**, have a role in cell metabolism. Moreover, a number of coenzymes, including flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD^+), and coenzyme A, contain adenine nucleotides as structural components.

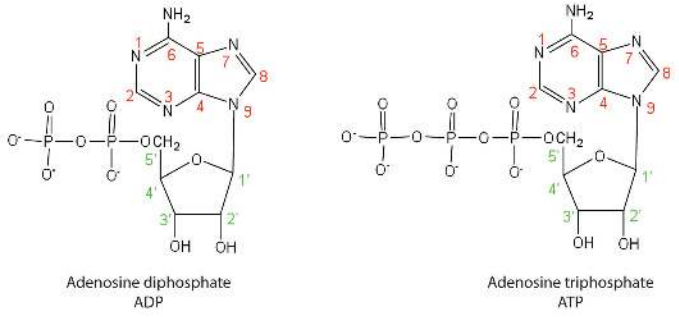


Figure **14.3.3**: Structures of Two Important Adenine-Containing Nucleotides

Primary Structure of Nucleic Acids

Nucleotides are joined together through the phosphate group of one nucleotide connecting in an ester linkage to the OH group on the 3' carbon atom of the sugar unit of a second nucleotide. This unit joins to a third nucleotide, and the process is repeated to produce a long nucleic acid chain (Figure 28.1.4). The backbone of the chain consists of alternating phosphate and sugar units (2-deoxyribose in DNA and ribose in RNA). The purine and pyrimidine bases branch off this backbone.

Like proteins, nucleic acids have a primary structure that is defined as the sequence of their nucleotides. Unlike proteins, which have 20 different kinds of amino acids, there are only 4 different kinds of nucleotides in nucleic acids. For amino acid sequences in proteins, the convention is to write the amino acids in order, starting with the N-terminal amino acid. In writing nucleotide sequences for nucleic acids, the convention is to write the nucleotides (usually using the one-letter abbreviations for the bases, shown in Figure \(\PageIndex{4}\)) starting with the nucleotide having a free phosphate group, which is known as the 5′ end, and indicate the nucleotides in order. For DNA, a lowercase *d* is often written in front of the sequence to indicate that the monomers are deoxyribonucleotides. The final nucleotide has a free OH group on the 3′ carbon atom and is called the *3′ end*. The sequence of nucleotides in the DNA segment shown in Figure **14.3.4** would be written 5′-dG-dT-dA-dC-3′, which is often further abbreviated to dGTAC or just GTAC.

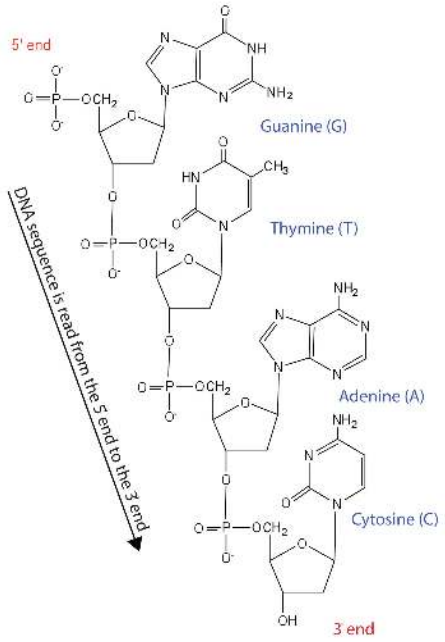


Figure **14.3.4**: Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2′, and uracil would replace thymine.

Note

Each phosphate group has one acidic hydrogen atom that is ionized at physiological pH. This is why these compounds are known as nucleic acids.

Study Notes

The five bases that are found in nucleotides are often represented by their initial letter: adenine, A; guanine, G; cytosine, C; thymine, T; and uracil, U. Note that A, G, C and T occur in DNA; A, G, C and U occur in RNA. You are not required to memorize the structures of these bases, but you must know how each one bonds to the sugar unit in a nucleotide.

To fulfill Objective 6, you should be able to reproduce the figure below.

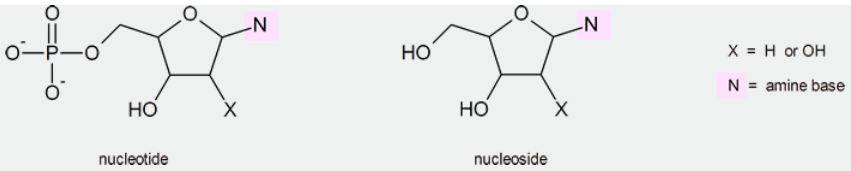


Figure **14.3.5** The Pyrimidine and Purine Nucleotides below.

? Exercise 14.3.1

Classify each compound as a pentose sugar, a purine, or a pyrimidine.

a. Adenine. b. guanine. c. deoxyribose. d. thymine. e. ribose. f. cytosine

Answer

a. purine. b. purine. c. pentose sugar. d. pyrimidine. e. pentose sugar. f. pyrimidine

? Exercise 14.3.2

Identify the three molecules needed to form the nucleotides in each nucleic acid.

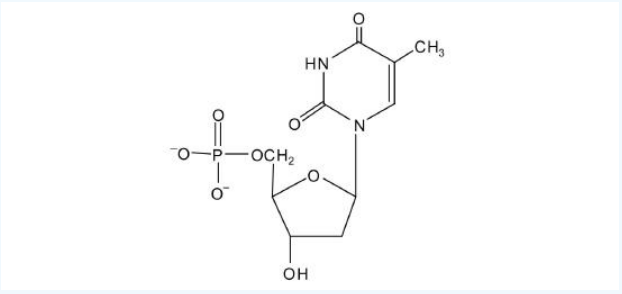
a. DNA
b. RNA

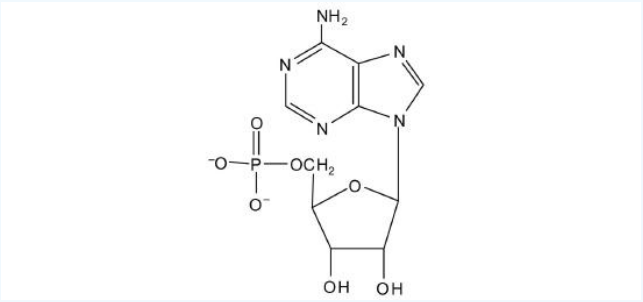
Answer

a. nitrogenous base (adenine, guanine, cytosine, and thymine), 2-deoxyribose, and H_3PO_4
b. nitrogenous base (adenine, guanine, cytosine, and uracil), ribose, and H_3PO_4

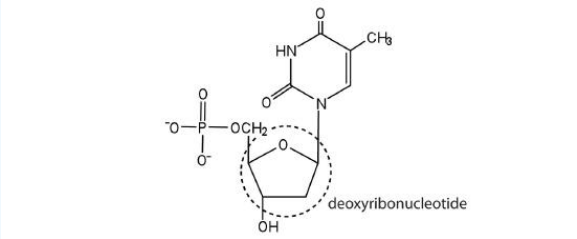
? Exercise 14.3.3

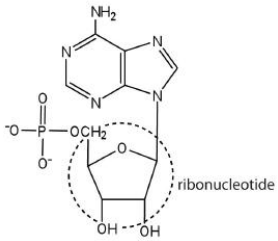
For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

a. 

b. 

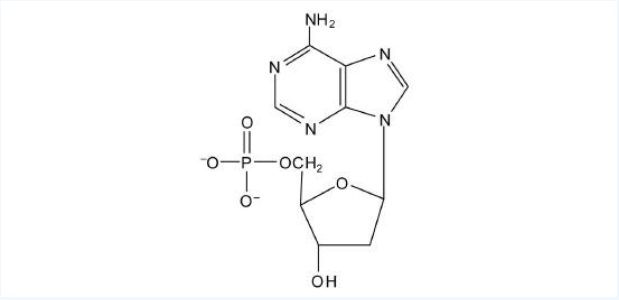
Answer

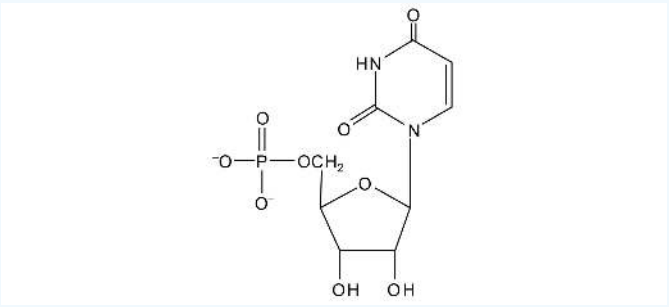
a. 

b. 

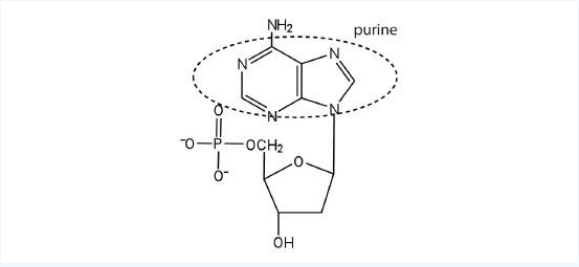
Exercise 14.3.4

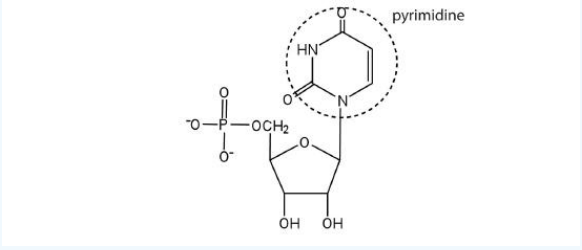
For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 

b. 

Answer

a. 

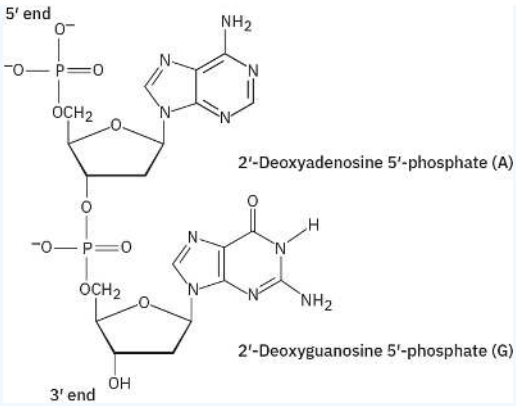
b. 

Exercise 14.3.5

Draw the full structure of the DNA dinucleotide AG.

Answer

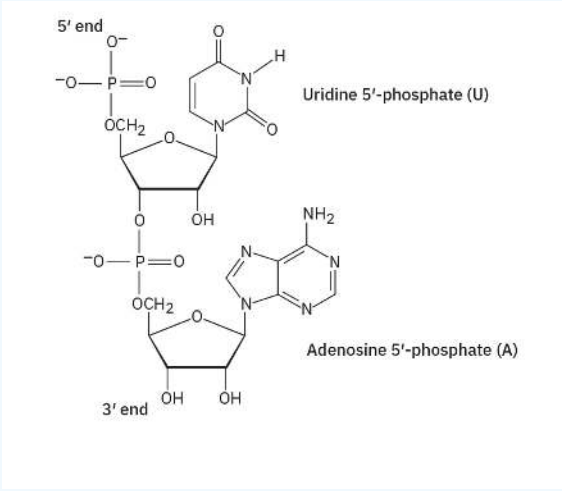
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Exercise 14.3.6

Draw the full structure of the RNA dinucleotide UA.

Answer



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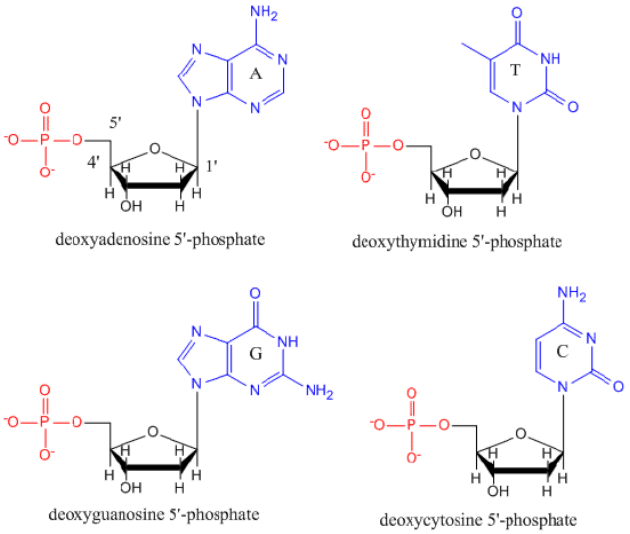
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14.1: Base Pairing in DNA - The Watson-Crick Model

Objectives

After completing this section, you should be able, given the necessary Kekulé structures, to show how hydrogen bonding can occur between thymine and adenine, and between guanine and cytosine; and to explain the significance of such interactions to the primary and secondary structures of DNA.

The nucleic acids RNA and DNA are involved in the storage and expression of genetic information in a cell. Both are polymers of monomeric nucleotides. DNA exists in the cell as double-stranded helices, while RNA typically is a single-stranded molecule that can fold in 3D space to form complex secondary (double-stranded helices) and tertiary structures in a fashion similar to proteins. The complex 3D structures formed by RNA allow it to perform functions other than simple genetic information storage, such as catalysis. Hence, most scientists believe that RNA preceded both DNA and proteins in evolution as it can both store genetic information and catalyze chemical reactions.



Intermolecular Forces in Nucleic Acids

In 1950, Erwin Chargaff of Columbia University showed that the molar amount of adenine (A) in DNA was always equal to that of thymine (T). Similarly, he showed that the molar amount of guanine (G) was the same as that of cytosine (C). Chargaff's findings clearly indicate that some heterocyclic amine base pairing exists in the DNA structure. In double-stranded DNA, the guanine (G) base on one strand can form three H-bonds with a cytosine (C) base on another strand (this is called a GC base pair). The thymine (T) base on one strand can form two H-bonds with an adenine (A) base on the other strand (this is called an AT base pair). Double-stranded DNA has a regular geometric structure with a fixed distance between the two backbones. This requires the bases to consist of one base with a two-ring (bicyclic) structure (these bases are called purines) and one with a single-ring structure (these bases are called pyrimidines). Hence, a G and A or a T and C are not possible base pair partners. This complementary base-pairing thus explains why A and T are always found in equal amounts, as are G and C.

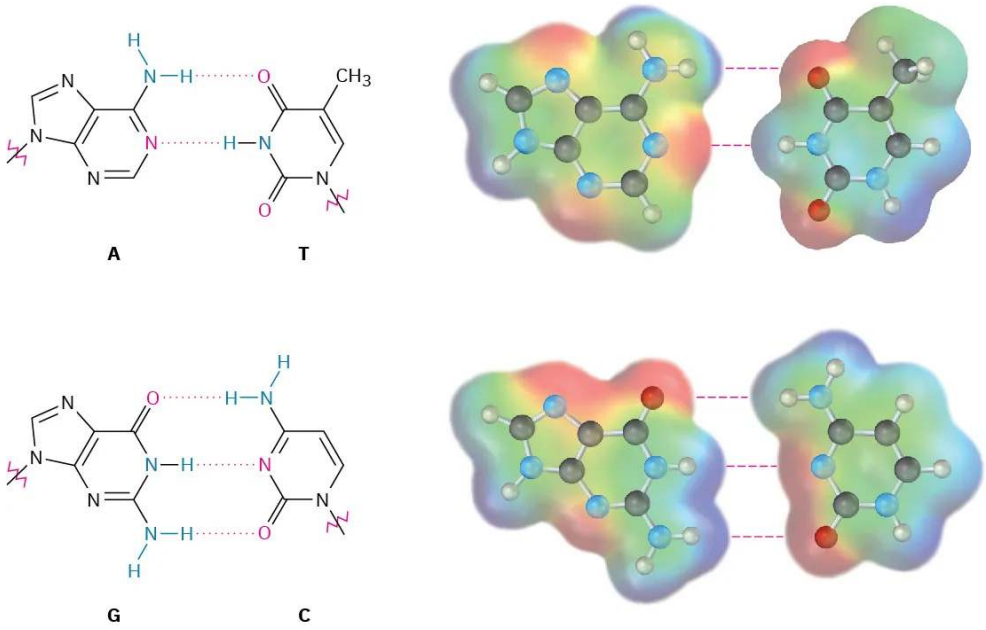
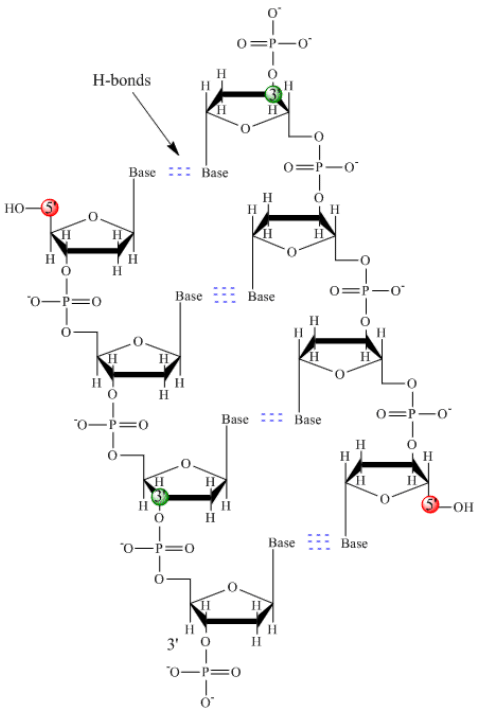


Figure **14.1.1**: Hydrogen-bonding between base pairs in the DNA double helix. Electrostatic potential maps show that the faces of the bases are relatively **neutral**, while the edges have **positive** and **negative** regions. Pairing G with C and A with T brings together oppositely charged regions.

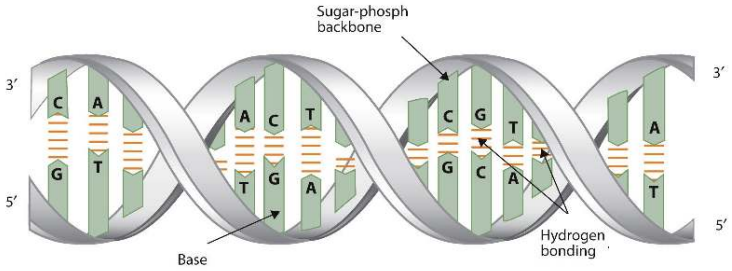
DNA

DNA is a polymer, consisting of monomers called deoxynucleotides. The monomer contains a simple sugar (deoxyribose, shown in black above), a phosphate group (in red), and a cyclic organic R group (in blue) that is analogous to the side chain of an amino acid. Only four bases are used in DNA (in contrast to the 20 different side chains in proteins), which we will abbreviate, for simplicity, as A, G, C, and T. They are bases since they contain amine groups that can accept protons. The polymer consists of a sugar - phosphate - sugar - phosphate backbone, with one base attached to each sugar molecule. As with proteins, the DNA backbone is polar but also charged. It is a polyanion. The bases, analogous to the side chains of amino acids, are predominantly polar. Given the charged nature of the backbone, you might expect that DNA does not fold to a compact globular (spherical) shape, even if positively charged cations like Mg bind to and stabilize the charge on the polymer. Instead, DNA usually exists as a double-stranded (ds) structure with the sugar-phosphate backbones of the two different strands running in opposite directions (5'-3' and the other 3'-5'). The strands are held together by hydrogen bonds between bases on complementary strands. Hence, like proteins, DNA has secondary structure, but in this case, the hydrogen bonds are not within the backbone but between the "side chain" bases on opposing strands. It is actually a misnomer to call dsDNA a molecule, since it really consists of two different, complementary strands held together by hydrogen bonds. A structure of ds-DNA showing the opposite polarity of the strands is shown below.



Secondary Structure of DNA

The three-dimensional structure of DNA was the subject of an intensive research effort in the late 1940s to early 1950s. DNA exists as a double-stranded molecule that twists around its axis to form a helical structure,stabilized through Watson-Crick hydrogen bonding between purines and pyrimidines, and through pi-pi stacking interactions among the bases arranged in structure. helical column. Each strand is a complement to the other; the nucleotides on one strand hydrogen-bond with complementary nucleotides on the opposite strand—that is, side-by-side with the 5′ end of one chain next to the 3′ end of the other. The purine and pyrimidine bases face the inside of the helix, with guanine always opposite cytosine and adenine always opposite thymine. The double helical "twist" occurs because of the angular geometry of each bonded nucleotide.



Initial work revealed the DNA polymer had a regular repeating pattern X-ray diffraction data shows that a repeating helical pattern is 20 Angstrom units wide and occurs every 34 Angstrom units with 10 nucleotide subunits per turn. Each subunit occupies 3.4 Angstrom units which is the same amount of space occupied by a single nucleotide unit. The helix is Under most conditions, the two strands are slightly offset, which creates a 12 Angstrom major groove on one face of the double helix, and a 6 Angstrom minor groove on the other. The overall DNA polymer varies in length (number of sugar-phosphate units connected), base composition (how many of each set of bases), and sequence (the order of the bases in the backbone).

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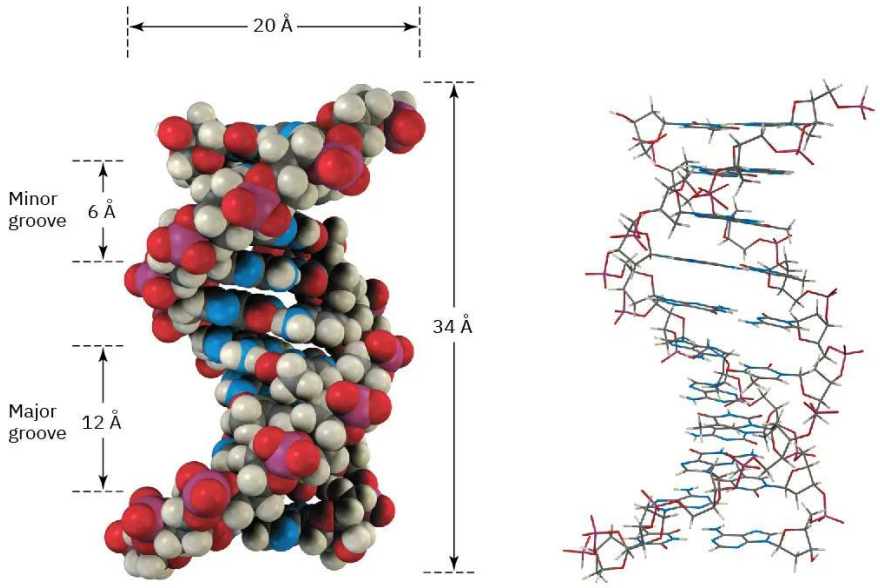


Figure **14.1.2**: A turn of the DNA double helix in both space-filling and wire-frame formats. The sugar–phosphate backbone runs along the outside of the helix, and the amine bases hydrogen bond to one another on the inside. Both major and minor grooves are visible.

Notice in Figure **14.1.2** that the major groove is slightly deeper than the minor groove, and both are lined by flat heterocyclic bases. As a result, a variety of other polycyclic aromatic molecules are able to slip sideways, or *intercalate*, between the stacked bases. Many cancer-causing and cancer-preventing agents function by interacting with DNA in this way.

An organism's genetic information is stored as a sequence of deoxyribonucleotides strung together in the DNA chain. For the information to be preserved and passed on to future generations, a mechanism must exist for copying DNA. For the information to be used, a mechanism must exist for decoding the DNA message and implementing the instructions it contains.

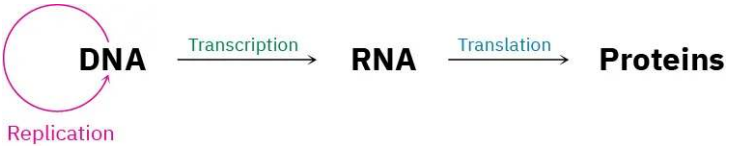
What do we mean when we say information is encoded in the DNA molecule? An organism's DNA can be compared to a book containing directions for assembling a model airplane or for knitting a sweater. Letters of the alphabet are arranged into words, and these words direct the individual to perform certain operations with specific materials. If all the directions are followed correctly, a model airplane or sweater is produced.

In DNA, the particular sequences of nucleotides along the chains encode the directions for building an organism. Just as *saw* means one thing in English and *was* means another, the sequence of bases CGT means one thing, and TGC means something different. Although there are only four letters—the four nucleotides—in the genetic code of DNA, their sequencing along the DNA strands can vary so widely that information storage is essentially unlimited.

Deoxyribonucleic acid (DNA) stores genetic information, while ribonucleic acid (RNA) is responsible for transmitting or expressing genetic information by directing the synthesis of thousands of proteins found in living organisms. But how do the nucleic acids perform these functions?

Three processes are required:

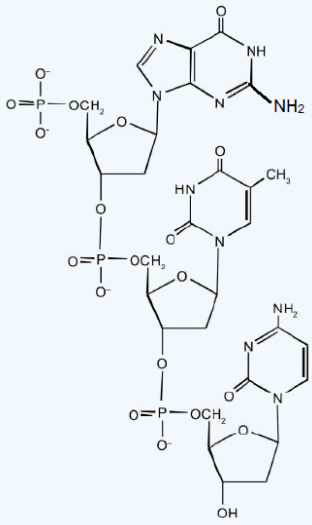
1. ***Replication***, in which new copies of DNA are made.
2. ***Transcription***, in which a segment of DNA is used to produce RNA.
3. ***Translation***, in which the information in RNA is translated into a protein sequence.



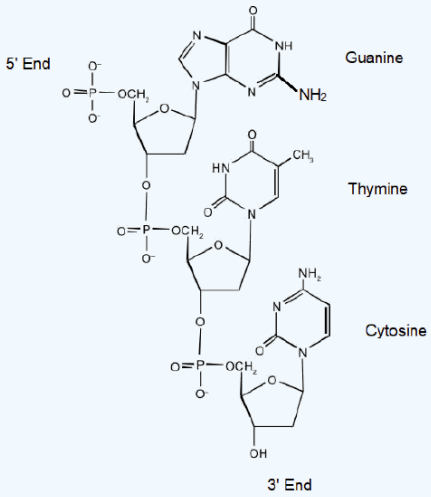
Exercise 14.1.1

For this short DNA segment,

a. Identify the 5′ end and the 3′ end of the molecule.
b. Circle the atoms that comprise the backbone of the nucleic acid chain.
c. Write the nucleotide sequence of this DNA segment.



Answer



Exercise 14.1.2

Which nitrogenous base in DNA pairs with each listed nitrogenous base?

a. Cytosine
b. Adenine
c. Guanine
d. Thymine

Answer

a. Guanine
b. Thymine

c. Cytosine
d. Adenine

? Exercise 14.1.3

How many hydrogen bonds can form between the two strands in the short DNA segment shown below?

5′ ATGCGACTA 3′ 3′ TACGCTGAT 5′

Answer

22 (2 between each AT base pair and 3 between each GC base pair).

? Exercise 14.1.4

A segment of one strand from a DNA molecule has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

Answer

Knowing that the two strands are antiparallel and that T base pairs with A, while C base pairs with G, the sequence of the complementary strand will be 3′-AGGTACTCAACT-5′ (can also be written as TCAACTCATGGA).

Study Notes

Watson and Crick received the Nobel Prize in 1962 for elucidating the structure of DNA and proposing the mechanism for gene reproduction. Their work rested heavily on X-ray crystallographic work done on RNA and DNA by Franklin and Wilkins. Wilkins shared the Nobel Prize with Watson and Crick, but Franklin had been dead four years at the time of the award (you cannot be awarded the Nobel Prize posthumously).

The history of Watson and Crick's proposed DNA model is controversial and a travesty of scientific ethics. Rosalind Franklin was deeply involved in the determination of the structure of DNA, and had collected numerous diffraction patterns. Watson attended a departmental colloquium at King's College given by Franklin, and came into possession of an internal progress report she had written. Both departmental colloquia and progress reports are merely methods of discussion between colleagues; works presented in these fora are not considered by scientists to be "published" works, and therefore are not in the public domain. Watson and Crick not only were aware of Franklin's work, but used her unpublished data, presented in confidence within her own college.

The final blow came about a year after the colloquium. Watson visited Wilkins at King's College, and Wilkins inexplicably handed over Franklin's diffraction photographs without her consent. Had Franklin's work not been secretly taken from her, she might quite possibly have solved the DNA structure before Watson and Crick, who at the time did not yet have their own photographs. This is truly one of the sadder episodes of questionable scientific ethics and discovery that I have ever encountered.

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Maddox, B. Rosalind Franklin: The Dark Lady of DNA. New York: HarperCollins, 2002.

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13.3: Transcription of DNA

As noted previously, RNA is structurally similar to DNA but contains ribose rather than deoxyribose and uracil rather than thymine. RNA has three major types, each of which serves a specific purpose. In addition, there are a number of small RNAs that appear to control a wide variety of important cellular functions. All RNA molecules are much smaller than DNA, and all remain single-stranded rather than double-stranded.

- Messenger RNA (mRNA) carries genetic messages from DNA to ribosomes, small granular particles in the cytoplasm of a cell where protein synthesis takes place.
- Ribosomal RNA (rRNA) complexed with protein provides the physical makeup of the ribosomes.
- Transfer RNA (tRNA) transports amino acids to the ribosomes, where they are joined together to make proteins.
- Small RNAs, also called **functional RNAs**, have a variety of functions within the cell, including silencing transcription and catalyzing chemical modifications of other RNA molecules.

The genetic information in DNA is contained in segments called genes, each of which consists of a specific nucleotide sequence that encodes a specific protein. The conversion of that information from DNA into proteins begins in the nucleus of cells with the synthesis of mRNA by transcription of DNA. In bacteria, the process begins when RNA polymerase recognizes and binds to a *promoter sequence* on DNA, typically consisting of around 40 base pairs located upstream (5′) of the transcription start site. Within the promoter are two hexameric *consensus sequences*, one located 10 base pairs upstream of the start and the second located 35 base pairs upstream.

Following formation of the polymerase–promoter complex, several turns of the DNA double helix untwist, forming a bubble and exposing 14 or so base pairs of the two strands. Appropriate ribonucleotides then line up by hydrogen-bonding to their complementary bases on DNA, bond formation occurs in the 5′ → 3′ direction, the RNA polymerase moves along the DNA chain, and the growing RNA molecule unwinds from DNA (Figure 13.3.1). At any one time, about 12 base pairs of the growing RNA remain hydrogen-bonded to the DNA template.

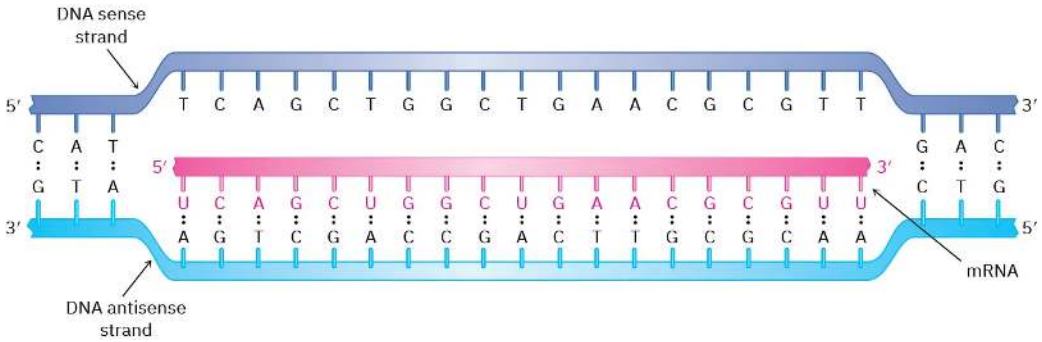


Figure 13.3.1: Biosynthesis of RNA using a DNA segment as a template.

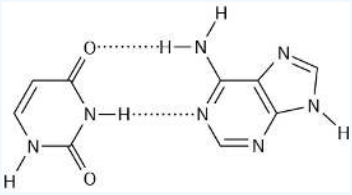
Unlike what happens in DNA replication, where both strands are copied, only one of the two DNA strands is transcribed into mRNA. The DNA strand that contains the gene is often called the sense strand, or *coding strand*, and the DNA strand that gets transcribed to give RNA is called the antisense strand, or *noncoding strand.* Because the sense strand and the antisense strand in DNA are complementary, and because the DNA antisense strand and the newly formed RNA strand are also complementary, the RNA molecule produced during transcription is a copy of the DNA sense strand. That is, the complement of the complement is the same as the original. The only difference is that the RNA molecule has a U everywhere that the DNA sense strand has a T.

Another part of the picture in vertebrates and flowering plants is that genes are often not continuous segments of the DNA chain. Instead, a gene will begin in one small section of DNA called an *exon*, then be interrupted by a noncoding section called an *intron*, and then take up again farther down the chain in another exon. The final mRNA molecule results only after the noncoded sections are cut out of the transcribed mRNA and the remaining pieces are joined together by spliceosome enzymes. The gene for triose phosphate isomerase in maize, for instance, contains eight noncoding introns accounting for approximately 70% of the DNA base pairs and nine coding exons accounting for only 30% of the base pairs.

Exercise 13.3.1

Show how uracil can form strong hydrogen bonds to adenine.

Answer



Exercise 13.3.2

What RNA base sequence is complementary to the following DNA base sequence?

(5′) GATTACCGTA (3′)

Answer

(3′) CUAAUGGCAU (5′)

Exercise 13.3.3

From what DNA base sequence was the following RNA sequence transcribed?

(5′) UUCGCAGAGU (3′)

Answer

(5′) ACTCTGCGAA (3′)

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13.4: Translation of RNA - Protein Biosynthesis

The primary cellular function of mRNA is to direct the biosynthesis of the thousands of diverse peptides and proteins required by an organism—as many as 150,000 in a human. The mechanics of protein biosynthesis take place on ribosomes, small granular particles in the cytoplasm of a cell that consist of about 60% ribosomal RNA and 40% protein.

The specific ribonucleotide sequence in mRNA forms a message that determines the order in which amino acid residues are to be joined. Each "word," or codon, along the mRNA chain consists of a sequence of three ribonucleotides that is specific for a given amino acid. For example, the series UUC on mRNA is a codon directing incorporation of the amino acid phenylalanine into the growing protein. Of the $4^3 = 64$ possible triplets of the four bases in RNA, 61 code for specific amino acids and 3 code for chain termination. Table 13.4.1 shows the meaning of each codon.

Table 13.4.1: Codon Assignments of Base Triplets

		Third base (3′ end)			
First base (5′ end)	Second base	U	C	A	G
U	U	Phe	Phe	Leu	Leu
	C	Ser	Ser	Ser	Ser
	A	Tyr	Tyr	Stop	Stop
	G	Cys	Cys	Stop	Trp
C	U	Leu	Leu	Leu	Leu
	C	Pro	Pro	Pro	Pro
	A	His	His	Gln	Gln
	G	Arg	Arg	Arg	Arg
A	U	Ile	Ile	Ile	Met
	C	Thr	Thr	Thr	Thr
	A	Asn	Asn	Lys	Lys
	G	Ser	Ser	Arg	Arg
G	U	Val	Val	Val	Val
	C	Ala	Ala	Ala	Ala
	A	Asp	Asp	Glu	Glu
	G	Gly	Gly	Gly	Gly

The message embedded in mRNA is read by transfer RNA (tRNA) in a process called translation. There are 61 different tRNAs, one for each of the 61 codons that specify an amino acid. A typical tRNA is single-stranded and has roughly the shape of a cloverleaf, as shown in Figure 13.4.1. It consists of about 70 to 100 ribonucleotides and is bonded to a specific amino acid by an ester linkage through the 3′ hydroxyl on ribose at the 3′ end of the tRNA. Each tRNA also contains on its middle leaf a segment called an anticodon, a sequence of three ribonucleotides complementary to the codon sequence. For example, the codon sequence UUC present on mRNA is read by a phenylalanine-bearing tRNA having the complementary anticodon base sequence GAA. [Remember that nucleotide sequences are written in the 5′ → 3′ direction, so the sequence in an anticodon must be reversed. That is, the complement to (5′)-UUC-(3′) is (3′)-AAG-(5′), which is written as (5′)-GAA-(3′).]

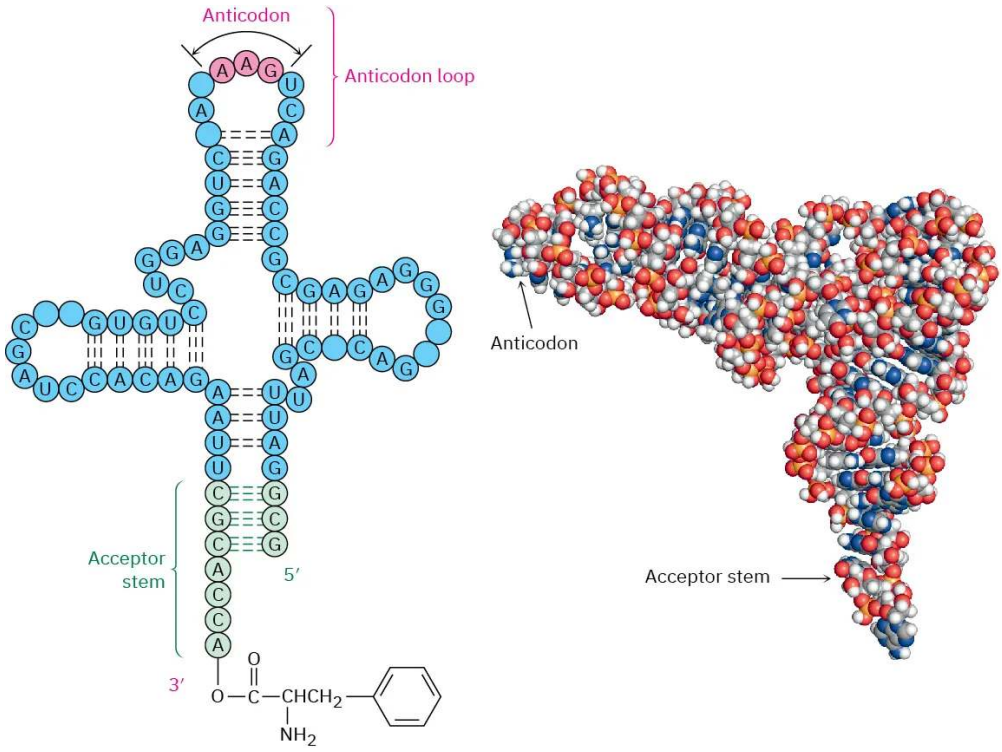


Figure 13.4.1: Structure of a tRNA molecule. The tRNA is a roughly cloverleaf-shaped molecule containing an anticodon triplet on one "leaf" and an amino acid unit attached covalently at its 3′ end. The example shown is a yeast tRNA that codes for phenylalanine. The nucleotides not specifically identified are chemically modified analogs of the four common nucleotides.

As each successive codon on mRNA is read, different tRNAs bring the correct amino acids into position for enzyme-mediated transfer to the growing peptide. When synthesis of the proper protein is completed, a "stop" codon signals the end, and the protein is released from the ribosome. This process is illustrated in Figure 13.4.2.

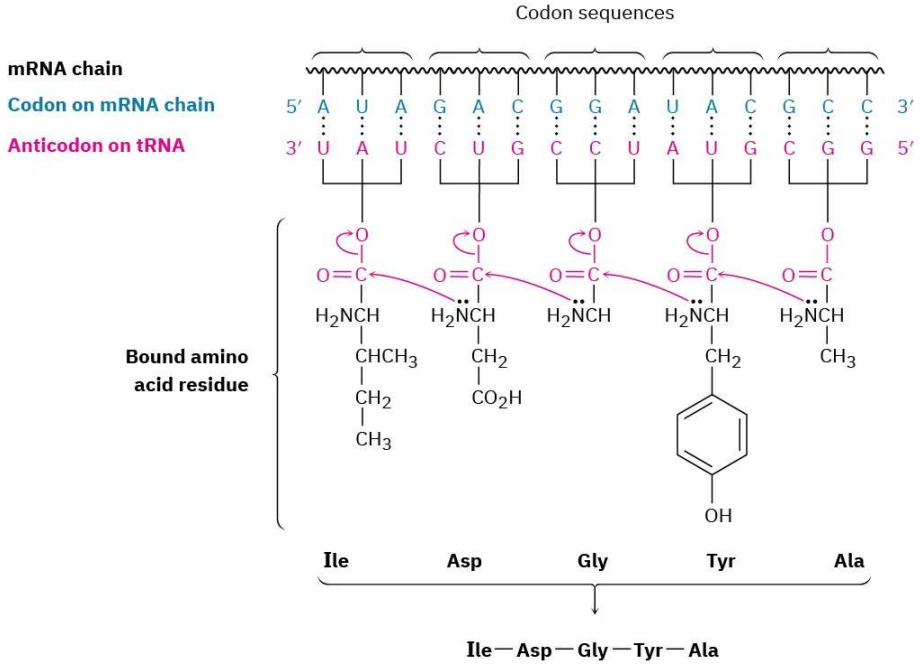


Figure 13.4.2: A representation of protein biosynthesis. The codon base sequences on mRNA are read by tRNAs containing complementary anticodon base sequences. Transfer RNAs assemble the proper amino acids into position for incorporation into the growing peptide.

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Worked Example 13.4.1: Predicting the Amino Acid Sequence Transcribed from DNA

What amino acid sequence is coded by the following segment of a DNA coding strand (sense strand)?

(5′) CTA-ACT-AGC-GGG-TCG-CCG (3′)

Strategy

The mRNA produced during translation is a copy of the DNA coding strand, with each T replaced by U. Thus, the mRNA has the sequence

(5′) CUA-ACU-AGC-GGG-UCG-CCG (3′)

Each set of three bases forms a codon, whose meaning can be found in Table 13.4.1.

Solution

Leu-Thr-Ser-Gly-Ser-Pro.

Exercise 13.4.1

Add exercises text here.

a. Ala
b. Phe
c. Leu
d. Tyr

Answer

a. GCU, GCC, GCA, GCG
b. UUU, UUC
c. UUA, UUG, CUU, CUC, CUA, CUG
d. UAU, UAC

Exercise 13.4.2

List anticodon sequences on the tRNAs carrying the following amino acids.

a. Ala
b. Phe
c. Leu
d. Tyr

Answer

a. AGC, GGC, UGC, CGC
b. AAA, GAA
c. UAA, CAA, GAA, GAG, UAG, CAG
d. AUA, GUA

Exercise 13.4.3

What amino acid sequence is coded by the following mRNA base sequence?

CUU-AUG-GCU-UGG-CCC-UAA

Answer

Leu-Met-Ala-Trp-Pro-Stop

Exercise 13.4.4

What is the base sequence in the original DNA strand on which the mRNA sequence in Problem 28-9 was made?

Answer

(5′) TTA-GGG-CCA-AGC-CAT-AAG (3′)

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13.5: Drugs and Infectious Diseases

Learning Objectives

- Differentiate between antibiotics and antiviral agents.
- Know the different antibiotics and antiviral agents and their mode of action.

The World Health Organization's (WHO) International Classification of Diseases (ICD) is used in clinical fields to classify diseases and monitor morbidity (the number of cases of a disease) and mortality (the number of deaths due to a disease). In this section, we will introduce terminology used by the ICD (and in health-care professions in general) to describe and categorize various types of disease.

An **infectious disease** is any disease caused by the direct effect of a pathogen. A pathogen may be cellular (bacteria, parasites, and fungi) or acellular (viruses, viroids, and prions). Some infectious diseases are also communicable, meaning they can be spread from person to person through direct or indirect contact. Some infectious communicable diseases are also considered contagious diseases, meaning they are easily spread from person to person. Not all contagious diseases are equally so; the degree to which a disease is contagious usually depends on how the pathogen is transmitted. For example, measles is a highly contagious viral disease that can be transmitted when an infected person coughs or sneezes and an uninfected person breathes in droplets containing the virus. Gonorrhea is not as contagious as measles because transmission of the pathogen (*Neisseria gonorrhoeae*) requires close intimate contact (usually sexual) between an infected person and an uninfected person.

Antibiotics

The modern era of the chemotherapy of infection started with the clinical use of sulfanilamide in 1936. The "golden age" of antimicrobial therapy began with the production of penicillin in 1941, when this compound was mass-produced and first made available for limited clinical trial. More than 30% of all hospitalized patients now receive one or more courses of therapy with antibiotics, and millions of potentially fatal infections have been cured. However, at the same time, these pharmaceutical agents have become among the most misused of those available to the practicing physician. One result of widespread use of antimicrobial agents has been the emergence of antibiotic-resistant pathogens, which in turn has created an ever-increasing need for new drugs. Many of these agents have also contributed significantly to the rising costs of medical care.

An antibiotic is any substance produced by a microorganism that is excreted to harm or kill another microorganism. Technically, antibiotics are microbial or fungal products. But these substances can be synthesized and mass produced in the laboratory to use against harmful microorganisms in the environment. Thus, the synthetic chemist has added greatly to our therapeutic armamentarium. Synthetic drugs such as isonaizid and theambutol represent important contributions for the treatment of tuberculosis. While many such antimicrobial agents are not properly termed antibiotics, since they are not produced by living organisms, little distinction should now be made between compounds of natural and synthetic origin.

Synthetic Antibiotics - Sulfonamides

Sulfonamide is the basis of several groups of drugs. The original antibacterial sulfonamides (sometimes called sulfa drugs or sulpha drugs) are synthetic antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based on the antibacterial sulfonamides.

Sulfa allergies are common, and medications containing sulfonamides are prescribed carefully. It is important to make a distinction between sulfa drugs and other sulfur-containing drugs and additives, such as sulfates and sulfites, which are chemically unrelated to the sulfonamide group and do not cause the same hypersensitivity reactions seen in the sulfonamides.

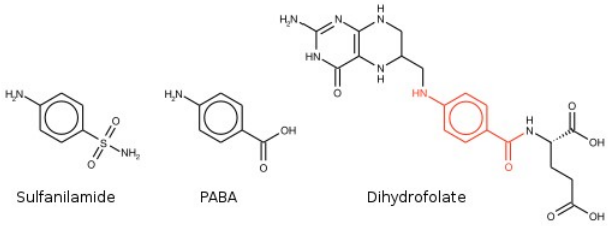


Figure 13.5.1 Structural similarity between sulfanilamide, a common sulfa drug (left) and PABA (center) is the basis for the inhibitory activity of sulfa drugs on dihydrofolate biosynthesis. Source: Wiikipedia

Sulfonamides are structural analogs and competitive antagonists of para-aminobenzoic acid (PABA), and thus prevent normal bacterial utilization of PABA for the synthesis of the vitamin folic acid (Figure 13.5.1). More specifically, sulfonamides are competitive inhibitors of the bacterial enzyme sulfihydropteroate synthase, which is responsible for the conversion of PABA into dihydrofolic acid, the immediate precursor of folic acid. Sensitive microorganisms are those that must synthesis their own folic acid; bacteria that can utilize preformed folic acid are not affected.

Cell Wall Synthesis Inhibitors - Penicillin and Cepalosphorins

The penicillins were the first antibiotics discovered as natural products from the mold Penicillium and was effective against Gram-positive bacteria. All penicillin derivatives produce their bacteriocidal effects by inhibition of bacterial cell wall synthesis. Specifically, the cross linking of peptides on the mucosaccharide chains is prevented. If cell walls are improperly made cell walls allow water to flow into the cell causing it to burst. A number of natural penicillins have been discovered, but only two purified compounds are in clinical use: penicillin G (intravenous use) and penicillin V (given by mouth). Several semisynthetic penicillins are effective against a broader spectrum of bacteria: these include the antistaphylococcal penicillins, aminopenicillins and the antipseudomonal penicillins.

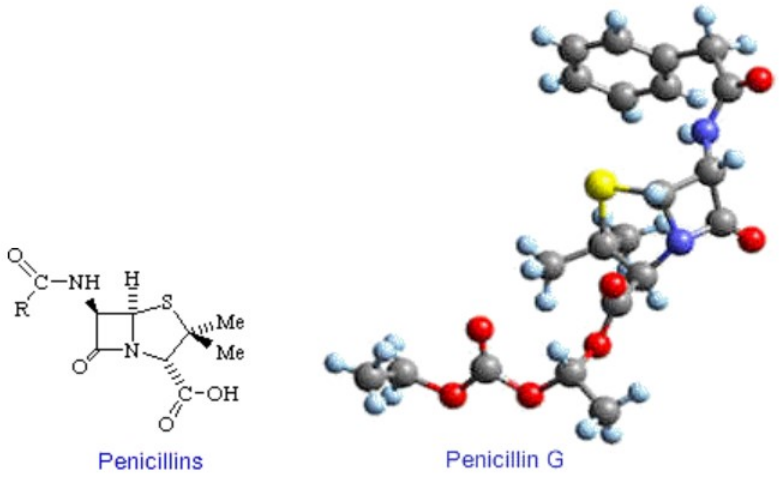


Figure 13.5.2 Penicillins.

Like penicillin, cephalosporins are valuable because of their low toxicity and their broad spectrum of action against various diseases. In this way, cephalosporin is very similar to penicillin. Cephalosporins are one of the most widely used antibiotics, and economically speaking, has about 29% of the antibiotic market. The cephalosporins are possibly the single most important group of antibiotics today and are equal in importance to penicillin. The structure and mode of action of the cephalosporins are similar to that of penicillin. They affect bacterial growth by inhibiting cell wall synthesis, in Gram-positive and -negative bacteria.

Figure 13.5.3 Cephalosporins.

Erythromycin is an orally effective antibiotic discovered in 1952 in the metabolic products of a strain of Streptocyces erythreus, originally obtained from a soil sample collected in the Philippine Archipelago. Erythromycin may be either bacteriostatic or bactericidal, depending on the microorganism and the concentration of the drug.

Erythromycin is an antibiotic used for the treatment of a number of bacterial infections. This includes respiratory tract infections, skin infections, chlamydia infections, pelvic inflammatory disease, and syphilis. It may also be used during pregnancy to prevent Group B streptococcal infection in the newborn, as well as to improve delayed stomach emptying. It can be given intravenously and by mouth. An eye ointment is routinely recommended after delivery to prevent eye infections in the newborn.

Erythromycin and other macrolide antibiotics inhibit protein synthesis by binding to 50 S ribosomal subunits of sensitive microorganisms. (Humans do not have 50 S ribosomal subunits, but have ribosomes composed of 40 S and 60 S subunits). Certain resistant microorganisms with mutational changes in components of this subunit of the ribosome fail to bind the drug.

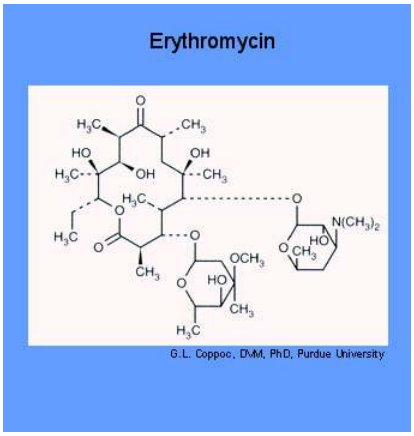


Figure 13.5.4 Erythromycin.

Tetracyclines have the broadest spectrum of antimicrobial activity. These may include: Aureomycin, Terramycin, and Panmycin. Four fused 6-membered rings, as shown in the figure below, form the basic structure from which the various tetracyclines are made. The various derivatives are different at one or more of four sites on the rigid, planar ring structure. The classical tetracyclines were derived from *Streptomyces spp*., but the newer derivatives are semisynthetic as is generally true for newer members of other drug groups.

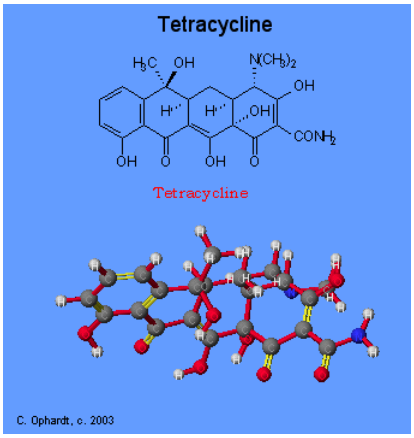


Figure 13.5.5 Tetracycline.

Tetracyclines inhibit bacterial protein synthesis by blocking the attachment of the transfer RNA-amino acid to the ribosome. More precisely they are inhibitors of the codon-anticodon interaction. Tetracyclines can also inhibit protein synthesis in the host, but are less likely to reach the concentration required because eukaryotic cells do not have a tetracycline uptake mechanism.

Streptomycin

Streptomycin is effective against gram-negative bacteria, although it is also used in the treatment of tuberculosis. Streptomycin binds to the 30S ribosome and changes its shape so that it and inhibits protein synthesis by causing a misreading of messenger RNA information.

Chloramphenicol

Chloromycetin is also a broad spectrum antibiotic that possesses activity similar to the tetracylines. At present, it is the only antibiotic prepared synthetically. It is reserved for treatment of serious infections because it is potentially highly toxic to bone marrow cells. It inhibits protein synthesis by attaching to the ribosome and interferes with the formation of peptide bonds between amino acids. It behaves as an antimetabolite for the essential amino acid phenylalanine at ribosomal binding sites.

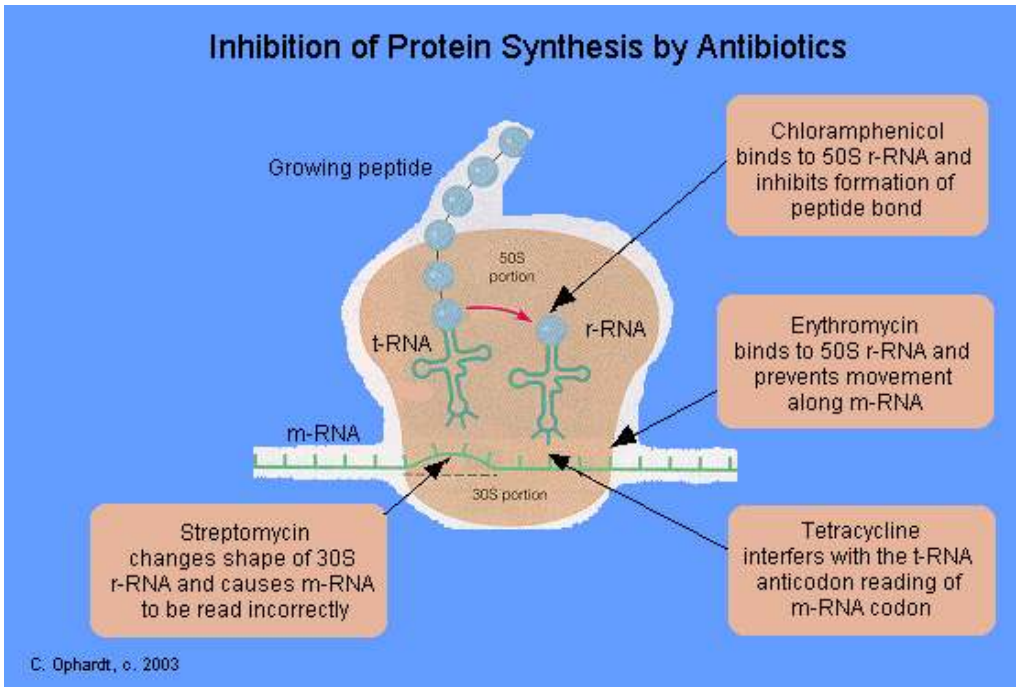


Figure 13.5.6 Inhibition of protein synthesis by erythtomycin, teracycline, streptomycin, and chloramphenicol.

A summary of the key features of different antibiotics is given in Table 13.5.1.

Table 13.5.1 *Some Clinically Important Antibiotics.*

Antibiotic	Producer organism	Activity	Site or mode of action
Penicillin	*Penicillium chrysogenum*	Gram-positive bacteria	Wall synthesis
Cephalosporin	*Cephalosporium acremonium*	Broad spectrum	Wall synthesis
Griseofulvin	*Penicillium griseofulvum*	Dermatophytic fungi	Microtubules
Bacitracin	*Bacillus subtilis*	Gram-positive bacteria	Wall synthesis
Polymyxin B	*Bacillus polymyxa*	Gram-negative bacteria	Cell membrane
Amphotericin B	*Streptomyces nodosus*	Fungi	Cell membrane
Erythromycin	*Streptomyces erythreus*	Gram-positive bacteria	Protein synthesis
Neomycin	*Streptomyces fradiae*	Broad spectrum	Protein synthesis
Streptomycin	*Streptomyces griseus*	Gram-negative bacteria	Protein synthesis
Tetracycline	*Streptomyces rimosus*	Broad spectrum	Protein synthesis
Vancomycin	*Streptomyces orientalis*	Gram-positive bacteria	Protein synthesis
Gentamicin	*Micromonospora purpurea*	Broad spectrum	Protein synthesis
Rifamycin	*Streptomyces mediterranei*	Tuberculosis	Protein synthesis

History of Penicillin and General Information

Alexander Fleming loved to play, both in the laboratory and out. He always loved snooker and golf and had many whimsical variants on the rules. In the lab he made "germ paintings," in which he would draw with his culture loop using spores of highly pigmented bacteria, which were invisible when he made the painting, but when cultured developed into brightly colored scenes. He followed what Max Delbruck would later call the "principle of limited sloppiness." Fleming abhorred a tidy, meticulous lab; he left culture dishes lying around for weeks and would often discover interesting things in them. Though the story has been told in many sometimes conflicting ways, something like this resulted in the discovery of penicillin. He seems to have left a culture dish lying on the lab bench and then gone away on vacation. When he returned a few spores of an unusual mold had germinated on the plate. When he cultured the bacteria on the plate he found that they grew up to within a few centimeters of the mold, but there were killed. A crude extract of the mold was then shown to have antibacterial properties. Fleming made this discovery in 1928 and by 1929 had named it penicillin (he was told by a colleague that the mold was a type of Penicillium and "penicillozyme" must have seemed cumbersome).

Fleming continued to use penicillin in his lab but not with any great enthusiasm and certainly not to the exclusion of many other projects. He never developed it into a clinically useful compound, though in 1929 he suggested that it might have important clinical applications. Because he was a bacteriologist and not a chemist, Fleming did not attempt to purify penicillin. He seems to have run into a dead end with penicillin and so during the 1930s, though he kept it in his lab, he did not do much with it. In the late 1930s Australian Howard Florey came to London to work with Charles Sherrington. He worked on lysozyme for a while and then became interested in penicillin. It was Florey, with Chain and other of his group that developed penicillin into a clinical antibiotic. They did this during 1940-41. Fleming, Florey, and Chain shared the 1945 Nobel Prize in Physiology for Medicine.

Fleming became world-famous for penicillin, and was rightly acknowledged as the father of modern antibiotics, but Florey was just as rightly miffed at being denied much of the credit for creating the powerful medical tool we now know. Evidence does not suggest that Fleming deliberately denied Florey his due credit, but Fleming's peculiar, dry sense of humor seems to have caused him not to deny even the wildest attributions to him.

Viruses and Antiviral Drugs

Viruses cause a variety of diseases in animals, including humans, ranging from the common cold to potentially fatal illnesses like meningitis (FIgure 13.5.1). These diseases can be treated by antiviral drugs or by vaccines, but some viruses, such as HIV, are capable of both avoiding the immune response and mutating to become resistant to antiviral drugs.

Antiviral drugs are a class of medications used to treat viral infections. Most antivirals target specific viruses, while a broad-spectrum antiviral is effective against a wide range of viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead, they inhibit its development.

Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and antiparasitic drugs, or antiviral drugs based on monoclonal antibodies. Most antivirals are considered relatively safe to the host, and therefore can be used to treat infections. They should be distinguished from viricides, which are not medications but deactivate or destroy virus particles, either inside or outside the body. Natural viricides are produced by some plants such as eucalyptus and Australian tea trees.

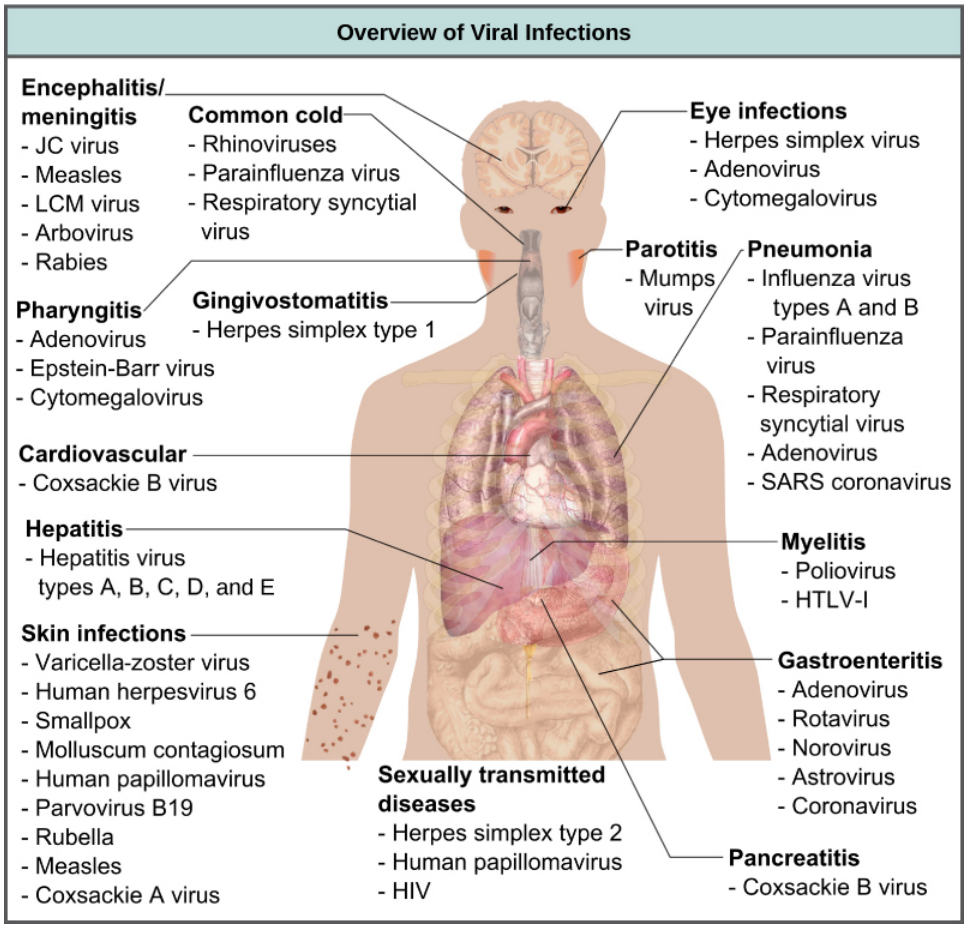


Figure 13.5.7: Viruses can cause dozens of ailments in humans, ranging from mild illnesses to serious diseases. (credit: modification of work by Mikael Häggström)

DNA Viruses and RNA Viruses

Viruses are visible only under an electron microscope. They come in a variety of shapes, ranging from spherical to rod shaped. The fact that they contain either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)—*but never both*—allows them to be divided into two major classes: DNA viruses and RNA viruses (Figure 13.5.1).

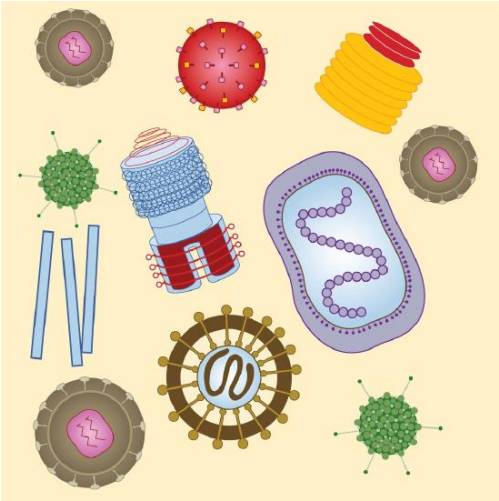


Figure 13.5.8: Viruses. Viruses come in a variety of shapes that are determined by their protein coats.

Most *RNA viruses* use their nucleic acids in much the same way as the DNA viruses, penetrating a host cell and inducing it to replicate the viral RNA and synthesize viral proteins. The new RNA strands and viral proteins are then assembled into new viruses. Some RNA viruses, however, called retroviruses (Figure 13.5.2), synthesize DNA in the host cell, in a process that is the reverse of the DNA-to-RNA transcription that normally occurs in cells. The synthesis of DNA from an RNA template is catalyzed by the enzyme reverse transcriptase.

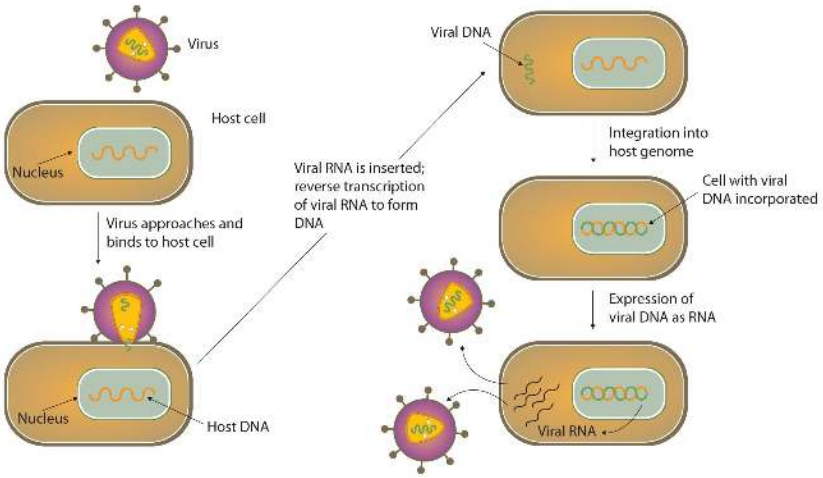


Figure 13.5.9: Life Cycle of a Retrovirus

Anti-viral Drugs

Antiviral drugs often have limited success in curing viral disease, but in many cases, they have been used to control and reduce symptoms for a wide variety of viral diseases. For most viruses, these drugs can inhibit the virus by blocking the actions of one or more of its proteins. It is important that the targeted proteins be encoded by viral genes and that these molecules are not present in a healthy host cell. In this way, viral growth is inhibited without damaging the host. There are large numbers of antiviral drugs available to treat infections, some specific for a particular virus and others that can affect multiple viruses.

Antivirals have been developed to treat genital herpes (herpes simplex II) and influenza. For genital herpes, drugs such as acyclovir can reduce the number and duration of episodes of active viral disease, during which patients develop viral lesions in their skin cells. As the virus remains latent in nervous tissue of the body for life, this drug is not curative but can make the symptoms of the disease more manageable. For influenza, drugs like Tamiflu (oseltamivir) (Figure 13.5.3) can reduce the duration of “flu” symptoms by 1 or 2 days, but the drug does not prevent symptoms entirely. Tamiflu works by inhibiting an enzyme (viral neuraminidase) that allows new virions to leave their infected cells. Thus, Tamiflu inhibits the spread of virus from infected to uninfected cells. Other

antiviral drugs, such as Ribavirin, have been used to treat a variety of viral infections, although its mechanism of action against certain viruses remains unclear.

By far, the most successful use of antivirals has been in the treatment of the retrovirus HIV, which causes a disease that, if untreated, is usually fatal within 10–12 years after infection. Anti-HIV drugs have been able to control viral replication to the point that individuals receiving these drugs survive for a significantly longer time than the untreated.

Anti-HIV drugs inhibit viral replication at many different phases of the HIV replicative cycle (Figure 13.5.4). Drugs have been developed that inhibit the fusion of the HIV viral envelope with the plasma membrane of the host cell (fusion inhibitors), the conversion of its RNA genome into double-stranded DNA (reverse transcriptase inhibitors), the integration of the viral DNA into the host genome (integrase inhibitors), and the processing of viral proteins (protease inhibitors).

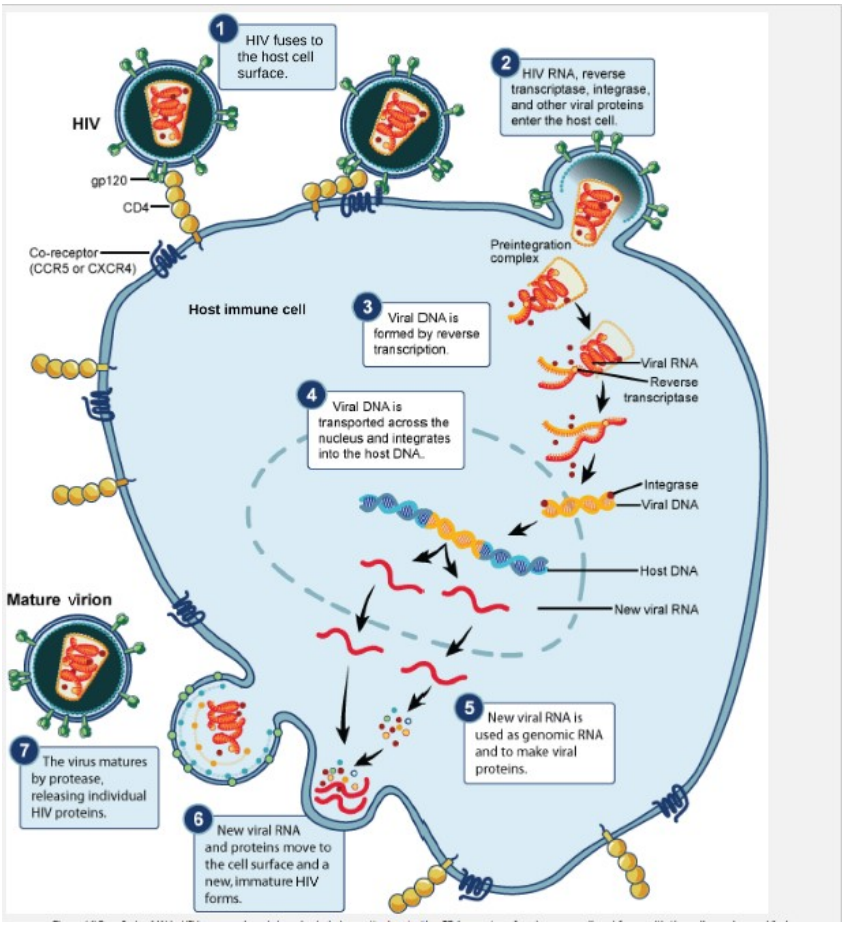
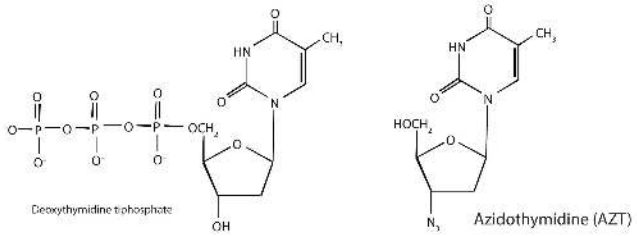
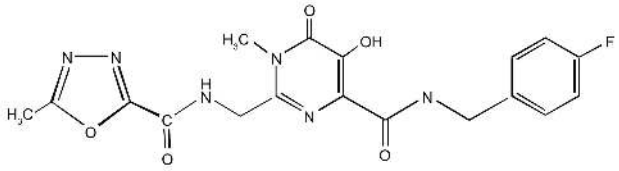


Figure 13.5.10: HIV, an enveloped, icosahedral virus, attaches to the CD4 receptor of an immune cell and fuses with the cell membrane. Viral contents are released into the cell, where viral enzymes convert the single-stranded RNA genome into DNA and incorporate it into the host genome. (credit: NIAID, NIH)

In 1987, azidothymidine (AZT, also known as zidovudine or the brand name Retrovir) became the first drug approved for the treatment of AIDS. It works by binding to reverse transcriptase in place of deoxythymidine triphosphate, after which, because AZT does not have a 3′OH group, further replication is blocked. In the past 10 years, several other drugs have been approved that also act by inhibiting the viral reverse transcriptase.



Raltegravir (Isentress) is a newer anti-AIDS drug that was approved by the FDA in October 2007. This drug inhibits the integrase enzyme that is needed to integrate the HIV DNA into cellular DNA, an essential step in the production of more HIV particles.



Raltegravir

A major problem in treating HIV infections is that the virus can become resistant to any of these drugs. One way to combat the problem has been to administer a “cocktail” of drugs, typically a combination of two reverse transcriptase inhibitors along with a protease inhibitor. These treatments can significantly reduce the amount of HIV in an infected person.

The **management of HIV/AIDS** normally includes the use of multiple antiretroviral drugs in an attempt to control HIV infection. There are several classes of antiretroviral agents that act on different stages of the HIV life-cycle. The use of multiple drugs that act on different viral targets is known as **highly active antiretroviral therapy** (**HAART**). HAART decreases the patient's total burden of HIV, maintains function of the immune system, and prevents opportunistic infections that often lead to death. HAART also prevents the transmission of HIV between serodiscordant same sex and opposite sex partners so long as the HIV-positive partner maintains an undetectable viral load.

A more detailed list of antivirals other than HIV is given in Table 13.5.1.

Table 13.5.1 Antivirals Used for Viruses Other Than HIV

Antiviral	Brand Name	Use
amantadine	*Symmetrel*	used prophylactically against influenza A) in high-risk individuals. It prevents influenza A viruses from the uncoating step necessary for viral replication.
rimantidine	*Flumadine*	used for the treatment and prophylaxis of influenza A. It prevents influenza A viruses from the uncoating step necessary for viral replication.
zanamivir:	*Relenza*	used to limit the duration of influenza A and B infections. It is an inhibitor of the influenza virus surface enzyme called neuraminidase that is needed for the release of newly formed influenza viruses from the infected cell.
oseltamivir	*Tamiflu*	used to limit the duration of influenza infections. It is an inhibitor of the influenza virus surface enzyme called neuraminidase that is needed for the release of newly formed influenza viruses from the infected cell.
acyclovir	Zovirax	used against herpes simplex viruses (HSV) to treat genital herpes, mucocutaneous herpes in the immunosuppressed, HSV encephalitis, neonatal herpes, and to reduce the rate of recurrences of genital herpes. It is also used against varicella zoster viruses (VZV)) to treat shingles. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
trifluridine	*Viroptic*	used to treat eye infection (keratitis and conjunctivitis) caused by HSV. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
famciclovir	Famvir	used to treat HSV and VZV infections. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain, it inhibits further viral DNA replication.
valacyclovir	Valtrex	used to treat HSV and VZV infections. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain, it inhibits further viral DNA replication.
penciclovir	Denavir	used in treating HSV infections. It

Antiviral	Brand Name	Use
		chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain, it inhibits further viral DNA replication.
gancyclovir	Cytovene; Vitrasert	used in treating severe cytomegalovirus (CMV) infections such as retinitis. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
valganciclovir	Valcyte	used in treating severe CMV infections such as retinitis. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain, it inhibits further viral DNA replication.
foscarnet	Foscavir	used in treating severe CMV infections such as retinitis. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain, it inhibits further viral DNA replication.
cidofovir	Vistide	used in treating CMV retinitis. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain, it inhibits further viral DNA replication.
fomivirsen	Vitravene	used in treating CMV retinitis. Fomivirsen inhibits cytomegalovirus (CMV) replication through an antisense RNA (microRNA or miRNA mechanism. The nucleotide sequence of fomivirsen is complementary to a sequence in mRNA transcripts (Figure 13.5.1) that encodes several proteins responsible for the regulation of viral gene expression that are essential for the production of infectious CMV. The binding of fomivirsen to the target mRNA results in inhibition of protein synthesis, subsequently inhibiting virus replication.
ribavirin	Copegus; Rebetol; Virazole	used in treating severe acute respiratory syndrome (SARS). In combination with other drugs it is used to treat hepatitis C virus (HCV). It chemically resembles a normal RNA nucleoside. Once inserted into the

Antiviral	Brand Name	Use
		growing RNA chain, it inhibits further viral RNA replication.
telaprevir	Incivek	for the treatment of chronic hepatitis C (hepatitis C virus or HCV genotype 1). It is a protease inhibitor that binds to the active site of an HCV-encoded protease and prevents it from cleaving the long polyprotein from polycistronic HCV genes into proteins essential to the structure and function of HCV.
boceprevir	Victrelis	for the treatment of chronic hepatitis C (hepatitis C virus or HCV genotype 1) infection. It is used in combination with peginterferon alfa and ribavirin. Boceprevir is a protease inhibitor that binds to the active site of an HCV-encoded protease and prevent it from cleaving the long polyprotein from polycistronic HCV genes into proteins essential to the structure and function of HCV.
simeprevir	Olysio	use for the treatment of chronic hepatitis C (hepatitis C virus or HCV genotype 1) infection. Used in combination with peginterferon alfa and ribavirin. Simeprevir is a protease inhibitor that binds to the active site of an HCV-encoded protease and prevent it from cleaving the long polyprotein from polycistronic HCV genes into proteins essential to the structure and function of HCV.
sofosbuvir	*Sovaldi*	Use for the treatment of chronic hepatitis C infection. Used in combination with ribavirin for hepatitis C virus or HCV genotypes 2 and 4; used in combination with peginterferon alfa and ribavirin for HCV genotypes 1 and 4. The second indication is the first approval of an interferon-free regimen for the treatment of chronic HCV infection. Sofosbuvir is a nucleotide polymerase inhibitor that binds to the active site of an HCV-encoded RNA polymerase preventing the synthesis of the viral RNA genome.
lamivudine	*Epivir-HBV*	used in treating chronic hepatitis B. It chemically resembles a normal DNA nucleoside. Once inserted into the

Antiviral	Brand Name	Use
		growing DNA chain, it inhibits further viral DNA replication.
adefovir dipivoxil	*Hepsera*	used in treating hepatitis B.

Web Link

A list of FDA-approved Antiretroviral drugs (last updated on April 12, 2018) used in the treatment of HIV infection can be found on the website: www.fda.gov/patients/hiv-treatment/antiretroviral-drugs-used-treatment-hiv-infection

Basic Research and Drug Development

The general idea behind modern antiviral drug design is to identify viral proteins, or parts of proteins, that can be disabled. These "targets" should generally be as unlike any proteins or parts of proteins in humans as possible, to reduce the likelihood of side effects. The targets should also be common across many strains of a virus, or even among different species of virus in the same family, so a single drug will have broad effectiveness. For example, a researcher might target a critical enzyme synthesized by the virus, but not by the patient, that is common across strains, and see what can be done to interfere with its operation.

Once targets are identified, candidate drugs can be selected, either from drugs already known to have appropriate effects or by actually designing the candidate at the molecular level with a computer-aided design program.

The target proteins can be manufactured in the lab for testing with candidate treatments by inserting the gene that synthesizes the target protein into bacteria or other kinds of cells. The cells are then cultured for mass production of the protein, which can then be exposed to various treatment candidates and evaluated with "rapid screening" technologies.

Prevention of Viral Diseases with Vaccination

While we do have limited numbers of effective antiviral drugs, such as those used to treat HIV and influenza, the primary method of controlling viral disease is by vaccination, which is intended to prevent outbreaks by building immunity to a virus or virus family (Figure 13.5.1). Vaccines may be prepared using live viruses, killed viruses, or molecular subunits of the virus. The killed viral vaccines and subunit viruses are both incapable of causing disease.

Live viral vaccines are designed in the laboratory to cause few symptoms in recipients while giving them protective immunity against future infections. Polio was one disease that represented a milestone in the use of vaccines. Mass immunization campaigns in the 1950s (killed vaccine) and 1960s (live vaccine) significantly reduced the incidence of the disease, which caused muscle paralysis in children and generated a great amount of fear in the general population when regional epidemics occurred. The success of the polio vaccine paved the way for the routine dispensation of childhood vaccines against measles, mumps, rubella, chickenpox, and other diseases.

The danger of using live vaccines, which are usually more effective than killed vaccines, is the low but significant danger that these viruses will revert to their disease-causing form by back mutations. Live vaccines are usually made by attenuating (weakening) the “wild-type” (disease-causing) virus by growing it in the laboratory in tissues or at temperatures different from what the virus is accustomed to in the host. Adaptations to these new cells or temperatures induce mutations in the genomes of the virus, allowing it to grow better in the laboratory while inhibiting its ability to cause disease when reintroduced into conditions found in the host. These attenuated viruses thus still cause infection, but they do not grow very well, allowing the immune response to develop in time to prevent major disease. Back mutations occur when the vaccine undergoes mutations in the host such that it readapts to the host and can again cause disease, which can then be spread to other humans in an epidemic. This type of scenario happened as recently as 2007 in Nigeria where mutations in a polio vaccine led to an epidemic of polio in that country.

Some vaccines are in continuous development because certain viruses, such as influenza and HIV, have a high mutation rate compared to other viruses and normal host cells. With influenza, mutations in the surface molecules of the virus help the organism evade the protective immunity that may have been obtained in a previous influenza season, making it necessary for individuals to get vaccinated every year. Other viruses, such as those that cause the childhood diseases measles, mumps, and rubella, mutate so infrequently that the same vaccine is used year after year.



Figure 13.5.11: Vaccinations are designed to boost immunity to a virus to prevent infection. (credit: USACE Europe District)

Summary

- An infectious disease is any disease caused by the direct effect of a pathogen (bacteria, parasites, fungi, viruses, viroids, and prions).
- Diseases can either be noninfectious (due to genetics and environment) or infectious (due to pathogens). Some infectious diseases are communicable (transmissible between individuals) or contagious (easily transmissible between individuals); others are noncommunicable, but may be contracted via contact with environmental reservoirs or animal.
- An antibiotic is any substance produced by a microorganism that is excreted to harm or kill another microorganism. Technically, antibiotics are microbial or fungal products.
- Most antibiotics inhibit bacterial growth by inhibiting cell wall synthesis or protein synthesis.
- **Antiviral drugs** are a class of medication used for treating viral infections. Most antivirals target specific viruses, while a broad-spectrum antiviral is effective against a wide range of viruses.
- The management of HIV/AIDS normally includes the use of multiple in an attempt to control .
- The primary method of controlling viral disease is by vaccination, which is intended to prevent outbreaks by building immunity to a virus or virus family

Contributors and Attributions

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- NIH MedlinePlus
- US FDA
- Libretext: The Basics of GOB Chemistry (Ball et al
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13.6: Chemicals Against Cancer

Learning Objective

- List the different types of cancer drugs and their mechanism of action.

Chemotherapy is a type of cancer treatment that uses one or more anti-cancer drugs (chemotherapeutic agents) as part of a standardized chemotherapy regimen. Chemotherapy may be given with a curative intent (which almost always involves combinations of drugs), or it may aim to prolong life or to reduce symptoms (palliative chemotherapy). Chemotherapy is one of the major categories of the medical discipline specifically devoted to pharmacotherapy for cancer, which is called *medical oncology*.

When fighting cancer, the entire population of neoplastic cells must be eradicated in order to obtain desired results. The concept of "total cell-kill" applies to chemotherapy as it does to other means of treatment: total excision of the tumor is necessary for surgical care, and complete destruction of all cancer cells is required for a cure with radiation therapy.

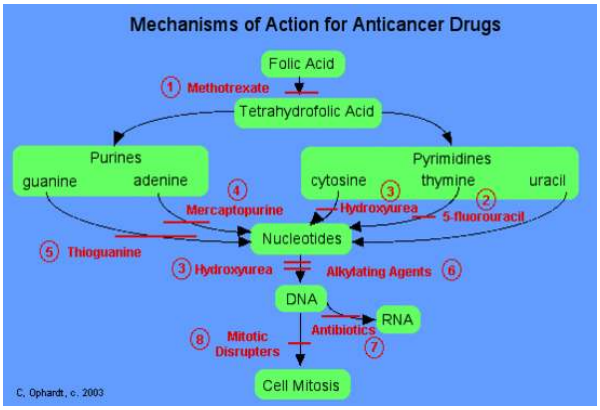
The available anticancer drugs have distinct mechanisms of action which may vary in their effects on different types of normal and cancer cells. A single "cure" for cancer has proved elusive since there is not a single type of cancer but as many as 100 different types of cancer. In addition, there are very few demonstrable biochemical differences between cancerous cells and normal cells. For this reason the effectiveness of many anticancer drugs is limited by their toxicity to normal rapidly growing cells in the intestinal and bone marrow areas. A final problem is that cancerous cells which are initially suppressed by a specific drug may develop a resistance to that drug. For this reason cancer chemotherapy may consist of using several drugs in combination for varying lengths of time.

Introduction

Chemotherapy drugs, are sometimes feared because of a patient's concern about toxic effects. Their role is to slow and hopefully halt the growth and spread of a cancer. There are three goals associated with the use of the most commonly-used anticancer agents.

1. Damage the DNA of the affected cancer cells.
2. Inhibit the synthesis of new DNA strands to stop the cell from replicating, because the replication of the cell is what allows the tumor to grow.
3. Stop mitosis or the actual splitting of the original cell into two new cells. Stopping mitosis stops cell division (replication) of the cancer and may ultimately halt the progression of the cancer.

Unfortunately, the majority of drugs currently on the market are not specific, which leads to the many common side effects associated with cancer chemotherapy. Because the common approach of all chemotherapy is to decrease the growth rate (cell division) of the cancer cells, the side effects are seen in bodily systems that naturally have a rapid turnover of cells including skin, hair, gastrointestinal, and bone marrow. These healthy, normal cells, also end up damaged by the chemotherapy program.



Categories of Chemotherapy Drugs

In general, chemotherapy agents can be divided into three main categories based on their mechanism of action as shown in the table below.

Table 13.6.1 Chemotherapy Drugs and Their Mechanism of Action

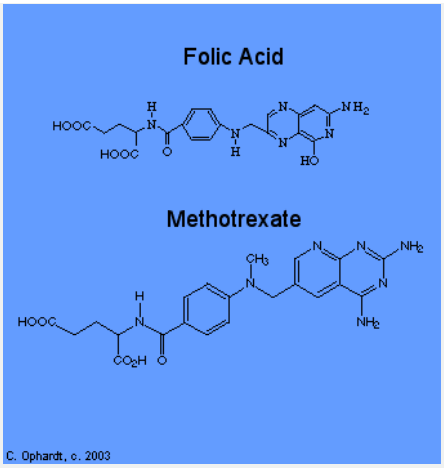
Category	Specific Mode of Action	Examples
Stop the synthesis of pre DNA molecule building blocks "Antimetabolites"	These agents work in a number of different ways. DNA building blocks are folic acid, heterocyclic bases, and nucleotides, which are made naturally within cells. All of these agents work to block some step in the formation of nucleotides or deoxyribonucleotides (necessary for making DNA). When these steps are blocked, the nucleotides, which arethe building blocks of DNA and RNA, can not be synthesized. Thus the cells can not replicate because they cannot make DNA without the nucleotides.	1) methotrexate (Abitrexate®),2) fluorouracil (Adrucil®), 3) hydroxyurea (Hydrea®), 4) mercaptopurine (Purinethol®) and 5) thioguanine.
Directly damage the DNA in the nucleus of the cell "Alkylating agents, antibiotics, topoisomerase inhibitors and intercalating agents."	These agents chemically damage DNA and RNA. They disrupt replication of the DNA and either totally halt replication or cause the manufacture of nonsense DNA or RNA (i.e. the new DNA or RNA does not code for anything useful).	5) cisplatin (Platinol®) and 7) antibiotics - daunorubicin (Cerubidine®), doxorubicin (Adriamycin®), and etoposide (VePesid®).
Effect the synthesis or breakdown of the mitotic spindles "Mitotic disrupters"	Mitotic spindles serve as molecular railroads with "North and South Poles" in the cell when a cell starts to divide itself into two new cells. These spindles are very important because they help to split the newly copied DNA such that a copy goes to each of the two new cells during cell division. These drugs disrupt the formation of these spindles and therefore interrupt cell division.	8) mitotic disrupters include: Vinblastine (Velban®), Vincristine (Oncovin®) and Pacitaxel (Taxol®).

Antimetabolites

Methotrexate

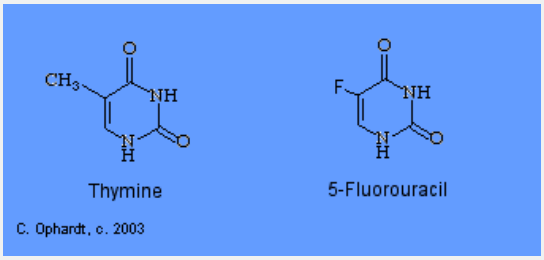
Methotrexate inhibits folic acid reductase which is responsible for the conversion of folic acid to tetrahydrofolic acid. At two stages in the biosynthesis of purines(adenine and guanine) and at one stage in the synthesis of pyrimidines (thymine, cytosine, and uracil), one-carbon transfer reactions occur which require specific coenzymes synthesized in the cell from tetrahydrofolic acid.

Tetrahydrofolic acid itself is synthesized in the cell from folic acid with the help of an enzyme, folic acid reductase. Methotrexate looks a lot like folic acid to the enzyme, so it binds to it thinking that it is folic acid. In fact, methotrexate looks so good to the enzyme that it binds to it quite strongly and inhibits the enzyme. Thus, DNA synthesis cannot proceed because the coenzymes needed for one-carbon transfer reactions are not produced from tetrahydrofolic acid because there is no tetrahydrofolic acid. Again, without DNA, no cell division.



5-Fluorouracil

5-Fluorouracil (5-FU; Adrucil®, Fluorouracil, Efudex®, Fluoroplex®) is an effective pyrimidine antimetabolite. Fluorouracil is synthesized into the nucleotide, 5-fluoro-2-deoxyuridine. This product acts as an antimetabolite by inhibiting the synthesis of 2-deoxythymidine because the carbon - fluorine bond is extremely stable and prevents the addition of a methyl group in the 5-position. The failure to synthesize the thymidine nucleotide results in little or no production of DNA. Two other similar drugs include: gemcitabine (Gemzar®) and arabinosylcytosine (araC). They all work through similar mechanisms.

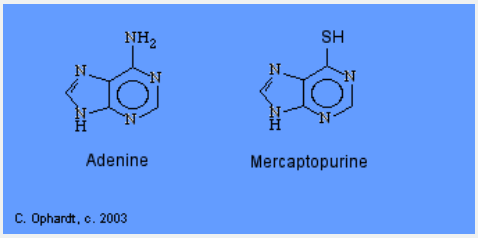


Hydroxyurea

Hydroxyurea blocks an enzyme which converts the cytosine nucleotide into the deoxy derivative. In addition, DNA synthesis is further inhibited because hydroxyurea blocks the incorporation of the thymidine nucleotide into the DNA strand.

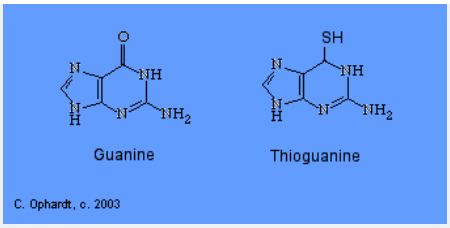
Mercaptopurine

Mercaptopurine, a chemical analog of the purine adenine, inhibits the biosynthesis of adenine nucleotides by acting as an antimetabolite. In the body, 6-MP is converted to the corresponding ribonucleotide. 6-MP ribonucleotide is a potent inhibitor of the conversion of a compound called inosinic acid to adenine Without adenine, DNA cannot be synthesized. 6-MP also works by being incorporated into nucleic acids as thioguanosine, rendering the resulting nucleic acids (DNA, RNA) unable to direct proper protein synthesis.



Thioguanine

Thioguanine is an antimetabolite in the synthesis of guanine nucleotides.

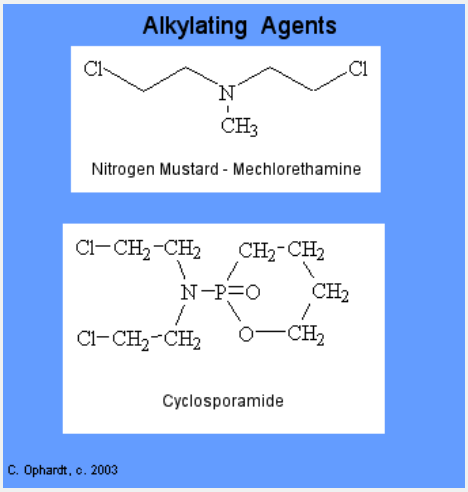


Alkylating Agents, Topoisomerase Inhibitors, Antibiotics, and Intercalating agents

Alkylating Agents

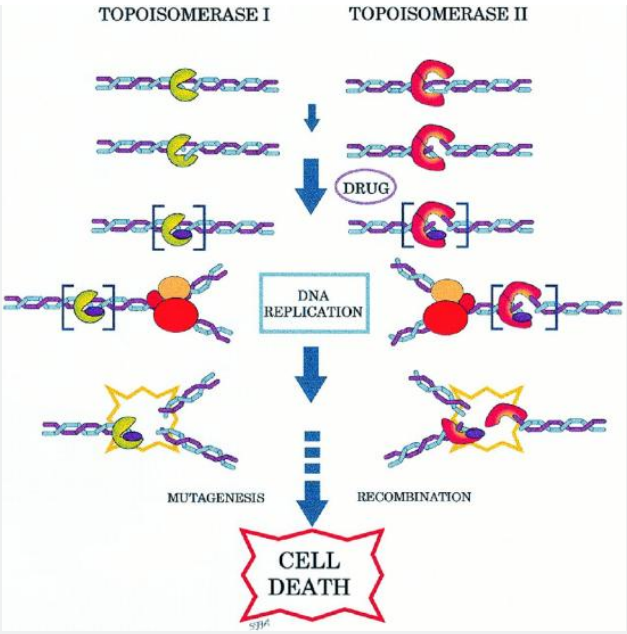
Alkylating agents involve reactions with guanine in DNA. These drugs add methyl or other alkyl groups onto molecules where they do not belong. This in turn inhibits their correct utilization by base pairing and causes a miscoding of DNA.

There are six groups of alkylating agents: nitrogen mustards; ethylenimes; alkylsulfonates; triazenes; piperazines; and nitrosureas. Cyclosporamide is a classical example of the role of the host metabolism in the activation of an alkylating agent and is one or the most widely used agents of this class. It was hoped that the cancer cells might posses enzymes capable of accomplishing the cleavage, thus resulting in the selective production of an ated nitrogen mustard in the malignant cells. Compare the top and bottom structures in the graphic on the left.



Topoisomerase Inhibitors

Topoisomerase inhibitors are drugs that affect the activity of two enzymes: topoisomerase I and topoisomerase II. Inhibition of topoisomerase I or II interferes with both replication and transcription.

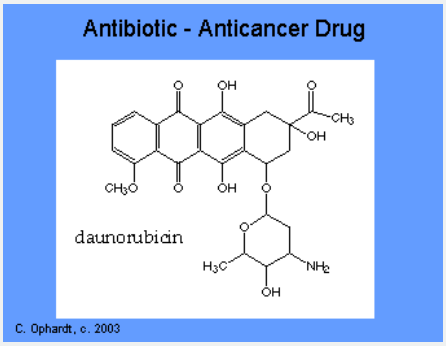


Two topoisomerase I inhibitors, irinotecan and topotecan, are semi-synthetically derived from camptothecin, which is obtained from the Chinese ornamental tree *Camptotheca acuminata*. Drugs that target topoisomerase II can be divided into two groups. The topoisomerase II inhibitors include etoposide, doxorubicin, mitoxantrone , teniposide, novobiocin, merbarone, and aclarubicin.

Antibiotics

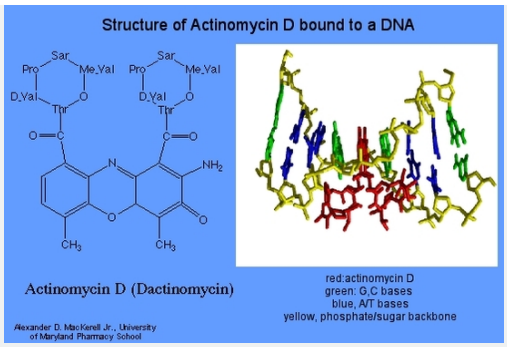
A number of **antibiotics** such as anthracyclines, dactinomycin, bleomycin, adriamycin, mithramycin, bind to DNA and inactivate it. Thus the synthesis of RNA is prevented. General properties of these drugs include: interaction with DNA in a variety of different ways including intercalation (squeezing between the base pairs), DNA strand breakage and inhibition with the enzyme topoisomerase II. Most of these compounds have been isolated from natural sources and antibiotics. However, they lack the specificity of the antimicrobial antibiotics and thus produce significant toxicity.

The **anthracyclines** are among the most important antitumor drugs available. Doxorubicin is widely used for the treatment of several solid tumors while **daunorubicin** and idarubicin are used exclusively for the treatment of leukemia. These agents have a number of important effects including: intercalating (squeezing between the base pairs) with DNA affecting many functions of the DNA including DNA and RNA synthesis. Breakage of the DNA strand can also occur by inhibition of the enzyme topoisomerase II.



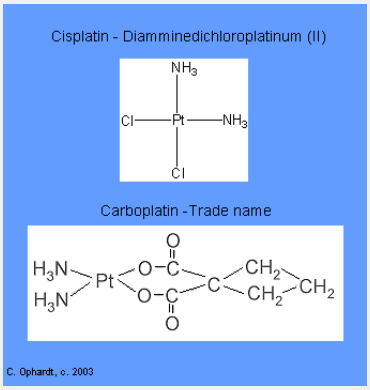
Dactinomycin (Actinomycin D)

At low concentrations dactinomycin inhibits DNA directed RNA synthesis and at higher concentrations DNA synthesis is also inhibited. All types of RNA are affected, but ribosomal RNA is more sensitive. Dactinomycin binds to double stranded DNA , permitting RNA chain initiation but blocking chain elongation. Binding to the DNA depends on the presence of guanine.



Intercalating Agents

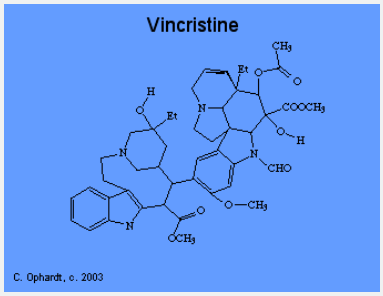
Intercalating agents wedge between bases along the DNA. The intercalated drug molecules affect the structure of the DNA, preventing polymerase and other DNA binding proteins from functioning properly. The result is prevention of DNA synthesis, inhibition of transcription and induction of mutations. Examples include: **Carboplatin and Cisplatin.**



Mitotic Disrupters

Mitotic Disrupters

Plant alkaloids like **vincristine** prevent cell division, or mitosis. There are several phases of mitosis, one of which is the metaphase. During metaphase, the cell pulls duplicated DNA chromosomes to either side of the parent cell in structures called "spindles". These spindles ensure that each new cell gets a full set of DNA. Spindles are microtubular fibers formed with the help of the protein "tubulin". Vincristine binds to tubulin, thus preventing the formation of spindles and cell division.



Taxol

Paclitaxel (taxol) was first isolated from the from the bark of the Pacific Yew (Taxus brevifolia). Docetaxel is a more potent analog that is produced semisynthetically. In contrast to other microtubule antagonists, taxol disrupts the equilibrium between free tubulin and mircrotubules by shifting it in the direction of assembly, rather than disassembly. As a result, taxol treatment causes both the stabilization of microtubules and the formation of abnormal bundles of microtubules. The net effect is still the disruption of mitosis.

Combination Chemotherapy

In 1965, a major breakthrough in cancer therapy occurred. James F. Holland, Emil Freireich, and Emil Frei hypothesized that cancer chemotherapy should follow the strategy of antibiotic therapy for tuberculosis with combinations of drugs, each with a different mechanism of action. Cancer cells could conceivably mutate to become resistant to a single agent, but by using different drugs *concurrently* it would be more difficult for the tumor to develop resistance to the combination. Holland, Freireich, and Frei simultaneously administered methotrexate (an antifolate), vincristine (a Vinca alkaloid), 6-mercaptopurine (6-MP) and prednisone — together referred to as the POMP regimen — and induced long-term remissions in children with acute lymphoblastic leukaemia (ALL). With incremental refinements of original regimens, using randomized clinical studies by St. Jude Children's Research Hospital, the Medical Research Council in the UK (UKALL protocols) and German Berlin-Frankfurt-Münster clinical trials group (ALL-BFM protocols), ALL in children has become a largely curable disease.

This approach was extended to the lymphomas in 1963 by Vincent T. DeVita and George Canellos at the NCI, who ultimately proved in the late 1960s that nitrogen mustard, vincristine, procarbazine and prednisone — known as the MOPP regimen — could cure patients with Hodgkin's and non-Hodgkin's lymphoma.

Currently, nearly all successful cancer chemotherapy regimens use this paradigm of multiple drugs given simultaneously, called **combination chemotherapy** or **polychemotherapy**.

Table 13.6.2 The Common Combination Chemotherapy Regimens

Cancer type	Drugs	Acronym
Breast cancer	Cyclophosphamide, methotrexate, 5-fluorouracil, vinorelbine	CMF
	Doxorubicin, cyclophosphamide	AC
Hodgkin's lymphoma	Docetaxel, doxorubicin, cyclophosphamide	TAC
	Doxorubicin, bleomycin, vinblastine, dacarbazine	ABVD
	Mustine, vincristine, procarbazine, prednisolone	MOPP
Non-Hodgkin's lymphoma	Cyclophosphamide, doxorubicin, vincristine, prednisolone	CHOP
Germ cell tumor	Bleomycin, etoposide, cisplatin	BEP
Stomach cancer	Epirubicin, cisplatin, 5-fluorouracil	ECF
	Epirubicin, cisplatin, capecitabine	ECX
Bladder cancer	Methotrexate, vincristine, doxorubicin, cisplatin	MVAC
Lung cancer	Cyclophosphamide, doxorubicin, vincristine, vinorelbine	CAV
Colorectal cancer	5-fluorouracil, folinic acid, oxaliplatin	FOLFOX

Summary

- **Chemotherapy** is a type of cancer treatment that uses one or more anti-cancer drugs (chemotherapeutic agents) as part of a standardized chemotherapy regimen.
- Chemo drugs can be classified into three main categories based on their mechanism of action namely:
  - Stop the synthesis of pre-DNA molecule building blocks
  - Directly damage the DNA in the nucleus of the cell

- Effect the synthesis or breakdown of the mitotic spindles.
- Currently, nearly all successful cancer chemotherapy regimens use this paradigm of multiple drugs given simultaneously, called combination chemotherapy or polychemotherapy.

Contributors

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13.7: Chemistry Matters—DNA Fingerprinting

The invention of DNA sequencing has affected society in many ways, few more dramatic than those stemming from the development of *DNA fingerprinting*. DNA fingerprinting arose from the discovery in 1984 that human genes contain short, repeating sequences of noncoding DNA, called *short tandem repeat* (STR) loci. Furthermore, the STR loci are slightly different for everyone except identical twins. By sequencing these loci, a pattern unique to each person can be obtained.

Perhaps the most common and well-publicized use of DNA fingerprinting is that carried out by crime laboratories to link suspects to biological evidence—blood, hair follicles, skin, or semen—found at a crime scene. Many thousands of court cases have been decided based on DNA evidence.

For use in criminal cases, forensic laboratories in the United States have agreed on 13 core STR loci that are most accurate for the identification of an individual. Based on these 13 loci, a Combined DNA Index System (CODIS) has been established to serve as a registry of convicted offenders. When a DNA sample is obtained from a crime scene, the sample is subjected to cleavage with restriction endonucleases to cut out fragments containing the STR loci, the fragments are amplified using the polymerase chain reaction, and the sequences of the fragments are determined.

If the profile of sequences from a known individual and the profile from DNA obtained at a crime scene match, the probability is approximately 82 billion to 1 that the DNA is from the same individual. In paternity cases, where the DNA of male parent and offspring are related but not fully identical, the identity of the male parent can be established with a probability of around 100,000 to 1. Even after several generations, paternity can still be inferred from DNA analysis of the Y chromosome of direct male-line descendants. The most well-known such case is that of Thomas Jefferson, one of the nation's founders, who likely impregnated enslaved person Sally Hemings. Although Jefferson himself has no male-line descendants, DNA analysis of the male-line descendants of Jefferson’s paternal uncle contained the same Y chromosome as a male-line descendant of Eston Hemings, the youngest son of Sally Hemings. Thus, a mixing of the two genomes is clear, although the male individual responsible for that mixing can’t be identified with 100% certainty.

Among its many other applications, DNA fingerprinting is widely used for the diagnosis of genetic disorders, both prenatally and in newborns. Cystic fibrosis, hemophilia, Huntington’s disease, Tay–Sachs disease, sickle cell anemia, and thalassemia are among the many diseases that can be detected, enabling early treatment of an affected child. Furthermore, by studying the DNA fingerprints of relatives with a history of a particular disorder, it’s possible to identify DNA patterns associated with the disease and perhaps obtain clues for an eventual cure. In addition, the U.S. Department of Defense requires blood and saliva samples from all military personnel. The samples are stored, and DNA is extracted if the need for identification of a casualty arises.

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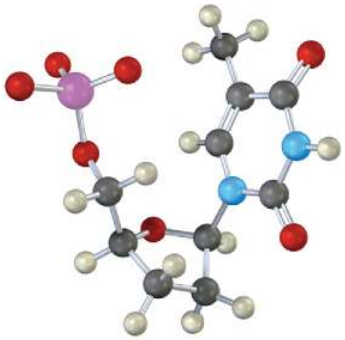
14.12: Additional Problems

Visualizing Chemistry

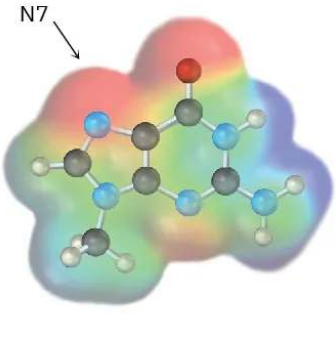
PROBLEM 14.13 Identify the following bases, and tell whether each is found in DNA, RNA, or both:

(a)  (b)  (c) 

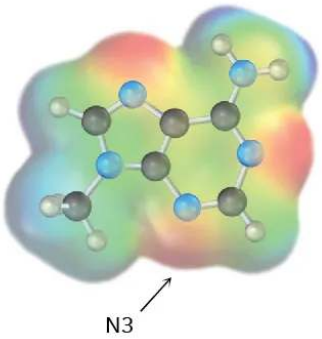
PROBLEM 14.14 Identify the following nucleotide, and tell how it is used:



PROBLEM 14.15 Amine bases in nucleic acids can react with alkylating agents in typical S_N2 reactions. Look at the following electrostatic potential maps, and tell which is the better nucleophile, guanine or adenine. The reactive positions in each are indicated.



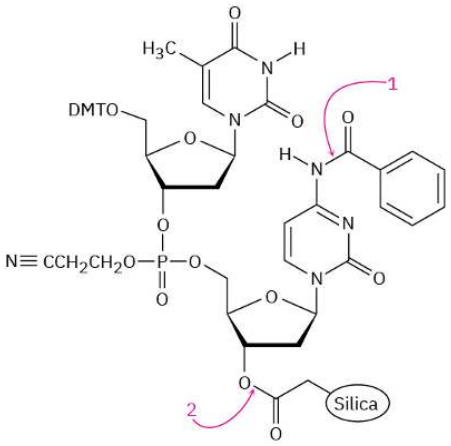
9-Methylguanine



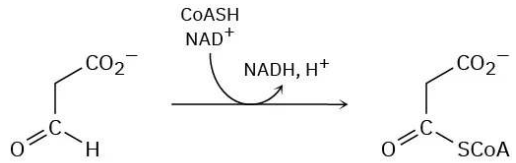
9-Methyladenine

Mechanism Problems

PROBLEM 14.16 The final step in DNA synthesis is deprotection by treatment with aqueous ammonia. Show the mechanisms by which deprotection occurs at the points indicated in the following structure:

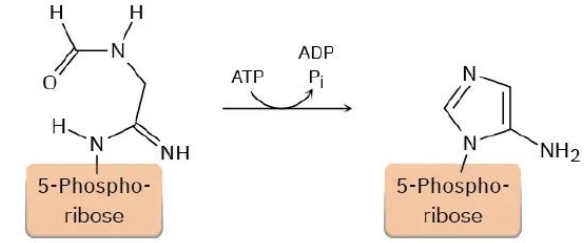


PROBLEM 14.17 The final step in the metabolic degradation of uracil is the oxidation of malonic semialdehyde to give malonyl CoA. Propose a mechanism.



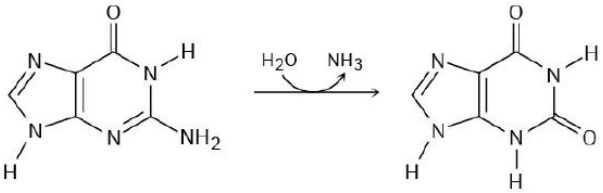
Malonic semialdehyde **Malonyl CoA**

PROBLEM 14.18 One of the steps in the biosynthesis of a nucleotide called inosine monophosphate is the formation of aminoimidazole ribonucleotide from formylglycinamidine ribonucleotide. Propose a mechanism.



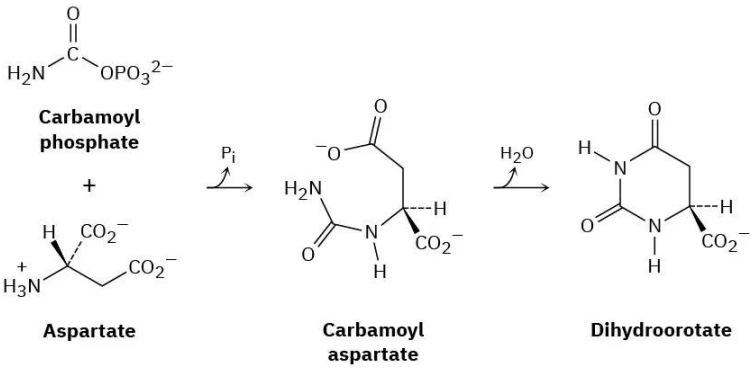
Formylglycinamidine ribonucleotide **Aminoimidazole ribonucleotide**

PROBLEM 14.19 One of the steps in the metabolic degradation of guanine is hydrolysis to give xanthine. Propose a mechanism.



Guanine **Xanthine**

PROBLEM 14.20 One of the steps in the biosynthesis of uridine monophosphate is the reaction of aspartate with carbamoyl phosphate to give carbamoyl aspartate followed by cyclization to form dihydroorotate. Propose mechanisms for both steps.



General Problems

PROBLEM 14.21 Human brain natriuretic peptide (BNP) is a small peptide of 32 amino acids used in the treatment of congestive heart failure. How many nitrogen bases are present in the DNA that codes for BNP?

PROBLEM 14.22 Human and horse insulin both have two polypeptide chains, with one chain containing 21 amino acids and the other containing 30 amino acids. They differ in primary structure at two places. At position 9 in one chain, human insulin has Ser and horse insulin has Gly; at position 30 in the other chain, human insulin has Thr and horse insulin has Ala. How must the DNA for the two insulins differ?

PROBLEM 14.23 The DNA of sea urchins contains about 32% A. What percentages of the other three bases would you expect in sea urchin DNA? Explain.

PROBLEM 14.24 The codon UAA stops protein synthesis. Why does the sequence UAA in the following stretch of mRNA not cause any problems?

-GCA-UUC-GAG-GUA-ACG-CCC-

PROBLEM 14.25 Which of the following base sequences would most likely be recognized by a restriction endonuclease? Explain

(a) GAATTC (b) GATTACA (c) CTCGAG

PROBLEM 14.26 For what amino acids do the following ribonucleotide triplets code?

(a) AAU (b) GAG (c) UCC (d) CAU

PROBLEM 14.27 From what DNA sequences were each of the mRNA codons in Problem 14-26 transcribed?

PROBLEM 14.28 What anticodon sequences of tRNAs are coded for by the codons in Problem 14-26?

PROBLEM 14.29 Draw the complete structure of the ribonucleotide codon UAC. For what amino acid does this sequence code?

PROBLEM 14.30 Draw the complete structure of the deoxyribonucleotide sequence from which the mRNA codon in Problem 28-29 was transcribed.

PROBLEM 14.31 Give an mRNA sequence that will code for the synthesis of metenkephalin.

Tyr-Gly-Gly-Phe-Met

PROBLEM 14.32 Give an mRNA sequence that will code for the synthesis of angiotensin II.

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe

PROBLEM 14.33 What amino acid sequence is coded for by the following DNA coding strand (sense strand)?

(5′) CTT-CGA-CCA-GAC-AGC-TTT (3′)

PROBLEM 14.34 What amino acid sequence is coded for by the following mRNA base sequence?

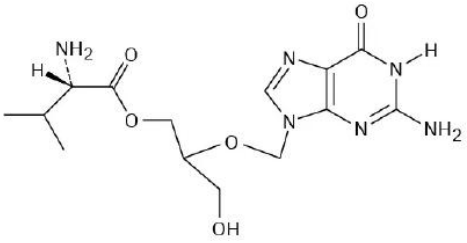
(5′) CUA-GAC-CGU-UCC-AAG-UGA (3′)

PROBLEM 14.35 If the DNA coding sequence -CAA-CCG-GAT- were miscopied during replication and became -CGA-CCG-GAT-, what effect would there be on the sequence of the protein produced?

PROBLEM 14.36 Show the steps involved in a laboratory synthesis of the DNA fragment with the sequence CTAG.

PROBLEM 14.37 Draw the structure of cyclic adenosine monophosphate (cAMP), a messenger involved in the regulation of glucose production in the body. Cyclic AMP has a phosphate ring connecting the 3′- and 5′-hydroxyl groups on adenosine.

PROBLEM 14.38 Valganciclovir, marketed as Valcyte, is an antiviral agent used for the treatment of cytomegalovirus. Called a *prodrug*, valganciclovir is inactive by itself but is rapidly converted in the intestine by hydrolysis of its ester bond to produce an active drug, called ganciclovir, along with an amino acid.



Valganciclovir

- (a) What amino acid is produced by hydrolysis of the ester bond in valganciclovir?
- (b) What is the structure of ganciclovir?
- (c) What atoms present in the nucleotide deoxyguanine are missing from ganciclovir?
- (d) What role do the atoms missing from deoxyguanine play in DNA replication?
- (e) How might valganciclovir interfere with DNA synthesis?

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14.S: Biomolecules - Nucleic Acids (Summary)

DNA (deoxyribonucleic acid) and **RNA (ribonucleic acid)** are biological polymers that act as chemical carriers of an organism's genetic information. Enzyme-catalyzed hydrolysis of nucleic acids yields **nucleotides**, the monomer units from which RNA and DNA are constructed. Further enzyme-catalyzed hydrolysis of the nucleotides yields **nucleosides** plus phosphate. Nucleosides, in turn, consist of a purine or pyrimidine base linked to the C1 of an aldopentose sugar—ribose in RNA and 2-deoxyribose in DNA. The nucleotides are joined by phosphate links between the 5′ phosphate of one nucleotide and the 3′ hydroxyl on the sugar of another nucleotide.

Molecules of DNA consist of two complementary polynucleotide strands held together by hydrogen bonds between heterocyclic bases on the different strands and coiled into a **double helix**. Adenine and thymine form hydrogen bonds to each other, as do cytosine and guanine.

Three processes take place in deciphering the genetic information of DNA:

- **Replication** of DNA is the process by which identical DNA copies are made. The DNA double helix unwinds, complementary deoxyribonucleotides line up in order, and two new DNA molecules are produced.
- **Transcription** is the process by which RNA is produced to carry genetic information from the nucleus to the ribosomes. A short segment of the DNA double helix unwinds, and complementary ribonucleotides line up to produce **messenger RNA (mRNA)**.
- **Translation** is the process by which mRNA directs protein synthesis. Each mRNA is divided into **codons**, ribonucleotide triplets that are recognized by small amino acid–carrying molecules of **transfer RNA (tRNA)**, which deliver the appropriate amino acids needed for protein synthesis.

Sequencing of DNA is carried out by the **Sanger dideoxy method**, and small DNA segments can be synthesized in the laboratory by automated instruments. Small amounts of DNA can be amplified by factors of 10^6 using the **polymerase chain reaction (PCR)**.

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CHAPTER OVERVIEW

14: Biomolecules - Lipids

Learning Objectives

- When you have completed Chapter 14, you should be able to
- fulfill all of the detailed objectives listed under each individual section.
- distinguish among fats and oils, phospholipids, prostaglandins, terpenes, and steroids, and be familiar with the sources and biological roles of these substances.
- define, and use in context, the key terms introduced in this chapter.

14.0: Introduction to Lipids
14.1: Waxes, Fats, and Oils
14.2: Soap
14.3: Phospholipids
14.4: Prostaglandins and Other Eicosanoids
14.5: Terpenoids
14.6: Steroids
14.7: Hormones - The Regulators
14.8: Biosynthesis of Steroids
14.9: Additional Problems
14.S: Biomolecules - Lipids (Summary)

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13.0: Introduction to Lipids

Objectives

After completing this section, you should be able to identify fats and steroids as being examples of lipids.

Lipids are naturally occurring organic compounds that can be extracted from cells and tissues using nonpolar solvents. Although many lipids have complex structures, their chemistry can often be understood quite readily by applying the basic concepts you have studied in previous chapters. We begin the chapter with a study of fats and oils, and explain the different origins of these structurally similar substances. A discussion of soaps follows, as soap is obtained by the reaction of a fat with sodium hydroxide.



Figure **13.0.1**: Soap bubbles, so common yet so beautiful, are made from animal fat, a lipid. (credit: "Reflections in soap bubbles" by Image Picture Photography/Flickr, CC BY 2.0)

Phospholipids are substances whose structures are somewhat similar to those of fats, except that the former contain a phosphate group. Prostaglandins are lipids that play important roles in biological systems and are of great interest to those involved in the medical and pharmaceutical professions. Terpenoids form a series of compounds whose structural similarity can be seen through the application of the isoprene rule. The chapter concludes with a discussion of steroids, with particular attention being paid to the stereochemistry of these substances.

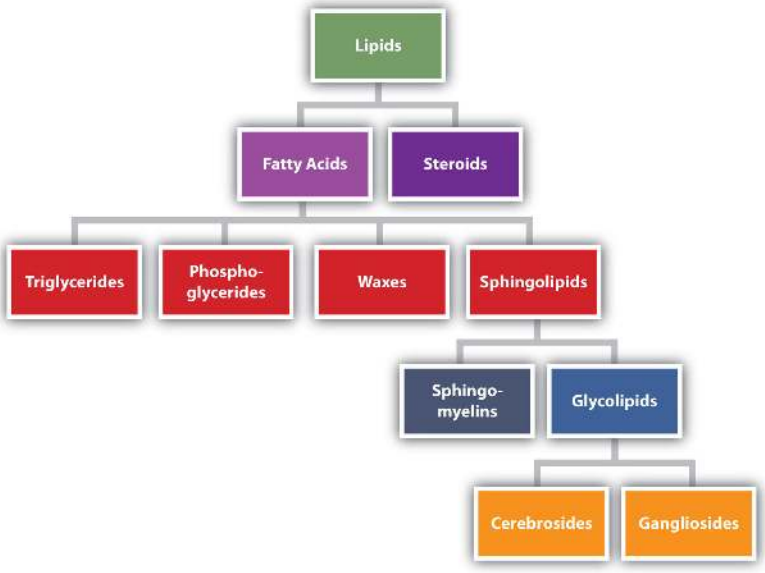
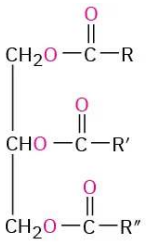


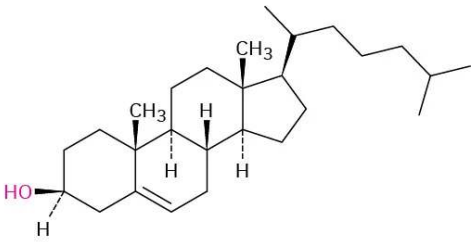
Figure **13.0.2**: Lipid Organization Based on Structural Relationships

Lipids are not defined by the presence of specific functional groups, as carbohydrates are, but by a physical property—solubility. Compounds isolated from body tissues are classified as lipids if they are more soluble in organic solvents, such as dichloromethane, than in water. By this criterion, the lipid category includes not only **fats and oils**, which are esters of the

trihydroxy alcohol glycerol and fatty acids, but also compounds that incorporate functional groups derived from phosphoric acid, carbohydrates, or amino alcohols, as well as **steroid compounds** such as cholesterol. Figure **13.0.2** presents one scheme for classifying the various kinds of lipids.



Animal fat—a triester
(R, R′, R″ = C_{11}–C_{19} chains)



Cholesterol

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14.1: Waxes, Fats, and Oils

Objectives

After completing this section, you should be able to

1. identify waxes as being mixtures of long-chain esters, and write the general structure for such compounds.
2. identify fats and oils as being triacylglycerols, and write a general structure for such compounds.
3. relate the physical properties of animal fats and vegetable oils to their structures.
4. predict the behaviour of a given fat or oil when it is subjected to some of the more common reactions discussed in previous units; examples would include hydrolysis, reduction and ozonolysis.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- fat, fatty acids, triacylglycerols

Study Notes

You are not expected to memorize the trivial names or formulas of the fatty acids listed in Table 14.1.1. The systematic names in these tables may be somewhat unfamiliar, but they are derived in exactly the same way as the names of the simpler carboxylic acids that we discussed in Chapter 6. You may wish to review the alkane names (CHEM 231) and the *E*,*Z* system to satisfy yourself that you understand how these names originate.

In many older textbooks, the term "fatty acid" is used to describe all carboxylic acids, not only those obtained by hydrolyzing triacylglycerols.

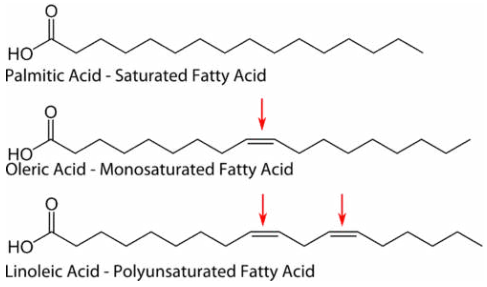
Fats play an important role in human nutrition, and most people are aware of the desirability of limiting their dietary intake of saturated fats, as these compounds have been associated with heart disease. Unsaturated fats are generally considered to be much more desirable from the point of view of good health. Notice that all the fatty acids derived from naturally occurring fats have a *Z* (i.e., cis) configuration.

Linoleic acid is an "essential" nutrient; that is, it cannot be made by the body in sufficient quantity to meet our physiological needs, and must be obtained from food. A deficiency in linoleic acid results in skin problems and liver abnormalities. Historically, linolenic and arachidonic acids were also considered essential nutrients, but recent research suggests they can be synthesized in the body when sufficient linoleic acid is available.

Fatty Acids

Fatty acids are structural components of fats, oils, and all other categories of lipids, except steroids. **Fatty acids** are long-chain carboxylic acids that have the general formula $CH_3(CH_2)_nCOOH$, where n usually ranges from 2 to 28 and is always an even number. More than 70 have been identified in nature. They are generally unbranched and can be classified by the presence and number of carbon-to-carbon double bonds.

A **saturated fat** is a fat that consists of triglycerides whose carbon chains consist entirely of carbon-carbon single bonds. Therefore, the carbon chains are saturated with the maximum number of hydrogen atoms possible. An **unsaturated fat** is a fat that consists of triglycerides whose carbon chains contain one or more carbon-carbon double bonds. A fat with one double bond is called monounsaturated, while a fat with multiple double bonds is called polyunsaturated (see figure below). Table 14.1.1 lists some of the commonly occurring fatty acids.



Each of the double bonds in unsaturated fatty acids can have either cis or trans stereochemistry and the type of fatty acid is further defined as a **cis fatty acid** or **trans fatty acid**. These are what are commonly referred to in food as cis or trans fats.

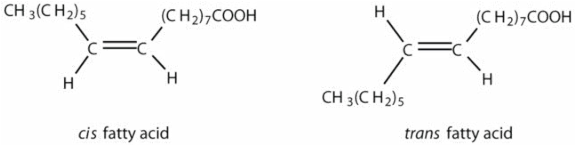


Table 14.1.1: Structures of Some Common Fatty Acids

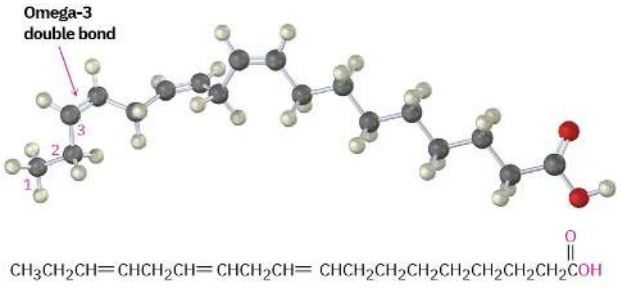
Common Name	Systematic Name	(#C : #=)	Melting point (°C)	Structure
		Saturated		
Lauric acid	dodecanoic acid	12:0	43.2	$CH_3(CH_2)_{10}CO_2H$
Myristic acid	tetradecanoic acid	14:0	53.9	$CH_3(CH_2)_{12}CO_2H$
Palmitic acid	hexadecanoic acid	16:0	63.1	$CH_3(CH_2)_{14}CO_2H$
Stearic acid	octadecanoic acid	18:0	68.8	$CH_3(CH_2)_{16}CO_2H$
Arachidic acid	eicosanoic acid	20:0	76.5	$CH_3(CH_2)_{18}CO_2H$
		Unsaturated		
Palmitoleic acid	(*Z*)-9-hexadecenoic acid	16:1	–0.1	$(Z)-CH_3(CH_2)_5CH=CH(CH$
Oleic acid	(*Z*)-9-octadecenoic acid	18:1	13.4	$(Z)-CH_3(CH_2)_7CH=CH(CH$
Linoleic acid	(*Z*,*Z*)-9,12-octadecadienoic acid	18:2	–12	$(Z,Z)-CH_3(CH_2)_4(CH=CHC$
Linolenic acid	(*Z*,*Z*,*Z*)-9,12,15-octadecatrienoic acid	18:3	–11	$(\text{all Z})-CH_3CH_2(CH=CHCH$
Arachidonic acid	(*Z*,*Z*,*Z*,*Z*)-5,8,11,14-eicosatetraenoic acid	20:4	–49.5	$(\text{all Z})-CH_3(CH_2)_4(CH=CH$

The higher melting points of the saturated fatty acids reflect the uniform rod-like shape of their molecules. Viewed as a whole, however, the saturated fatty acid molecule is relatively straight (Figure 17.1.2b). Such molecules pack closely together in a crystal lattice, maximizing dispersion forces and causing fatty acids and their derivatives to have relatively high melting points.



Stearic acid

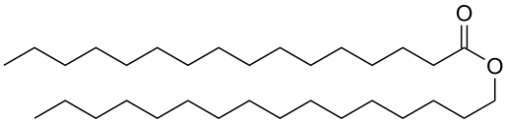
The cis-double bond(s) in the unsaturated fatty acids introduce a kink in their shape, which makes it more difficult to pack their molecules together in a stable repeating array or crystalline lattice. As a result, the intermolecular attractions of unsaturated fatty acids (and unsaturated fats) are weaker, causing these substances to have lower melting points. Most are liquids at room temperature.



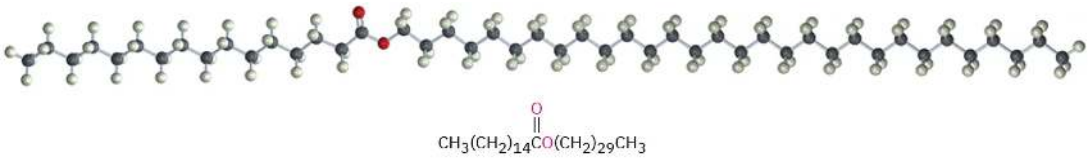
Linolenic acid, an omega-3 polyunsaturated fatty acid

Waxes

Waxes are esters of long-chain fatty acids with long-chain monohydric alcohols (one hydroxyl group). The carboxylic acid and the alcohol typically each have an even number of carbons. Cetyl palmitate is a typical wax, it is the ester of cetyl alcohol ($CH_3(CH_2)_{15}OH$) and palmitic acid ($CH_3(CH_2)_{14}COOH$). Most waxes have a similar structure.



Cetyl palmitate, a typical wax ester



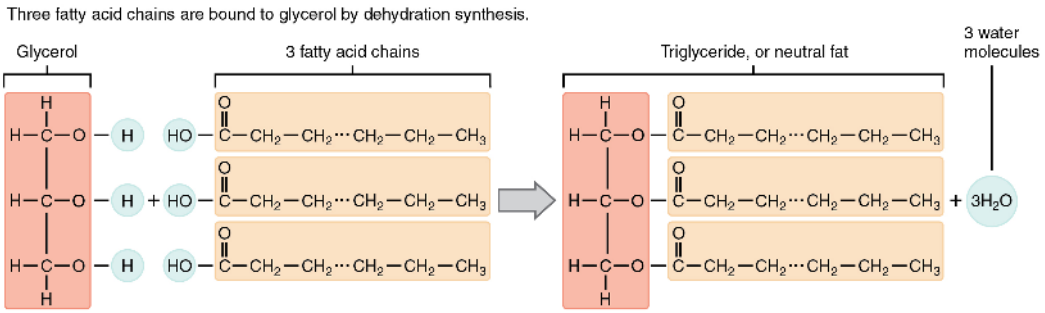
Triacontyl hexadecanoate (from beeswax)

Waxes are widely distributed in nature. The leaves and fruits of many plants have waxy coatings, which may protect them from dehydration and small predators. The feathers of birds and the fur of some animals have similar coatings that serve as a water repellent. Carnauba wax is valued for its toughness and water resistance. The formulas for three well-known waxes are given below, with the carboxylic acid moiety colored red and the alcohol colored blue.

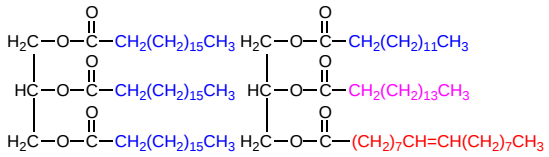
	Spermaceti	Beeswax	Carnauba wax
Alcohol	$CH_3(CH_2)_{14}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH
Fatty Acid	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{24}COOH$
Wax	$CH_3(CH_2)_{14}CO_2$-$(CH_2)_{15}CH_3$	$CH_3(CH_2)_{24}CO_2$-$(CH_2)_{29}CH_3$	$CH_3(CH_2)_{30}CO_2$-$(CH_2)_{33}CH_3$

Triglycerides (Fats)

Fats and oils often exist as **triglycerides** (or ***triacylcylgerols*** because they are esters composed of three fatty acid units joined to *glycerol*, a trihydroxy alcohol (IUPAC name is 1,2,3-propanetriol)):



If all three OH groups on the glycerol molecule are esterified with the same fatty acid, the resulting ester is called a ***simple triglyceride***. Although simple triglycerides have been synthesized in the laboratory, they rarely occur in nature. Instead, a typical triglyceride obtained from naturally occurring fats and oils contains two or three different fatty acid components and is thus termed a ***mixed triglyceride***.



Tristearin: a simple triglyceride (left) and a mixed triglyceride (right)

A triglyceride is called a **fat** if it is a solid at 25°C; it is called an **oil** if it is a liquid at that temperature. These differences in melting points reflect differences in the degree of unsaturation (as discussed above) and the number of carbon atoms in the constituent fatty acids. Triglycerides obtained from animal sources are usually solids, while those of plant origin are generally oils. Therefore, we commonly speak of animal fats and vegetable oils. No single formula can be written to represent the naturally occurring fats and oils because they are highly complex mixtures of triglycerides in which many different fatty acids are represented. The table below shows the fatty acid compositions of some common fats and oils. The composition of any given fat or oil can vary depending on the plant or animal species it comes from as well as on dietetic and climatic factors.

Table 14.1.2: Some common fats and oils, including fatty acid content, are listed below.

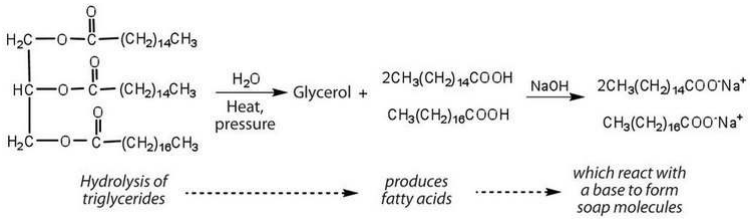
glycerides					
Fat or Oil	**Saturated**		**Unsaturated**		
	Palmitic	Stearic	Oleic	Linoleic	Other
Animal Origin					
Butter	29	9	27	4	31
Lard	30	18	41	6	5
Beef	32	25	38	3	2
Vegetable Origin					
Corn oil	10	4	34	48	4
Soybean	7	3	25	56	9
Peanut	7	5	60	21	7
Olive	6	4	83	7	-

Chemical Reactions

Fats and oils can participate in a variety of chemical reactions—for example, because triglycerides are esters, they can be hydrolyzed in the presence of an acid, a base, or specific enzymes known as lipases. The double bonds in fats and oils can undergo hydrogenation and oxidation.

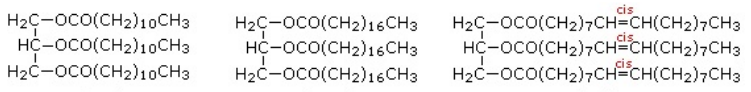
Saponification

The hydrolysis of fats and oils in the presence of a base is used to make soap and is called saponification. Today most soaps are prepared through the hydrolysis of triglycerides (often from tallow, coconut oil, or both) using water under high pressure and temperature [(~50 atm or 5,000 kPa) and 200°C]. Sodium carbonate or sodium hydroxide is then used to convert the fatty acids to their sodium salts (soap molecules):



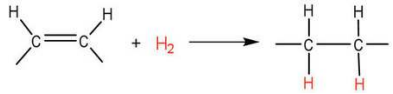
Chemical reaction of the saponification (base hydrolysis) of a triglyceride.

As might be expected from the properties of the fatty acids, fats have a predominance of saturated fatty acids, and oils are composed largely of unsaturated acids. Thus, the melting points of triglycerides reflect their composition, as shown by the following examples. Natural mixed triglycerides have somewhat lower melting points, the melting point of lard being near 30 ° C, whereas olive oil melts near -6 ° C. Since fats are valued over oils by some Northern European and North American populations, vegetable oils are extensively converted to solid triglycerides (e.g. Crisco) by partial hydrogenation of their unsaturated components. Some of the remaining double bonds are isomerized (to trans) in this operation. These saturated and trans-fatty acid glycerides in the diet have been linked to long-term health issues such as atherosclerosis.



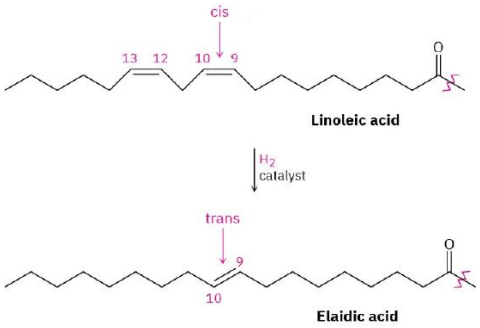
Hydrogenation

The hydrogenation of vegetable oils to produce semisolid fats is an important process in the food industry. Chemically, it is essentially identical to the catalytic hydrogenation reaction described for alkenes.



The C=C bonds in vegetable oils can be reduced by catalytic hydrogenation, typically carried out at high temperature using a nickel catalyst, to produce saturated solid or semisolid fats. Prior to 2015, industrially produced margarine and shortening were produced by hydrogenating soybean, peanut, or cottonseed oil until

the proper consistency is obtained. As of 2015, trans fats are no longer considered safe by the FDA and have since been phased out of industrially produced foods. Unfortunately, the hydrogenation reaction is accompanied by some cis–trans isomerization of the remaining double bonds, producing fats with about 10% to 15% trans unsaturated fatty acids. Dietary intake of trans fatty acids increases cholesterol levels in the blood, thereby increasing the risk of heart problems. The conversion of linoleic acid into elaidic acid is an example.



In commercial processes, the number of double bonds that are hydrogenated is carefully controlled to produce fats with the desired consistency (soft and pliable). Inexpensive and abundant vegetable oils (canola, corn, soybean) are thus transformed into margarine and cooking fats.

Many people have switched from butter to margarine or vegetable shortening because of concerns that saturated animal fats can raise blood cholesterol levels and result in clogged arteries. However, during the hydrogenation of vegetable oils, an isomerization reaction occurs that produces the trans fatty acids mentioned in the opening essay. However, studies have shown that trans fatty acids also raise cholesterol levels and increase the incidence of heart disease. Trans fatty acids do not have the bend in their structures, which occurs in cis fatty acids and thus pack closely together in the same way that the saturated fatty acids do. Consumers are now advised to use polyunsaturated oils and soft or liquid margarine, and to reduce their total fat intake to less than 30% of their total calorie intake each day.

Exercise 14.1.1

Why do unsaturated fatty acids have lower melting points than saturated fatty acids?

Answer

Unsaturated fatty acids cannot pack as tightly together as saturated fatty acids due to the presence of the cis double bond that puts a “kink” or bend in the hydrocarbon chain.

Exercise 14.1.2

Classify each fatty acid as saturated or unsaturated and indicate the number of carbon atoms in each molecule.

a. palmitoleic acid
b. myristic acid
c. linoleic acid

Answer

a. unsaturated; 16 carbon atoms
b. saturated; 14 carbon atoms
c. unsaturated; 18 carbon atoms

Exercise 14.1.3

Write the condensed structural formula for each fatty acid.

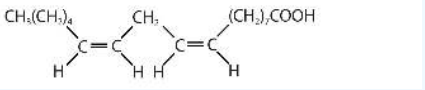
a. lauric acid
b. palmitoleic acid
c. linoleic acid

Answer

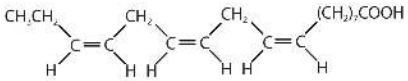
a. $CH_3(CH_2)_{10}COOH$
b. $CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
c. $CH_3(CH_2)_3(CH_2CH{=}CH)_2(CH_2)_7COOH$

Exercise 14.1.4

Arrange these fatty acids (all contain 18 carbon atoms) in order of increasing melting point. Justify your arrangement.

a) 

b) 

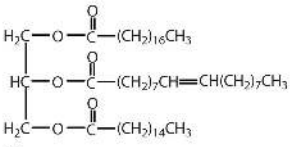
c) 

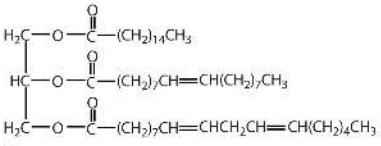
Answer

c < a < b; an increase in the number of double bonds will lower the melting point because it is more difficult to closely pack the fatty acids together.

Exercise 14.1.5

Which of these triglycerides would you expect to find in higher amounts in oils? In fats? Justify your choice.


(a)


(b)

Answer

The triglyceride labeled as (a) is expected to be present in higher amounts in fats because it is composed of a greater number of saturated fatty acids. The triglyceride labeled as (b) is expected to be present in higher amounts in oils because it is composed of a greater number of unsaturated fatty acids.

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14.2: Soap

Learning Objectives

After completing this section, you should be able to

- write an equation to represent the formation of a soap.
  - identify the structure of the fat required to produce a given soap.
  - identify the structure of a soap, given the structure of the fat from which it is produced.
- describe the mechanism by which soaps exert their cleansing action.
- give a chemical explanation of the problems encountered when carboxylate soaps are used in hard-water areas, and explain how they may be overcome by the use of sulphonate detergents.

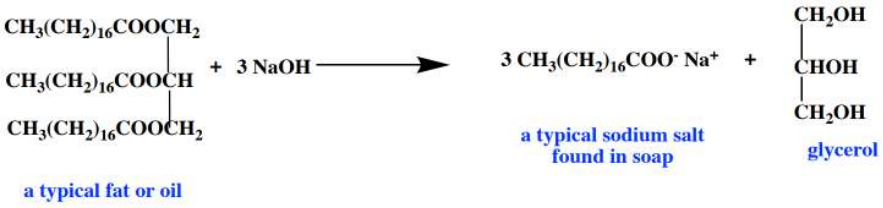
Key Terms

Make certain that you can define, and use in context, the key terms below.

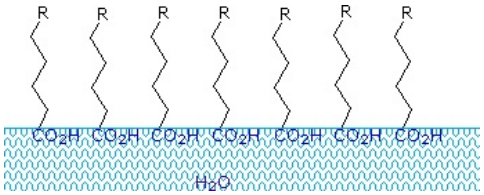
- hydrophilic
- lipophilic (hydrophobic)
- amphiphilic
- micelles

Soap making has remained unchanged over the centuries. The ancient Roman tradition called for mixing rain water, potash and animal tallow (rendered form of beef or mutton fat). Making soap was a long and arduous process. First, the fat had to be rendered (melted and filtered). Then, potash solution was added. Since water and oil do not mix, this mixture had to be continuously stirred and heated sufficiently to keep the fat melted. Slowly, a chemical reaction called saponification would take place between the fat and the hydroxide which resulted in a liquid soap. When the fat and water no longer separated, the mixture was allowed to cool. At this point salt, such as sodium chloride, was added to separate the soap from the excess water. The soap came to the top, was skimmed off, and placed in wooden molds to cure. It was aged many months to allow the reaction to run to completion.

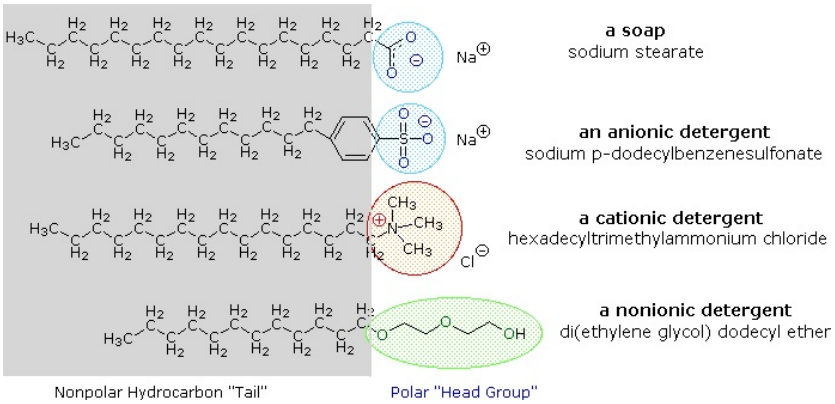
All soap is made from fats and oils, mixed with alkaline (basic) solutions. There are many kinds of fats and oils, both animal and vegetable. As previously discussed, fats are usually solid at room temperature, but many oils are liquid at room temperature. Liquid cooking oils originate from corn, peanuts, olives, soybeans, and many other plants. For making soap, all different types of fats and oils can be used – anything from lard to exotic tropical plant oils.



Carboxylic acids and salts having alkyl chains longer than eight carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed **amphiphilic** (Gk. amphi = both) or **amphipathic**. Fatty acids made up of ten or more carbon atoms are nearly insoluble in water, and because of their lower density, float on the surface when mixed with water. Unlike paraffin or other alkanes, which tend to puddle on the waters surface, these fatty acids spread evenly over an extended water surface, eventually forming a monomolecular layer in which the polar carboxyl groups are hydrogen bonded at the water interface, and the hydrocarbon chains are aligned together away from the water. This behavior is illustrated in the diagram on the right. Substances that accumulate at water surfaces and change the surface properties are called **surfactants**.



Alkali metal salts of fatty acids are more soluble in water than the acids themselves, and the amphiphilic character of these substances also make them strong surfactants. The most common examples of such compounds are soaps and detergents, four of which are shown below. Note that each of these molecules has a nonpolar hydrocarbon chain, the "tail", and a polar (often ionic) "head group". The use of such compounds as cleaning agents is facilitated by their surfactant character, which lowers the surface tension of water, allowing it to penetrate and wet a variety of materials.



When minute amounts of soaps are put into water, instead of forming simple solutions, the molecules become concentrated at the surface of the water, with the saltlike ends sticking down into the water and the hydrocarbon chains forming a layer on the surface. This arrangement greatly reduces the surface tension of the water and contributes to the startling properties of soap films and bubbles. At higher concentrations, the solutions become turbid as the result of **micelle** formation. Micelles are spherical aggregates of soap molecules, wherein the hydrocarbon chains form a region of low polarity that is stabilized by having the polar salt ends of the molecules in contact with the water. By gathering the hydrophobic chains together in the center of the micelle, disruption of the hydrogen bonded structure of liquid water is minimized, and the polar head groups extend into the surrounding water where they participate in hydrogen bonding.

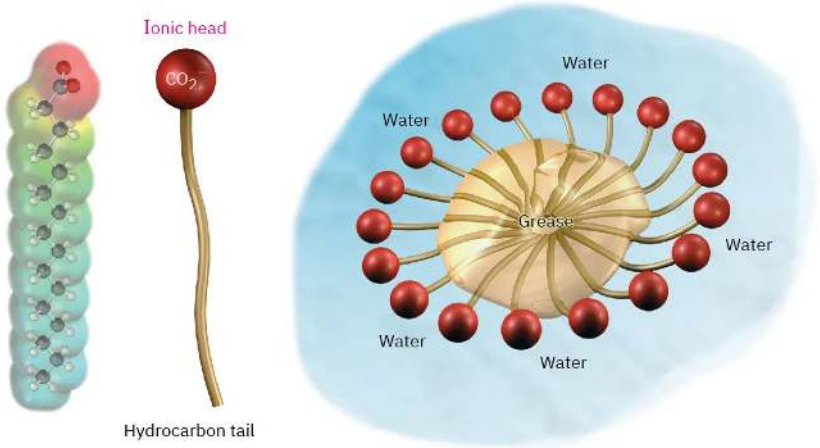


Figure 14.2.1: A soap micelle solubilizing a grease particle in water. An electrostatic potential map of a fatty acid carboxylate shows how the negative charge is located in the head group.

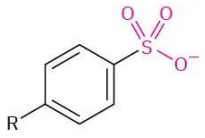
The importance of soap to human civilization is documented by history, but some problems associated with its use have been recognized. One of these is caused by the weak acidity (pKa ca. 4.9) of the fatty acids. Solutions of alkali metal soaps are slightly alkaline (pH 8 to 9) due to hydrolysis. If the pH of a soap solution is lowered by acidic contaminants, insoluble fatty acids

precipitate and form a scum. A second problem soaps are less effective in hard water, which is water that contains a significant concentration of magnesium, calcium and iron ions. These ions form precipitates with soap molecules, and this precipitate is often seen as a gray line on a bathtub or sink and is often called “soap scum”. Since soap forms a precipitate with these ions, it means that many of the soap molecules are no longer present in the solution. Therefore, soap will form fewer suds in hard water. “Soft water” is water that contains very few or no ions that precipitate with soap. Soap will therefore be much more effective in soft water than in hard water.

Detergents

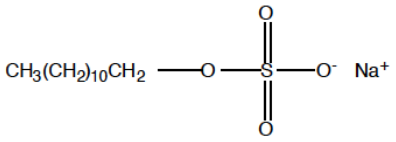
(Not included in CHEM 232)

These problems have been alleviated by the development of synthetic soaps called detergents. Detergents are similar to soaps in that they have a charged head group and a long nonpolar tail group, but they are not prepared from natural fats or oils. Detergents are useful because they do not form precipitates with magnesium, iron, or calcium ions, which means they work in soft and hard water. By using a much stronger acid for the polar head group, water-based detergent solutions are less sensitive to pH changes. Also, the sulfonate groups used in virtually all anionic detergents confer greater solubility on micelles that incorporate the alkaline-earth cations found in hard water.



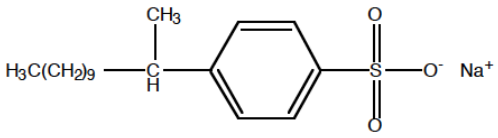
A synthetic detergent
(R = various C_{12} chains)

Variations on the detergent theme have led to the development of other classes, such as the cationic and nonionic detergents shown above. Cationic detergents often exhibit germicidal properties, and their ability to change surface pH has made them useful as fabric softeners and hair conditioners. These versatile chemical "tools" have dramatically transformed the household and personal care cleaning product markets over the past fifty years



Sodium Lauryl Sulfate (a non-biodegradable detergent)

After detergents started being widely used, it was discovered that they were not broken down in sewage treatment plants. Many streams and lakes became contaminated with detergents, and large amounts of foam appeared in natural waters. Biodegradable detergents were then developed. Shown below is an example of a biodegradable detergent, sodium laurylbenzenesulfonate.



Sodium Lauryl benzenesulfonate (a biodegradable detergent)

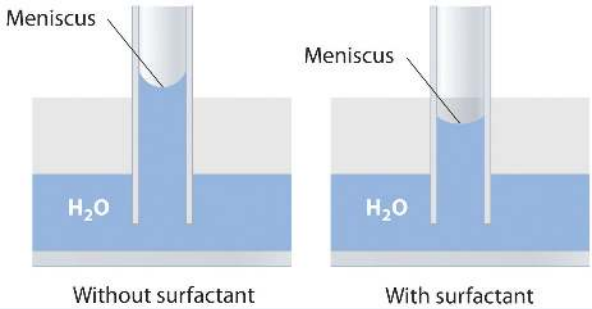
? Exercise 14.2.1

Explain how soaps or surfactants decrease the surface tension of a liquid. How does the meniscus of an aqueous solution in a capillary change if a surfactant is added? Illustrate your answer with a diagram.

Answer

Adding a soap or a surfactant to water disrupts the attractive intermolecular interactions between water molecules, thereby decreasing the surface tension. Because water is a polar molecule, one would expect that a soap or a surfactant would also

disrupt the attractive interactions responsible for adhesion of water to the surface of a glass capillary. As shown in the sketch, this would decrease the height of the water column inside the capillary, as well as making the meniscus less concave.



Exercise 14.2.2

Draw the structure of calcium stearate, a component of soap scum.

Answer

$(C_{17}H_{35}COO)_2Ca^{2+}$

Exercise 14.2.3

Draw the structure of magnesium oleate, a component of bathtub scum.

Answer

$$[CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2^-]_2\ Mg^{2+}$$

Exercise 14.2.4

Write the saponification reaction of glyceryl dioleate monopalmitate with aqueous NaOH.

Answer

Glyceryl dioleate monopalmitate → glycerol + 2 sodium oleate + sodium palmitate

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14.3: Phospholipids

Learning Objectives

After completing this section, you should be able to

- draw the general structure of a phosphoglyceride.
- describe the occurrence and importance of phosphoglycerides in plant and animal tissues.

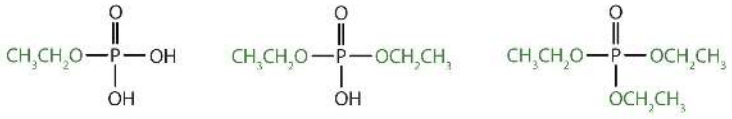
Key Terms

Make certain that you can define, and use in context, the key terms below.

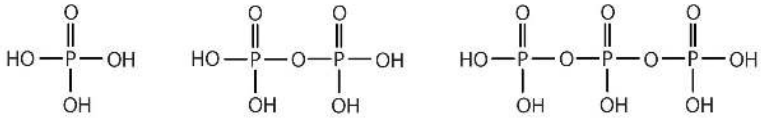
- phosphoglyceride
- phospholipid

Phosphate Esters

Similarly to carboxylic acids, inorganic acids such as nitric acid (HNO_3), sulfuric acid (H_2SO_4), and phosphoric acid (H_3PO_4) also can form esters. The esters of phosphoric acid are especially important in biochemistry. A phosphoric acid molecule can form a monoalkyl, a dialkyl, or a trialkyl ester by reaction with one, two, or three molecules of an alcohol.

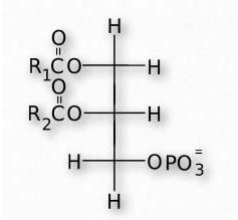


Esters of pyrophosphoric acid and triphosphoric acid are also important in biochemistry.

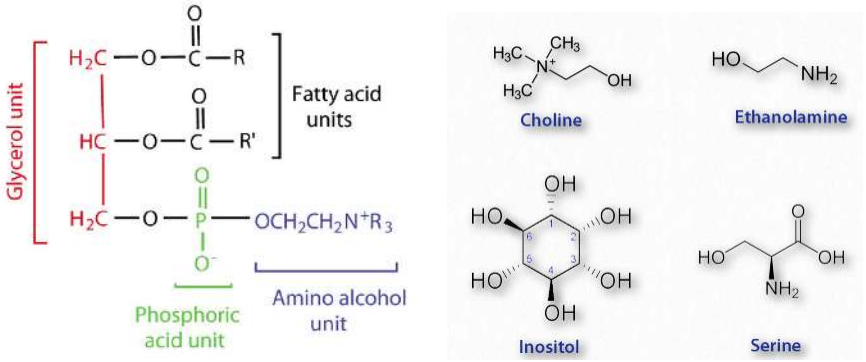


Phospholipids

The two main types of phospholipids are **glycerophospholipids** and **sphingomyelins**. Glycerophospholipids are important components of the lipid bilayer of cellular membranes. Glycerophospholipids are structurally related to fats, as both are derived from phosphatidic acid, which has the basic structure of glycerol with two ester bonds with fatty acids and one ester bond with phosphoric acid.



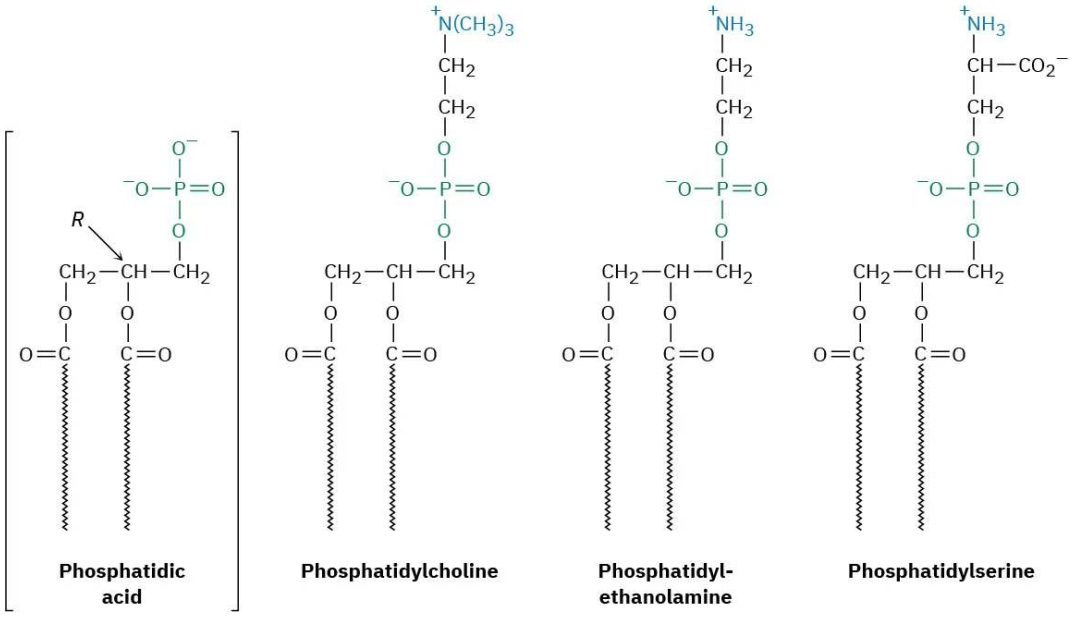
Phosphatidic acid is converted into a glycerophospholipid by esterifying various groups, such as ethanolamine, serine, choline, inositol, and others to the phosphate of phosphatidic acid. These compounds have a chiral center at C2 and have an R configuration when found in nature.



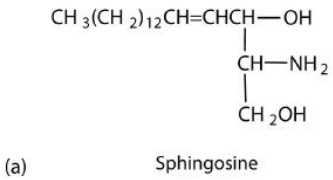
The **phosphatidylethanolamines** are found in all living cells and are one of the most common phosphatides. They are common constituents of brain tissue and in the spinal cord, making up as much as 45% of the total phospholipids. Phosphatidylethanolamines are asymmetrically distributed across membranes, being preferentially located on the inner leaflet (closest to the cytoplasm) of the plasma membrane.

Metabolically, phosphatidylethanloamines are precursors of **phosphatidylcholines**. Phosphatidylcholines are another group of important membrane components. They tend to be found more commonly on the outer leaflet of the plasma membrane. Nutritionally, the compounds are readily obtained from eggs and soybeans. Phosphatidylcholines are moved across membranes by Phosphatidylcholine transfer protein (PCTP).

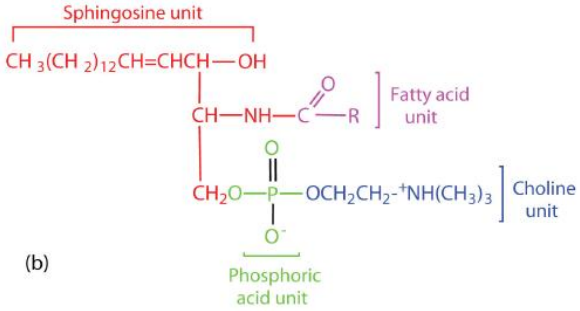
Like the phosphatidylethanolamines, **phosphatidylserines** are preferentially located on the inner leaflet of the plasma membrane. Phosphatidylserine is a polar phospholipid. A serine head group has been added on to a phosphate group on a glycerol functional group. When apoptosis (cell suicide) occurs, the preferential distribution is lost and the phosphatidylserines appear on the outer leaflet where they serve as a signal to macrophages to bind and destroy the cell.



Sphingomyelins, the simplest sphingolipids, each contain a fatty acid, a phosphoric acid, sphingosine, and choline. Because they contain phosphoric acid, they are also classified as phospholipids. Sphingomyelins are important constituents of the myelin sheath surrounding the axon of a nerve cell. Multiple sclerosis is one of several diseases resulting from damage to the myelin sheath.



(a) Sphingosine



(b)

Lipid Bilayer

Phospholipids are found widely in both plant and animal tissues and make up approximately 50% to 60% of cell membranes. Because they are like soaps in having a long, nonpolar hydrocarbon tail bound to a polar ionic head, phospholipids in the cell membrane organize into a lipid bilayer about 5.0 nm (50 Å) thick. As shown in Figure 14.3.1, the nonpolar tails aggregate in the center of the bilayer in much the same way that soap tails aggregate in the center of a micelle. This bilayer serves as an effective barrier to the passage of water, ions, and other components into and out of cells.

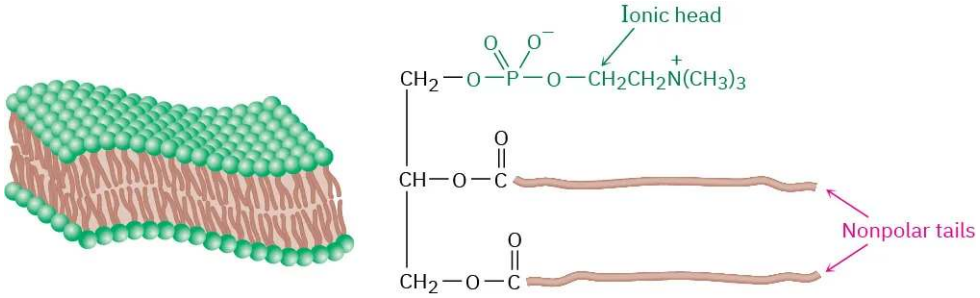


Figure 14.3.1: Aggregation of glycerophospholipids into the lipid bilayer that composes cell membranes.

In one sense, the polar lipids are like the anions of fatty acids, only more so. They contain two hydrophobic hydrocarbon tails and a head that may have several electrically charged sites. As in the case of soap and detergent molecules, the tails of polar lipids tend to avoid water and other polar substances, but the heads are quite compatible with such environments.

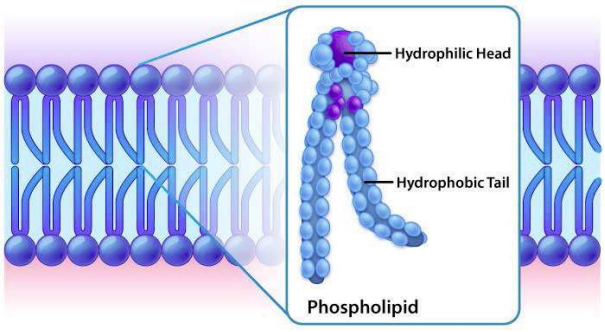


Figure 14.3.2: Lipid bilayer closeup Image by Aleia Kim

As ionic amphiphiles, phospholipids aggregate or self-assemble when mixed with water, but in a different manner than the soaps and detergents. Because of the two pendant alkyl chains present in phospholipids and the unusual mixed charges in their head groups, micelle formation is unfavorable relative to a bilayer structure. If a phospholipid is smeared over a small hole in a thin piece of plastic immersed in water, a stable planar bilayer of phospholipid molecules is created at the hole. As shown in the following diagram, the polar head groups on the faces of the bilayer contact water, and the hydrophobic alkyl chains form a nonpolar interior.

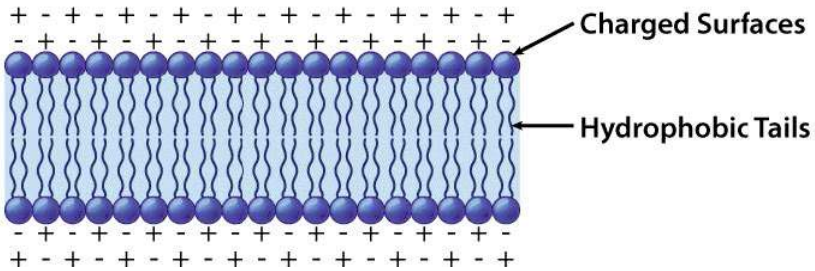


Figure 14.3.3: Organization of the lipid bilayer Image by Aleia Kim

The polar lipids are most commonly found as components of cell walls and other membranes. Nearly all hypotheses regarding membrane structure take as a fundamental component a lipid bilayer. Bilayers formed in the laboratory share many properties with membranes. Ions such as Na^+, K^+, and Cl^- cannot pass through them, but water molecules can. Certain carrier molecules can transport K^+ and other ions across a bilayer, apparently by wrapping a hydrophobic cloak around them to disguise their charges. Membrane proteins in a bilayer also allow for the transport of ions and other molecules across the bilayer, which could not cross otherwise.

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13.4: Prostaglandins and Other Eicosanoids

Learning Objectives

After completing this section, you should be able to

- describe the general structure of the prostaglandins, and identify a prostaglandin from a given list of organic structures.
- identify at least two important biological functions of prostaglandins.

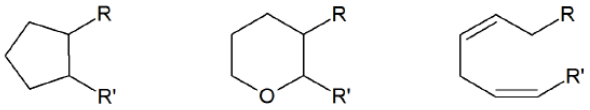
Key Terms

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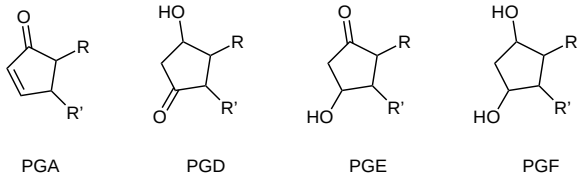
- eicosanoid
- prostaglandin

Eicosanoids

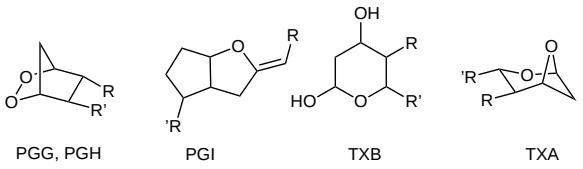
The members of this group of structurally related natural hormones have an extraordinary range of biological effects. They can lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses. Because their genesis in body tissues is tied to the metabolism of the essential fatty acid arachadonic acid (5,8,11,14-eicosatetraenoic acid) they are classified as **eicosanoids**. Many properties of the common drug aspirin result from its effect on the cascade of reactions associated with these hormones. Eicosanoids include prostaglandins, leukotrienes, and thromboxanes.



Eicosanoids are primarily named off the ring system present in the molecule prostaglandin (PG), thromboxane (TX), leukotriene (LT). Common substitution patterns on the ring system are indicated with a letter in the name. Also, the number of double bonds in the molecule is indicated with a subscript number.

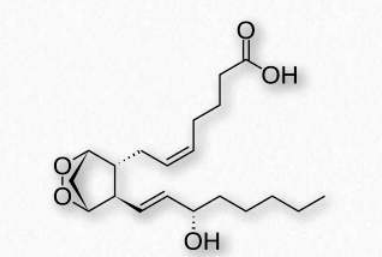


Prostaglandin structures for PGA, PGD, PGE and PGF



Structures for prostaglandins PGG, PGH and PGI and thromboxanes TXA and TXB

Thus the molecule PGH_2 means that it has the prostaglandin ring system with a type H Substitution pattern. The subscript 2 indicated that the molecule contains two double bonds.



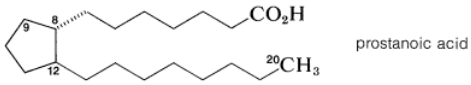
Prostaglandin PGH_2

Prostaglandins

Prostaglandins were first discovered and isolated from human semen in the 1930s by Ulf von Euler of Sweden. Thinking they had come from the prostate gland, he named them prostaglandins. It has since been determined that they exist and are synthesized in virtually every cell of the body. Prostaglandins, are like hormones in that they act as chemical messengers, but do not move to other sites, but work right within the cells where they are synthesized.

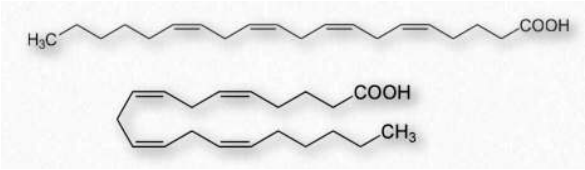
Prostaglandins are found in low concentrations distributed in a large number of organs, tissues, and body fluids of mammals. They exhibit a broad spectrum of physiological activity and are remarkably potent. Their precise biological role is not entirely clear, but they are known to induce strong contractions of smooth muscle tissue (lungs, uterus) and to lower blood pressure and sodium levels. Prostaglandins also have been implicated in the control of pituitary hormones released from the hypothalamus, and in the incidence of "pain" as a response to fever and inflammation. In fact, the analgesic property of aspirin possibly may result from the inhibition of prostaglandin biosynthesis

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon prostanoic acid, which is a C20 fatty acid in which there is a cyclopentane ring formed by connecting the C8 and C12 positions.



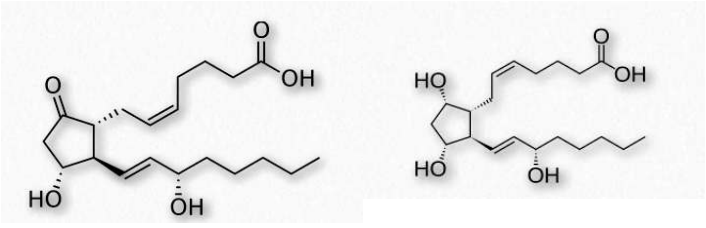
prostanoic acid

They are biochemically synthesized from the fatty acid, arachidonic acid. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring of the prostaglandin.



Arachidonic acid

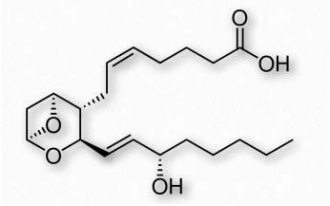
There are a variety of functional groups present in prostaglandin structures. The can have one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups. Some typical structures are shown below.



Prostaglandin E2 (left) and Prostaglandin $F_{2\alpha}$ (Right)

Thromboxanes

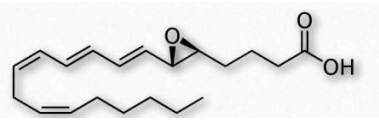
Thromboxanes play roles in clot formation and named for their role in thrombosis. They are potent vasoconstrictors and facilitate platelet aggregation. They are synthesized in platelets, as well. The anti-clotting effects of aspirin have their roots in the inhibition of synthesis of PGH2, which is the precursor of the thromboxanes. The most common thromboxanes are A2 (Figure 2.217) and B2.



Thromboxane $A2_2$

Leukotrienes

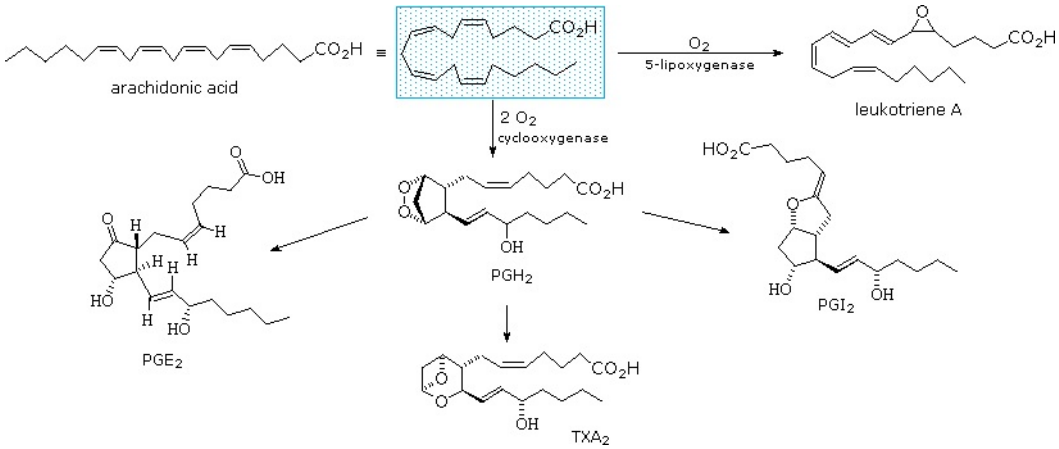
Another group of eicosanoid compounds are the leukotrienes (Figure 2.219). Like prostaglandins, leukotrienes are made from arachidonic acid. The enzyme catalyzing their formation is a dioxygenase known as arachidonate 5-lipoxygenase. Leukotrienes are involved in regulating immune responses. They are found in leukocytes and other immunocompetent cells, such as neutrophils, monocytes, mast cells, eosinophils, and basophils. Leukotrienes are associated with production of histamines and prostaglandins, which act as mediators of inflammation. Leukotrienes also trigger contractions in the smooth muscles of the bronchioles. When overproduced, they may pay a role in asthma and allergic reactions. Some treatments for asthma aim at inhibiting production or action of leukotrienes.



Leukotriene A_4 (LTA_4)

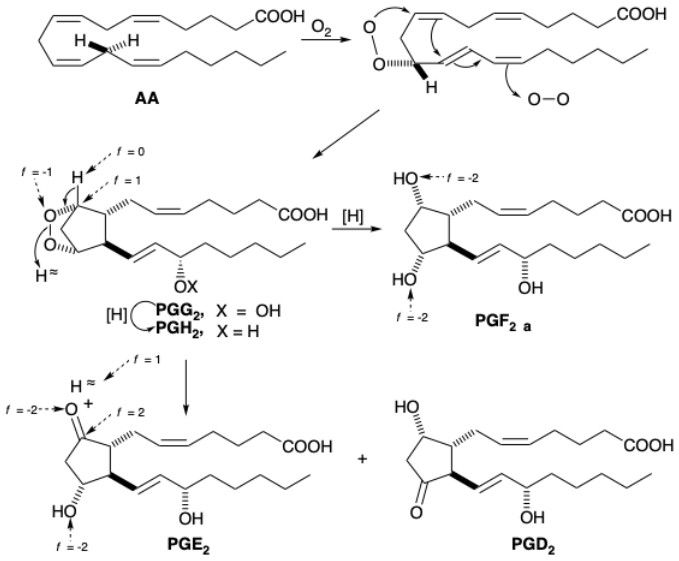
Eicosanoid Biosynthesis

The biosynthesis of eicosanoids begins with the reaction of arachidonic acid with $\mathbf{O_2}$ which can be catalyzed by two different cyclooxygenase enzymes (COX-1 & COX-2).



In nature, prostaglandins arise by an oxidative cyclization of poly-unsaturated twenty-carbon fatty acids, which begins with enantiospecific removal of the L-hydrogen atom of the prochiral methylene group at C-13 coupled with enantiospecific introduction of oxygen at the allylic C-15 position. Subsequent cyclization and termination by addition of a second molecule of oxygen leads to a 15-hydroperoxy bicyclic peroxide (PGG), that is reduced to a 15-hydroxy bicyclic peroxide (PGH). These intermediates, known as prostaglandin endoperoxides, have been isolated and shown to yield prostaglandins. Reduction of the peroxy bridge gives PGF, while disproportionation gives β-hydroxy ketones PGE and PGD. The carbons in prostaglandins are

numbered one to twenty starting at the carboxyl carbon and following the numbering system of the biosynthetic precursor fatty acids.



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14.5: Terpenoids

Objectives

After completing this section, you should be able to

1. identify a terpene from a given list of organic structures.
2. analyze the structure of a given terpene in terms of the isoprene rule.
3. classify a given terpene structure according to the number of isoprene units present; that is, determine whether a given terpene is a monoterpene, sesquiterpene, diterpene, etc.
4. identify and draw the structure of the precursors of isopentenyl diphosphate: (*R*) mevalonate or 1-deoxy-D-xylulose 5-phosphate.

Key Terms

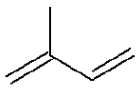
Make certain that you can define, and use in context, the key terms below.

- isoprene rule
- terpenoid
- terpene

Study Notes

You are not expected to memorize all the details of the synthetic mechanisms for terpenoids. However, you should know the overall general synthetic pathway illustrated under "Terpenoid Biosynthesis." As you read through the details of these mechanisms, realize that they may be complex, but they are based on experimental evidence. You should also note the important role of enzymes in many natural systems transformations. Finally, you will recognize that essentially, individual steps are often reactions you have already encountered in previous sections.

The terpenoids (aka isoprenoids) are a large (estimated 60% of known natural products) and diverse group of lipids derived from five-carbon isoprene units assembled in thousands of combinations. Although formally a *terpenoid* contains oxygen, while a hydrocarbon is called a **terpene**, we'll use the term **terpenoid** to refer to both for simplicity.



isoprene

Despite their apparent structural differences, all terpenoids contain a multiple of five carbons and are derived biosynthetically from the five-carbon precursor isopentenyl diphosphate (Figure 14.5.1).

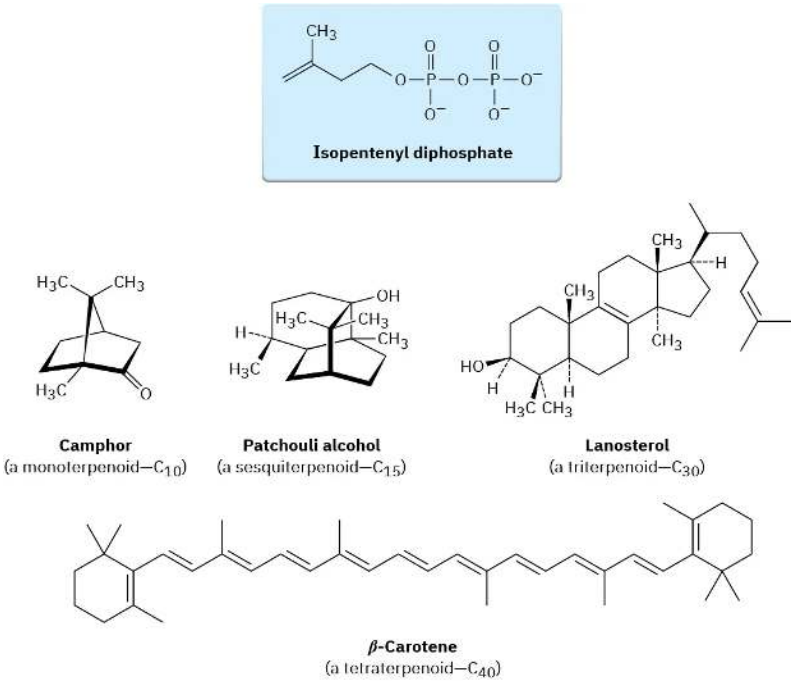


Figure 14.5.1: Structures of some representative terpenoids.

Isoprene Rule

Compounds classified as terpenes constitute what is arguably the largest and most diverse class of natural products. A majority of these compounds are found only in plants, but some of the larger and more complex terpenes (e.g. squalene & lanosterol) occur in animals. Terpenes that incorporate the most common functional groups are known, so this does not provide a useful means of classification. Instead, the number and structural organization of carbons are definitive characteristics. Terpenes may be considered to be made up of isoprene (more accurately isopentane) units, an empirical feature known as the isoprene rule. Because of this, terpenes usually have $5n$ carbon atoms (n is an integer), and are subdivided as follows:

Classification	Isoprene Units	Carbon Atoms
monoterpenes	2	C_{10}
sesquiterpenes	3	C_{15}
diterpenes	4	C_{20}
sesterterpenes	5	C_{25}
triterpenes	6	C_{30}

Isoprene itself, a C_5H_8 gaseous hydrocarbon, is emitted by the leaves of various plants as a natural byproduct of plant metabolism. Next to methane, it is the most common volatile organic compound found in the atmosphere. Examples of C10 and higher terpenes, representing the four most common classes, are shown in the following diagrams. Most terpenes may be structurally dissected into isopentane segments. How this is done can be seen in the diagram directly below.

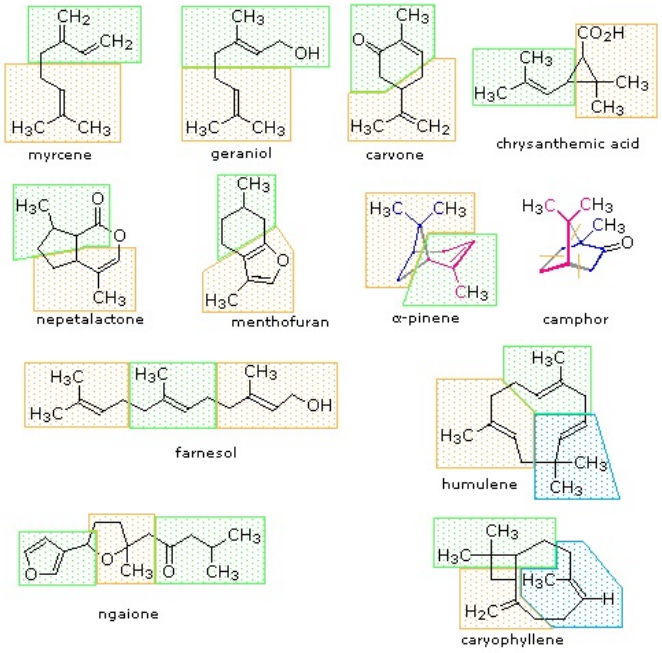


Figure 14.5.2: Monoterpenes and sesquiterpenes

The isopentane units in most of these terpenes are easy to discern and are defined by the shaded areas. In the case of the monoterpene camphor, the units overlap to such a degree that it is easier to distinguish them by coloring the carbon chains. This is also done for alpha-pinene. In the case of the triterpene lanosterol we see an interesting deviation from the isoprene rule. This thirty-carbon compound is clearly a terpene, and four of the six isopentane units can be identified. However, the ten carbons in the center of the molecule cannot be dissected in this manner. Evidence indicates that the two methyl groups circled in magenta and light blue have moved from their original isoprenoid locations (marked by small circles of the same color) to their current positions. This rearrangement is described in the biosynthesis section. Similar alkyl group rearrangements account for other terpenes that do not strictly follow the isoprene rule.

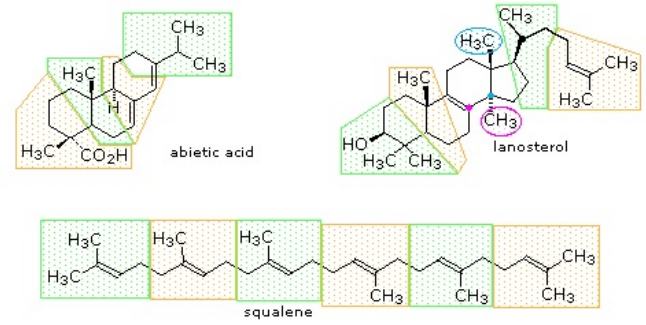
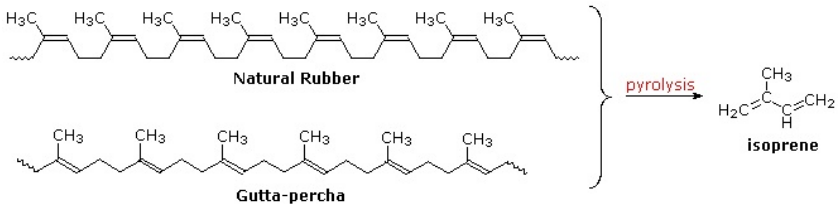


Figure 14.5.3: Triterpenes

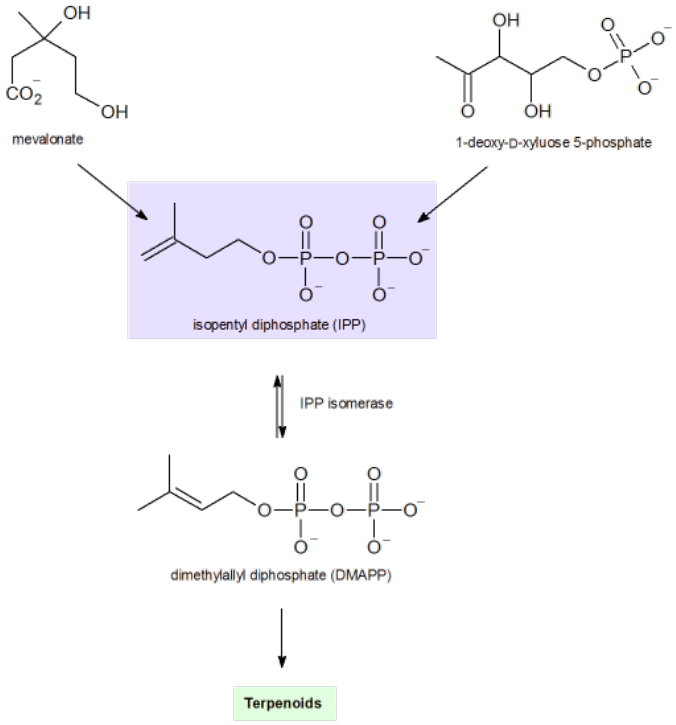
Polymeric isoprenoid hydrocarbons have also been identified. Rubber is undoubtedly the best known and most widely used compound of this kind. It occurs as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*). Rubber is a polyene, and exhibits all the expected reactions of the C=C function. Bromine, hydrogen chloride, and hydrogen all add with a stoichiometry of one molar equivalent per isoprene unit. Ozonolysis of rubber generates a mixture of levulinic acid, CH_3-CO-CH_2-CH_2-CO_2H, and the corresponding aldehyde. Pyrolysis of rubber produces the diene isoprene along with other products.



The double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation. This is reflected in the physical properties of rubber. Despite its high molecular weight (about one million), crude latex rubber is a soft, sticky, elastic substance. Chemical modification of this material is normal for commercial applications. Gutta-percha (structure above) is a naturally occurring E-isomer of rubber. Here, the hydrocarbon chains adopt a uniform zigzag or rod-like conformation, producing a more rigid and tough substance. Uses of gutta-percha include electrical insulation and the covering of golf balls.

Terpenoid Biosynthesis

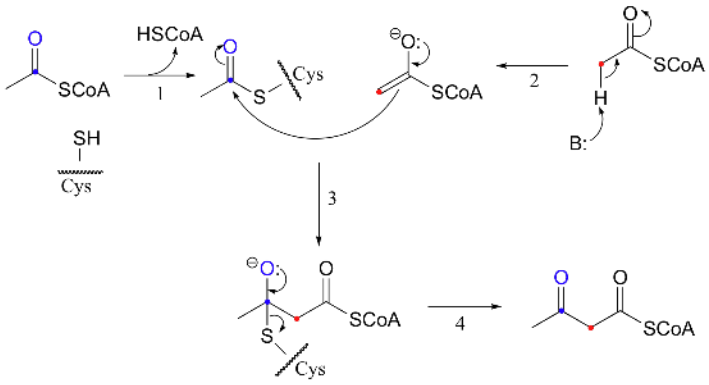
While we can identify isoprene units within a terpenoid structure and use that in its classification, the building block for terpenoid synthesis in nature is isopentenyl diphosphate (formerly called isopentenyl pyrophosphate and abbreviated IPP). There are two major routes to the synthesis of IPP; namely (1) the mevalonate pathway and (2) the 1-deoxyxylulose pathway.



Mevalonate Pathway

Step 1 - Claisen Condensation

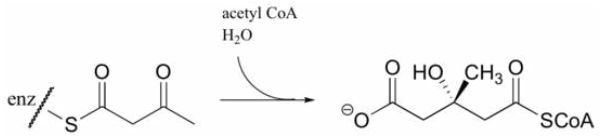
An early step in the biosynthesis of cholesterol and other ‘isoprenoid’ compounds is a Claisen condensation between two acetyl-CoA molecules. An initial trans-thioesterase process transfers the acetyl group of the first acetyl CoA to an enzymatic cysteine (Reaction 1). In the Claisen condensation phase of the reaction, the alpha-carbon of a second acetyl-CoA is deprotonated, forming an enolate (Reaction 2).



The enolate carbon attacks the electrophilic thioester carbon, forming a tetrahedral intermediate (Reaction 3) which quickly collapses to expel the cysteine thiol (Reaction 4) and produce acetoacetyl CoA.

Step 2 - **Aldol Condensation**

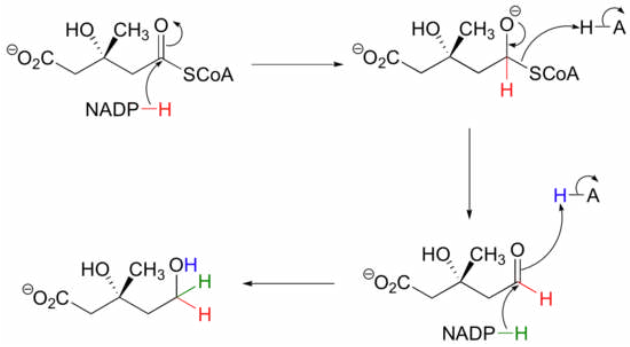
Acetyl CoA then reacts with the acetoacetyl CoA in an aldol-like addition. Subsequent hydrolysis produces (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).



Generating HMG-CoA

Step 3 - **Reduction of the Thioester**

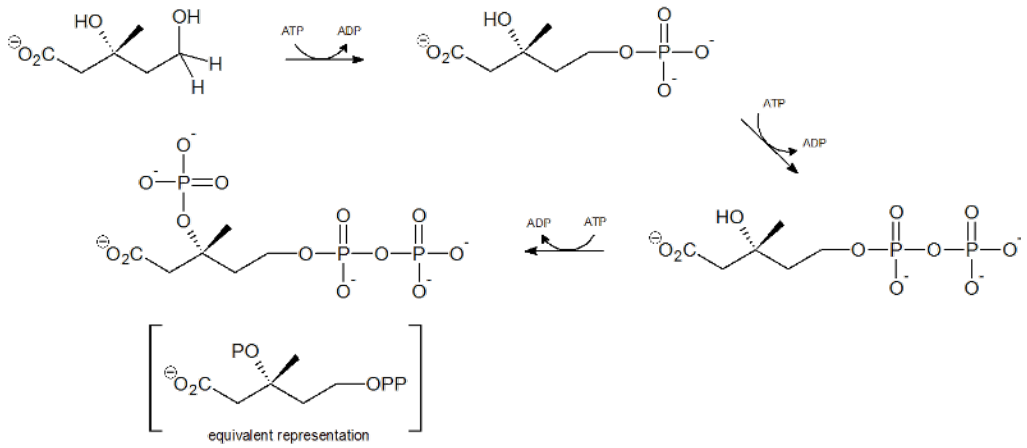
The thioester is reduced first to an aldehyde, then to a primary alcohol by two equivalents of NADPH, producing (*R*)-mevalonate. The enzyme catalyzing this reaction is the target of the statin family of cholesterol-lowering drugs.



Generating (*R*)-Mevalonate

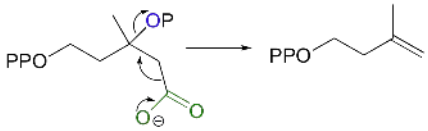
Step 4 - **Mevalonate Phosphorylation**

Two phosphorylations by adenosine triphosphate (ATP) occur at the terminal hydroxyl/phosphorus group through nucleophilic substitution, followed by a third ATP phosphorylation of the tertiary hydroxyl group.



Step 5 - **Decarboxylation**

Finally, isopentenyl diphosphate (IPP), the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.



Conversion of Isopentenyl Diphosphate to Terpenoids

The conversion of isopentenyl diphosphate (IPP) to terpenoids begins with its isomerization to dimethylallyl diphosphate, abbreviated DMAPP and formerly called dimethylallyl pyrophosphate. These two C_5 building blocks then combine to give the C_{10} unit geranyl diphosphate (GPP). The corresponding alcohol, geraniol, is itself a fragrant terpenoid that occurs in rose oil.

Further combination of GPP with another IPP gives the C_{15} unit farnesyl diphosphate (FPP), and so on, up to C_{25}. Terpenoids with more than 25 carbons—that is, triterpenoids (C_{30}) and tetraterpenoids (C_{40})—are synthesized by dimerization of C_{15} and C_{20} units, respectively (Figure 14.5.4). Triterpenoids and steroids, in particular, arise from dimerization of farnesyl diphosphate to give squalene.

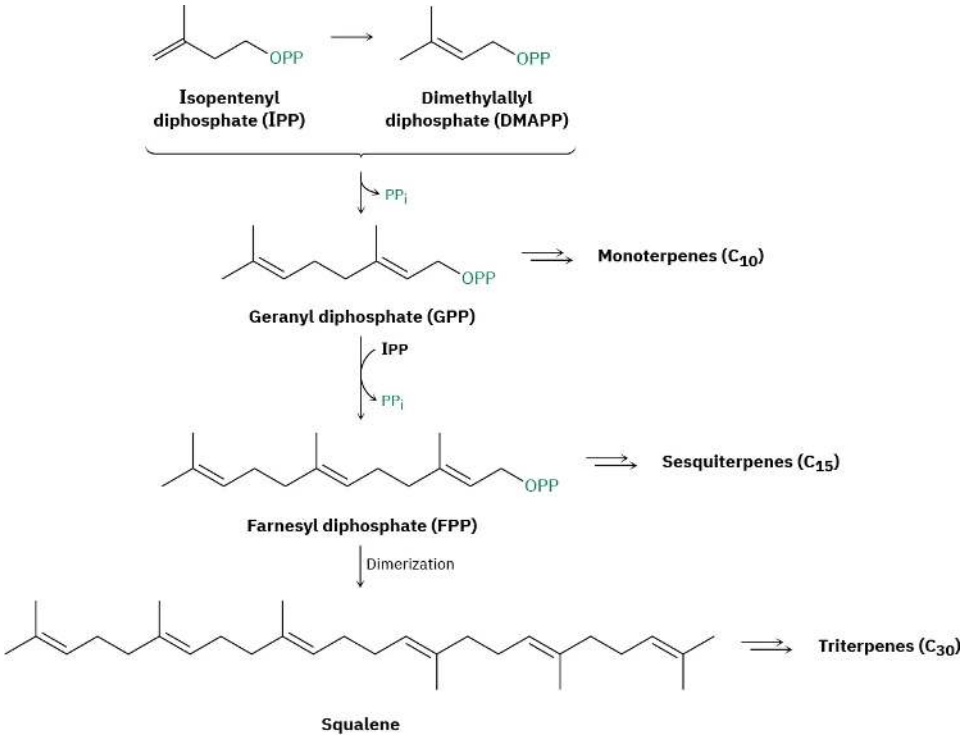
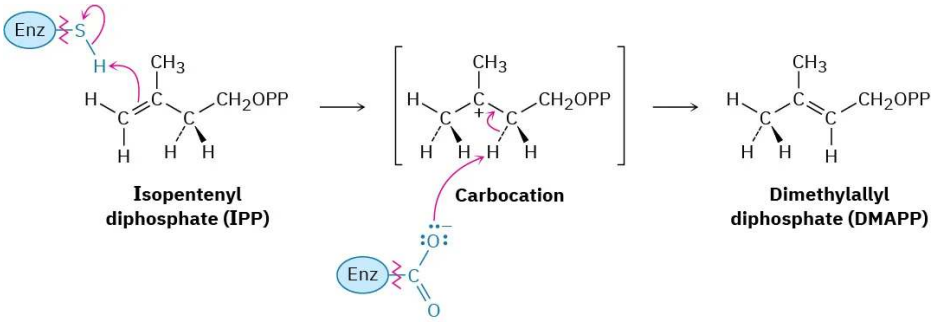


Figure 14.5.4: An overview of terpenoid biosynthesis from isopentenyl diphosphate.

The isomerization of isopentenyl diphosphate to dimethylallyl diphosphate is catalyzed by IPP isomerase and occurs through a carbocation pathway. Protonation of the IPP double bond by a hydrogen-bonded cysteine residue in the enzyme gives a tertiary carbocation intermediate, which is deprotonated by a glutamate residue as base to yield DMAPP. X-ray structural studies on the enzyme show that it holds the substrate in an unusually deep, well-protected pocket to shield the highly reactive carbocation from reaction with solvent or other external substances.



Both the initial coupling of DMAPP with IPP to give geranyl diphosphate and the subsequent coupling of GPP with a second molecule of IPP to give farnesyl diphosphate are catalyzed by farnesyl diphosphate synthase. The process requires Mg^{2+} ion, and the key step is a nucleophilic substitution reaction in which the double bond of IPP behaves as a nucleophile in displacing diphosphate ion leaving group (PP_i) or DMAPP. Evidence suggests that the DMAPP develops a considerable cationic character and that spontaneous dissociation of the allylic diphosphate ion in an S_N1-like pathway probably occurs (Figure 14.5.5).

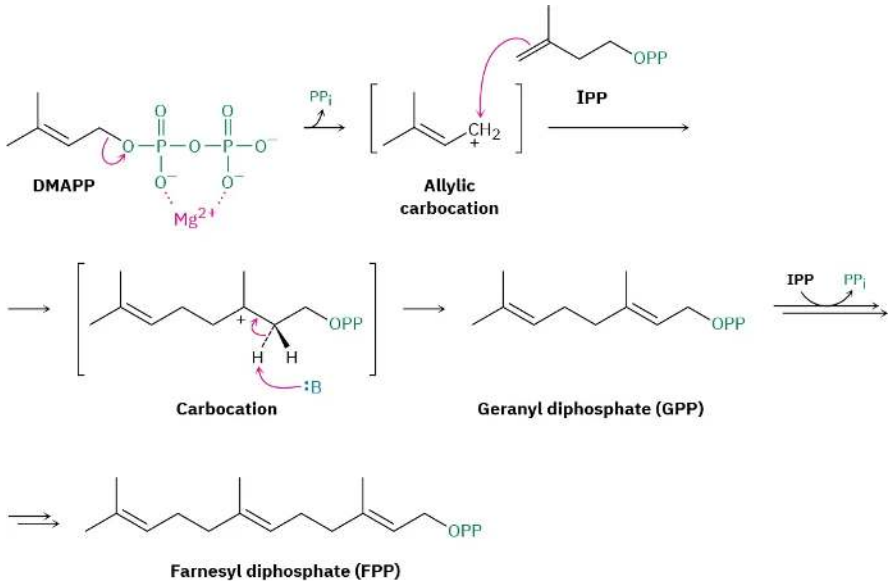


Figure 14.5.5: Mechanism of the coupling reaction of dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP), to give geranyl diphosphate (GPP).

Cholesterol Precursor

In this section, we will briefly examine the reaction catalyzed by an enzyme called squalene synthase, an important enzymatic transformation that involves some very interesting and unusual electrophilic additions, rearrangements, and reactive intermediates. This particular enzyme is also of interest because it represents a potential new target for cholesterol-lowering drugs.

Cholesterol, as we discussed earlier in this chapter, is derived from a 30-carbon isoprenoid molecule called squalene. Squalene, in turn, is derived from the condensation of two molecules of farnesyl diphosphate (FPP), a 15-carbon isoprenoid. You may recall that FPP is the product of the C_4 to C_1, or 'head to tail' electrophilic condensation of isoprenoid chains:

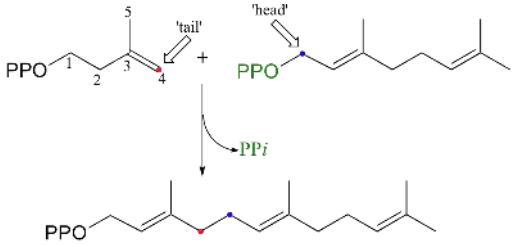


Figure 14.5.6: The condensation of two molecules of FPP to form squalene, however, is something different: this is a 'head to head' condensation, where C_1 of the first molecule forms a bond to C_1 of the second. The chemistry involved is quite a bit more complicated.

Monoterpenoids

Further conversion of geranyl diphosphate into monoterpenoids typically involves carbocation intermediates and multistep reaction pathways that are catalyzed by terpene cyclases. Monoterpene cyclases function by first isomerizing geranyl diphosphate to its allylic isomer linalyl diphosphate (LPP), a process that occurs by spontaneous S_N1-like dissociation to an allylic carbocation, followed by recombination. The effect of this isomerization is to convert the C2–C3 double bond of GPP into a single bond, thereby making cyclization possible and allowing *E*/*Z* isomerization of the double bond.

Further dissociation and cyclization by electrophilic addition of the cationic carbon to the terminal double bond then gives a cyclic cation, which might either rearrange, undergo a hydride shift, be captured by a nucleophile, or be deprotonated to give any of the several hundred known monoterpenoids. As just one example, limonene, a monoterpenoid found in many citrus oils, arises by the biosynthetic pathway shown in Figure 14.5.7.

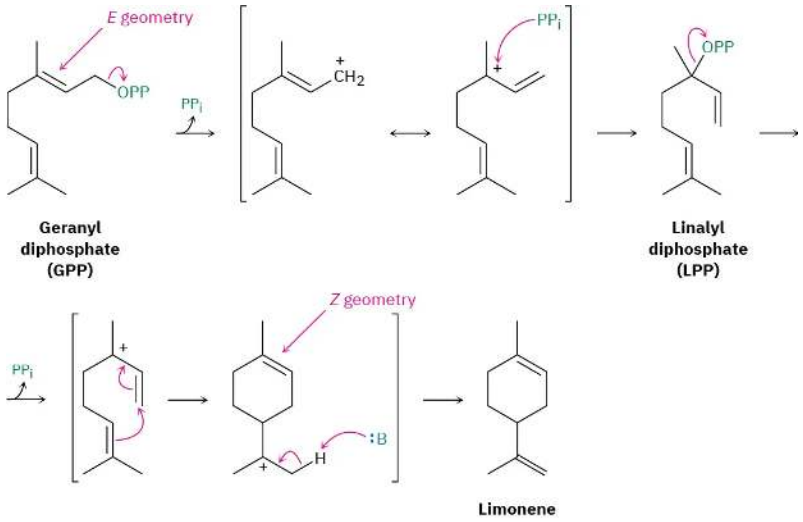
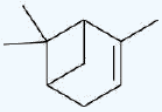


Figure 14.5.7: Mechanism for the formation of the monoterpenoid limonene from geranyl diphosphate.

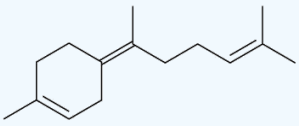
Exercises

Exercise 14.5.1

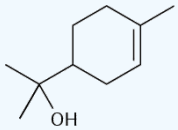
Identify the Isoprene Units in the following terpenoids:



a. **α-Pinene**



b. **γ-Bisabolene**



α-Terpineol

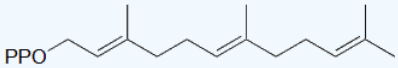
c.

Answers

a- 2. b- 3. c- 2.

Exercise 14.5.2

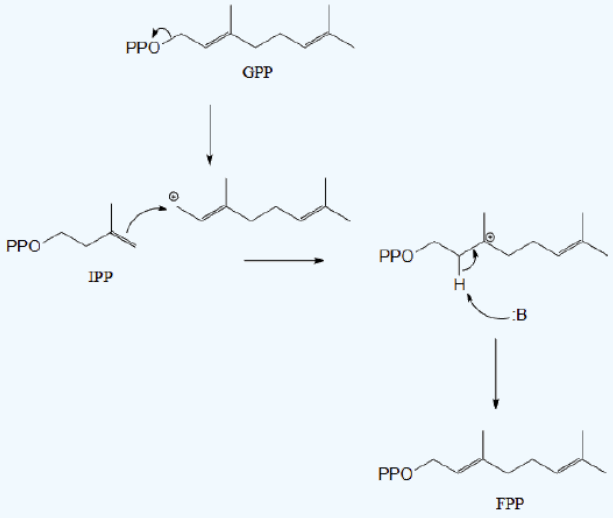
Farnesyl diphosphate (FPP) is synthesized by adding another five-carbon building block to geranyl diphosphate. What is this building block - IPP or DMAPP? Draw a mechanism for the formation of FPP.



farnesyl diphosphate

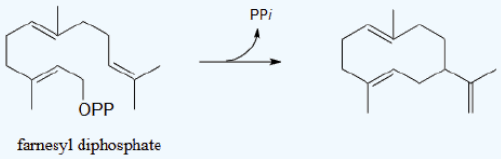
Answer

IPP is the five-carbon species added to geranyl diphosphate to make the 15-carbon farnesyl diphosphate.

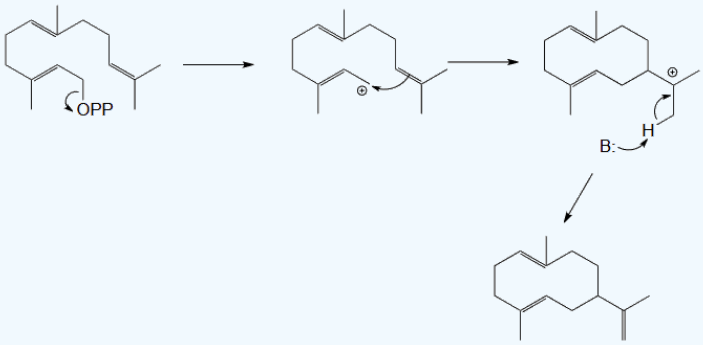


Exercise 14.5.3

Propose a likely mechanism for the following transformation, which is the first stage in a somewhat complex reaction in the synthesis of an isoprenoid compound in plants. (Science 1997, 277, 1815)



Answer



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14.6: Steroids

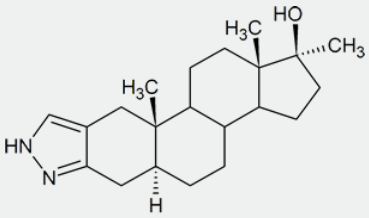
Objectives

After completing this section, you should be able to

1. draw the tetracyclic ring system on which the structure of all steroids is based.
2. identify the occurrence and biological roles of at least two common steroids.
3. sketch the stereochemical conformation of a steroid, given an adequate wedge and dash structure, and determine whether the ring substituents in such a compound occupy axial or equatorial positions.
4. construct a molecular model of a steroid, given a suitable written description or a wedge and dash structure from which to work.

Study Notes

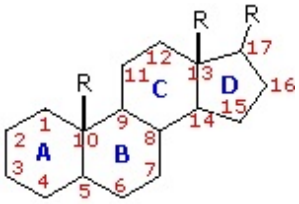
Since the 1988 Olympic Games in Seoul, even individuals who have no interest in chemistry or sport have heard the word "steroid" and are aware that some athletes use these substances to enhance their athletic abilities. Stanozolol, the substance which Canadian sprinter, Ben Johnson, was found to have used, has the structure shown below:



stanozolol

General Steroid Structure

The important class of lipids called **steroids** is actually a metabolic derivative of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram below. The four rings are designated A, B, C & D as noted, and the peculiar numbering of the ring carbon atoms (shown in red) is the result of an earlier misassignment of the structure. The substituents designated by R are often alkyl groups, but may also have functionality. The R group at the A:B ring fusion is most commonly methyl or hydrogen, while that at the C:D fusion is usually methyl. The substituent at C-17 varies considerably and is usually larger than methyl. The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Ring A is sometimes aromatic. Since a number of tetracyclic triterpenes also have this tetracyclic structure, it cannot be considered a unique identifier.

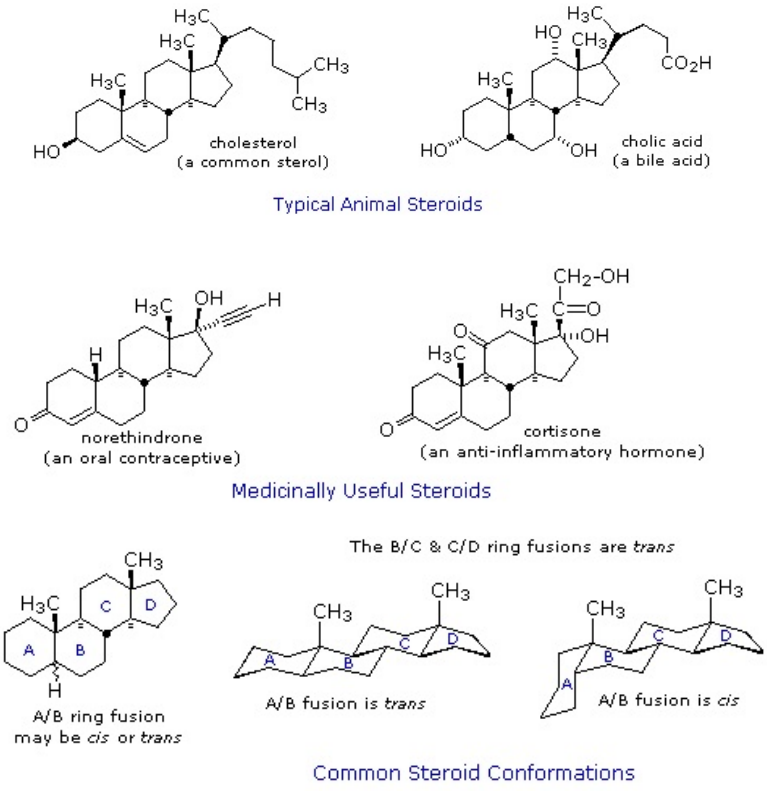


The Steroid
Carbon Skeleton

Common Steroids

Steroids are widely distributed in animals, where they are associated with numerous physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally.

The generic steroid structure drawn above has seven chiral stereocenters (carbons 5, 8, 9, 10, 13, 14 & 17), which means that it may have as many as 128 stereoisomers. With the exception of C-5, natural steroids generally have a single common configuration.



Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of the trans-fused rings. This fixed orientation influences chemical reactivity, largely due to the greater steric hindrance of axial groups versus their equatorial isomers. Thus, an equatorial hydroxyl group is esterified more rapidly than its axial isomer.

Decalin as a model system

It is instructive to examine a simple bicyclic system as a model for the fused rings of the steroid molecule. Decalin, short for decahydronaphthalene, exists as cis and trans isomers at the ring fusion carbon atoms. For purposes of discussion, the left ring is labeled A (colored blue) and the right ring B (colored red). In the conformational drawings the ring fusion and the angular hydrogens are black. The A and B rings can be either cis-fused or trans-fused.

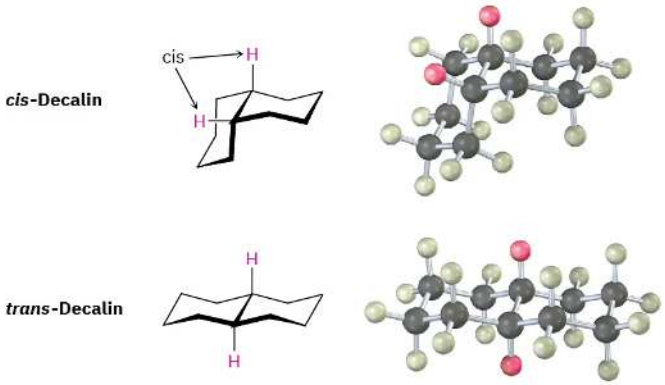


Figure 14.6.1: Decalin conformations. The 6-membered rings have chair conformations but are unable to undergo ring-flips. The A and B rings can be either cis-fused or trans-fused.

As shown in Figure 14.6.2, steroids can have either a cis or a trans fusion of the A and B rings, but the other ring fusions (B–C and C–D) are usually trans.

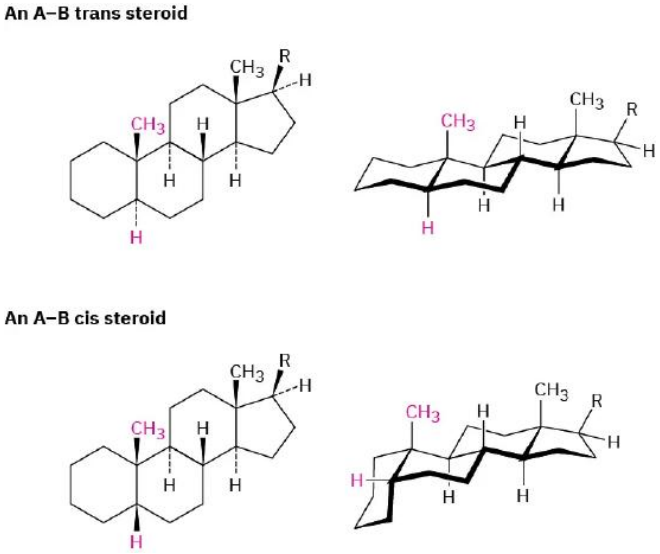
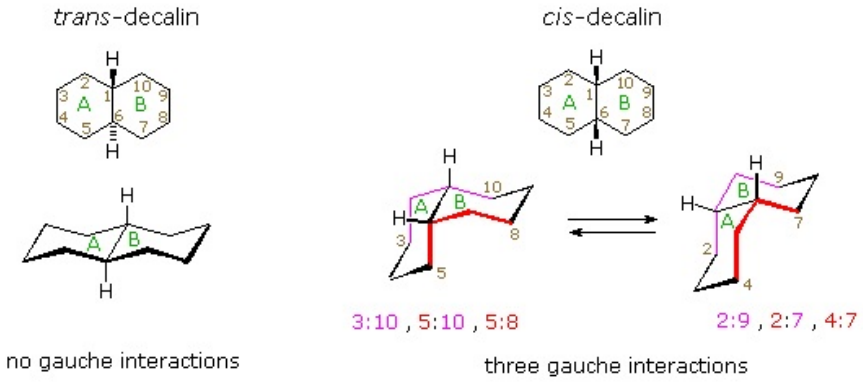


Figure 14.6.2: Steroid conformations. The three 6-membered rings have chair conformations but are unable to undergo ring-flips. The A and B rings can be either cis-fused or trans-fused.



The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (Ha) axial to both rings. Note that the bonds directed above the plane of the two rings alternate from axial to equatorial and back if we proceed around the rings from C-1 to C-10 in numerical order. The bonds directed below the rings also alternate in a complementary fashion.

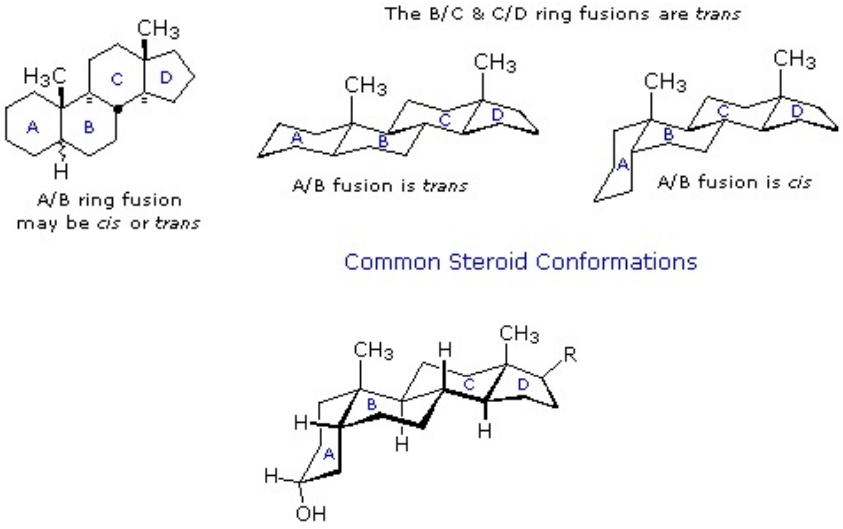
Conformational descriptions of cis- decalin are complicated by the fact that two energetically equivalent fusions of chair cyclohexanes are possible, and are in rapid equilibrium as the rings flip from one chair conformation to the other. In each of these all chair conformations the rings are fused by one axial and one equatorial bond, and the overall structure is bent at the ring fusion. In the conformer on the left, the red ring (B) is attached to the blue ring (A) by an axial bond to C-1 and an equatorial bond to C-6 (these terms refer to ring A substituents). In the conformer on the right, the carbon bond to C-1 is equatorial and the bond to C-6 is axial. Each of the angular hydrogens (Hae or Hea) is oriented axial to one of the rings and equatorial to the other. This relationship reverses when double ring flipping converts one cis-conformer into the other.

Cis-decalin is less stable than trans-decalin by about 2.7 kcal/mol (from heats of combustion and heats of isomerization data). This is due to steric crowding (hindrance) of the axial hydrogens in the concave region of both cis-conformers, as may be seen in the model display activated by the following button. This difference is roughly three times the energy of a gauche butane conformer

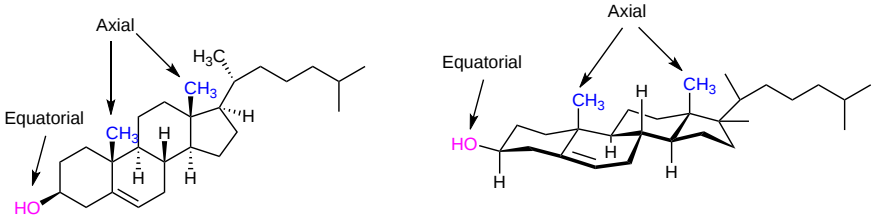
relative to its anti conformer. Indeed three gauche butane interactions may be identified in each of the cis-decalin conformations, as will be displayed by clicking on the above conformational diagram. These gauche interactions are also shown in the model.

Steroid Conformations

Steroids in which rings A and B are fused cis, such as the example on the right, do not have the same conformational mobility exhibited by cis-decalin. The fusion of ring C to ring B in a trans configuration prevents ring B from undergoing a conformational flip to another chair form. If this were to occur, ring C would have to be attached to ring B by two adjacent axial bonds directed 180º apart. This is too great a distance to be bridged by the four carbon atoms making up ring C. Consequently, the steroid molecule is locked in the all chair conformation shown here. Of course, all these steroids and decalins may have one or more six-membered rings in a boat conformation. However the high energy of boat conformers relative to chairs would make such structures minor components in the overall ensemble of conformations available to these molecules.



Much like cyclohexane substituents (CHEM 231), on a steroid ring system, they can be in either an axial or equatorial position. Fused rings make steroids rigid and unable to undergo cyclohexane ring flips. Because of sterics, substituents in the equatorial position tend to be more energetically favorable. The -OH group present in cholesterol is in the more stable equatorial position, while the two -CH_3 groups on the steroid ring are both in an axial position.



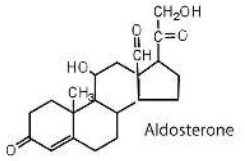
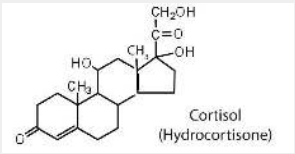
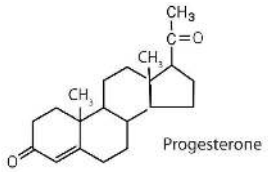
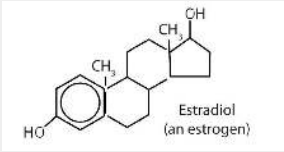
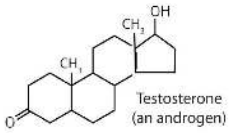
Steroid Hormones

Hormones are chemical messengers that are released in one tissue and transported through the circulatory system to one or more other tissues. One group of hormones is known as steroid hormones because these hormones are synthesized from cholesterol, which is also a steroid. There are two main groups of steroid hormones: adrenocortical hormones and sex hormones.

The adrenocortical hormones, such as aldosterone and cortisol (Table 14.6.1), are produced by the adrenal gland, which is located adjacent to each kidney. Aldosterone acts on most cells in the body, but it is particularly effective at enhancing the rate of reabsorption of sodium ions in the kidney tubules and increasing the secretion of potassium ions and/or hydrogen ions by the tubules. Because sodium ion concentration is the primary factor influencing water retention in tissues, aldosterone promotes water retention and reduces urine output. Cortisol regulates several key metabolic reactions (for example, increasing glucose production and mobilizing fatty acids and amino acids). It also inhibits the inflammatory response of tissue to injury or stress. Cortisol and its

analogs are therefore used pharmacologically as immunosuppressants after transplant operations and in the treatment of severe skin allergies and autoimmune diseases, such as rheumatoid arthritis.

Table 14.6.1 Representative Steroid Hormones and Their Physiological Effects

Hormone	Effect
 Aldosterone	Regulates salt metabolism; stimulates the kidneys to retain sodium and excrete potassium
 Cortisol (Hydrocortisone)	stimulates the conversion of proteins to carbohydrates
 Progesterone	regulates the menstrual cycle; maintains pregnancy
 Estradiol (an estrogen)	stimulates female sex characteristics; regulates changes during the menstrual cycle
 Testosterone (an androgen)	stimulates and maintains male sex characteristics

The sex hormones are a class of steroid hormones secreted by the gonads (ovaries or testes), the placenta, and the adrenal glands. Testosterone and androstenedione are the primary male sex hormones, or *androgens*, controlling the primary sexual characteristics of males, or the development of the male genital organs and the continuous production of sperm. Androgens are also responsible for the development of secondary male characteristics, such as facial hair, deep voice, and muscle strength. Two kinds of sex hormones are of particular importance in females: progesterone, which prepares the uterus for pregnancy and prevents the further release of eggs from the ovaries during pregnancy, and the estrogens, which are mainly responsible for the development of female secondary sexual characteristics, such as breast development and increased deposition of fat tissue in the breasts, the buttocks, and the thighs. Both males and females produce androgens and estrogens, differing in the amounts of secreted hormones rather than in the presence or absence of one or the other.

Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment option for prostate cancer because they block the release and activity of testosterone. Testosterone enhances prostate cancer growth. Sex hormones are also administered in preparation for sex-change operations, to promote the development of the proper secondary sexual characteristics. Oral contraceptives are synthetic derivatives of the female sex hormones; they work by preventing ovulation.

Adrenocorticoid Hormones

The adrenocorticoid hormones are products of the adrenal glands ("adrenal" means adjacent to the renal (kidney). The most important adrenocorticoid is **aldosterone**, which regulates the reabsorption of sodium and chloride ions in the kidney tubules and increases the loss of potassium ions. Aldosterone is secreted when blood sodium ion levels are too low to cause the kidney to retain sodium ions. If sodium levels are elevated, aldosterone is not secreted, so that some sodium will be lost in the urine. Aldosterone also controls swelling in the tissues.

Cortisol, the most important glucocortinoid, has the function of increasing glucose and glycogen concentrations in the body. These reactions are completed in the liver by taking fatty acids from lipid storage cells and amino acids from body proteins to make glucose and glycogen.

In addition, cortisol and its ketone derivative, **cortisone**, have the ability to anti-inflammatory effects. Cortisone or similar synthetic derivatives, such as prednisolone, are used to treat inflammatory diseases, rheumatoid arthritis, and bronchial asthma. There are many side effects associated with the use of cortisone drugs, so their use must be monitored carefully.

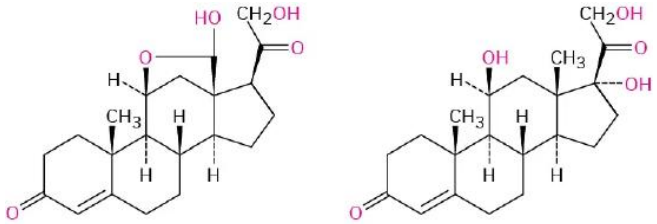
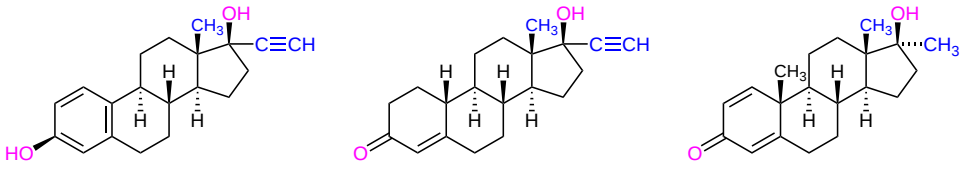


Figure 14.6.3: Glucocorticoid ointments are widely used to reduce swelling from exposure to poison oak or poison ivy.

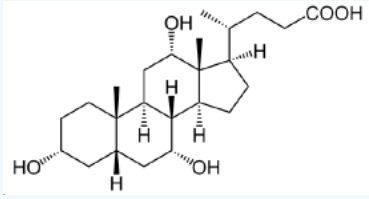
Synthetic Steroids

In the hope of producing new drugs, thousands of steroid derivatives have been synthesized and tested by pharmaceutical companies. The two classes of synthetic steroids most commonly known by the public are oral contraceptives and anabolic steroids. Oral contraceptives contain synthetic versions of the hormones estrogen (ethynylestradiol) and progestin (norethindrone). They prevent pregnancy by interfering with ovulation, fertilization, and/or implantation of the fertilized egg. Anabolic steroids (methandrostenolone) mimic the effects of natural testosterone.

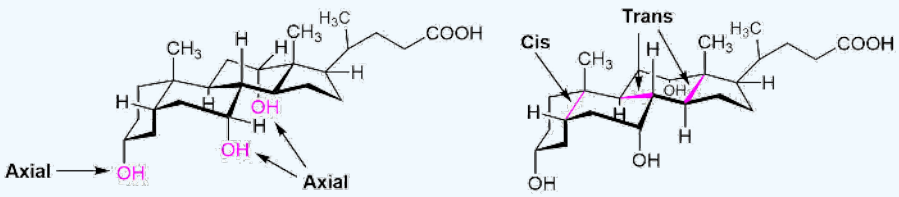


? Exercise 14.6.1

The following molecule is cholic acid. Draw it showing the chair conformations. Determine if the three fused bonds have a *cis* or *trans* configuration. Determine if the OH groups are axial or equatorial.

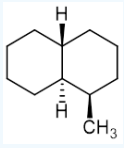
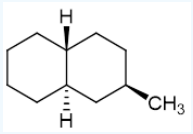


Answer

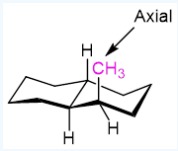
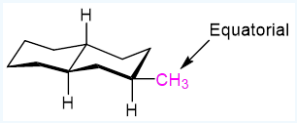


Exercise 14.6.2

Draw the following decalin molecules in chair conformations. Determine if the -CH_3 groups are axial or equatorial.

a)  b) 

Answer

a)  b) 

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14.7: Hormones - The Regulators

Learning Objectives

- Identify the major classes of hormones on the basis of chemical structure.
- Know the function of the common hormones.

Glands of the Endocrine System

The **endocrine system** is a network of **glands** that release chemical messenger molecules into the bloodstream. The messenger molecules of the endocrine system are called endocrine hormones. The major glands of the endocrine system are shown in Figure 14.7.1.

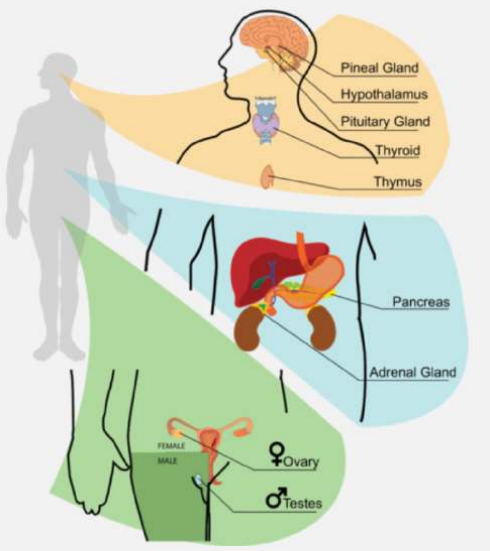


Figure 14.7.1 The endocrine glands. (Mariana Ruiz Villarreal; public domain; (LadyofHats/Wikimedia Commons; CK-12 foundation)

Although a given hormone may travel throughout the body in the bloodstream, it will affect the activity only of its target cells; that is, cells with receptors for that particular hormone. Once the hormone binds to the receptor, a chain of events is initiated that leads to the target cell's response. Hormones play a critical role in regulating physiological processes through their effects on target cell responses. These responses contribute to human reproduction, growth, and development of body tissues, metabolism, fluid, and electrolyte balance, sleep, and many other body functions. The major hormones of the human body and their effects are identified in Table 14.7.1.

Table 14.7.1 The Endocrine Glands and Their Major Hormones.

Endocrine gland	Associated hormones	Chemical class	Effect
Pituitary	Growth hormone (GH)	Protein	Promotes growth of body tissues
	Prolactin (PRL)	Peptide	Promotes milk production
	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release
	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production
	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by the gonads
	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by the kidneys
	Oxytocin	Peptide	Stimulates uterine contractions during childbirth
Thyroid	Thyroxine (T_4), triiodothyronine (T_3)	Amine	Stimulate basal metabolic rate
	Calcitonin	Peptide	Reduces blood Ca^{2+} levels
Parathyroid	Parathyroid hormone (PTH)	Peptide	Increases blood Ca^{2+} levels
Adrenal (cortex)	Aldosterone	Steroid	Increases blood Na^{+} levels
	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels
Adrenal (medulla)	Epinephrine, norepinephrine	Amine	Stimulate fight-or-flight response
Pineal	Melatonin	Amine	Regulates sleep cycles
Pancreas	Insulin	Protein	Reduces blood glucose levels
	Glucagon	Protein	Increases blood glucose levels
Testes	Testosterone	Steroid	Stimulates the development of male secondary sex characteristics and sperm production
Ovaries	Estrogens and progesterone	Steroid	Stimulate the development of female secondary sex characteristics and prepare the body for childbirth

Types of Hormones

The hormones of the human body can be divided into two major groups based on their chemical structure. Hormones derived from amino acids include amines, peptides, and proteins. Those derived from lipids include steroids (Figure 14.7.2). These chemical

groups affect a hormone's distribution, the type of receptors it binds to, and other aspects of its function.

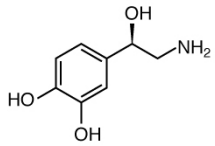
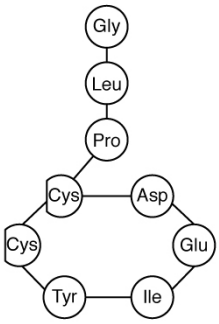
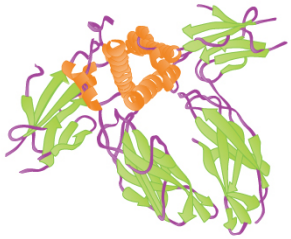
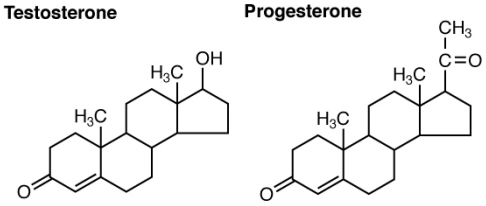
Hormone Class	Components	Example(s)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	**Norepinephrine** 
Peptide Hormone	Short chains of linked amino acids	**Oxytocin** 
Protein Hormone	Long chains of linked amino acids	**Human Growth Hormone** 
Steroid Hormones	Derived from the lipid cholesterol	**Testosterone** **Progesterone** 

Figure 14.7.2 *Amine, Peptide, Protein, and Steroid Hormone Structure.*

Amine Hormones

Hormones derived from the modification of amino acids are called amine hormones. Typically, the original structure of the amino acid is modified such that a –COOH, or carboxyl, group is removed, whereas the $-NH_3^+$, or amine, group remains.

Amine hormones are synthesized from the amino acids tryptophan or tyrosine. An example of a hormone derived from tryptophan is melatonin, which is secreted by the pineal gland and helps regulate circadian rhythm. Tyrosine derivatives include the metabolism-regulating thyroid hormones, as well as the catecholamines, such as epinephrine, norepinephrine, and dopamine. Epinephrine and norepinephrine are secreted by the adrenal medulla and play a role in the fight-or-flight response, whereas dopamine is secreted by the hypothalamus and inhibits the release of certain anterior pituitary hormones.

Peptide and Protein Hormones

Whereas the amine hormones are derived from a single amino acid, peptide and protein hormones consist of multiple amino acids that link to form an amino acid chain. Peptide hormones consist of short chains of amino acids, whereas protein hormones are longer polypeptides. Both types are synthesized like other body proteins: DNA is transcribed into mRNA, which is translated into an amino acid chain.

Examples of peptide hormones include antidiuretic hormone (ADH), a pituitary hormone important for fluid balance, and atrial natriuretic peptide, which is produced by the heart and helps lower blood pressure. Some examples of protein hormones include growth hormone, which is produced by the pituitary gland, and follicle-stimulating hormone (FSH), which has an attached carbohydrate group and is thus classified as a glycoprotein. FSH helps stimulate the maturation of eggs in the ovaries and sperm in the testes.

Steroid Hormones

Hormones are chemical messengers that are released in one tissue and transported through the circulatory system to one or more other tissues. One group of hormones is known as steroid hormones because these hormones are synthesized from cholesterol, which is also a steroid. There are two main groups of steroid hormones: adrenocortical hormones and sex hormones.

Adrenocortical hormones

The adrenocortical hormones, such as aldosterone and cortisol (Table 14.7.1), are produced by the adrenal gland, which is located adjacent to each kidney. Aldosterone acts on most cells in the body, but it is particularly effective at enhancing the rate of reabsorption of sodium ions in the kidney tubules and increasing the secretion of potassium ions and/or hydrogen ions by the tubules. Because the concentration of sodium ions is the major factor influencing water retention in tissues, aldosterone promotes water retention and reduces urine output. Cortisol regulates several key metabolic reactions (for example, increasing glucose production and mobilizing fatty acids and amino acids). It also inhibits the inflammatory response of tissue to injury or stress. Cortisol and its analogs are therefore used pharmacologically as immunosuppressants after transplant operations and in the treatment of severe skin allergies and autoimmune diseases, such as rheumatoid arthritis

Sex Hormones

The sex hormones are a class of steroid hormones secreted by the gonads (ovaries or testes), the placenta, and the adrenal glands. Testosterone and androstenedione are the primary male sex hormones, or *androgens*, controlling the primary sexual characteristics of males, or the development of the male genital organs and the continuous production of sperm. Androgens are also responsible for the development of secondary male characteristics, such as facial hair, deep voice, and muscle strength. Two kinds of sex hormones are of particular importance in females: progesterone, which prepares the uterus for pregnancy and prevents the further release of eggs from the ovaries during pregnancy, and the estrogens, which are mainly responsible for the development of female secondary sexual characteristics, such as breast development and increased deposition of fat tissue in the breasts, the buttocks, and the thighs. Both males and females produce androgens and estrogens, differing in the amounts of secreted hormones rather than in the presence or absence of one or the other.

Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment option for prostate cancer because they block the release and activity of testosterone. Testosterone enhances prostate cancer growth. Sex hormones are also administered in preparation for sex-change operations, to promote the development of the proper secondary sexual characteristics. Oral contraceptives are synthetic derivatives of the female sex hormones; they work by preventing ovulation.

Summary

- A hormone is any member of a class of signaling molecules, produced by glands in multicellular organisms to regulate physiology and behavior.
- The hormones of the human body can be divided into two major groups based on their chemical structure. Hormones derived from amino acids include amines, peptides, and proteins. Those derived from lipids include steroids.
- The two main groups of steroid hormones are adrenocortical hormones and sex hormones.

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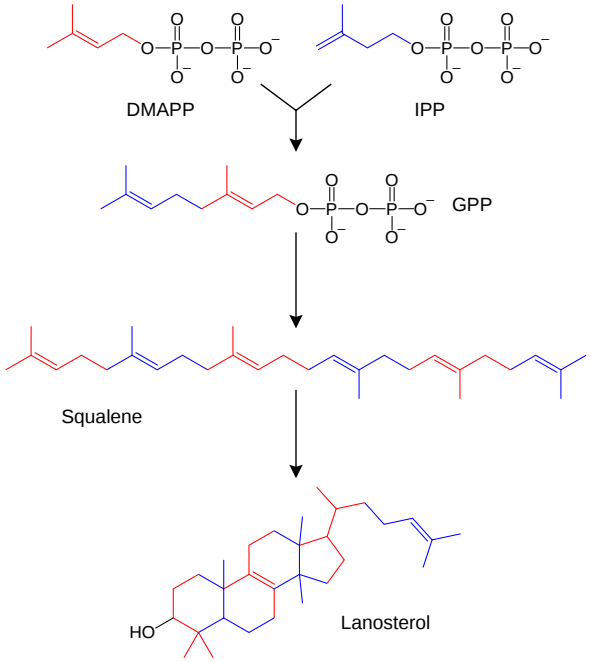
13.7: Biosynthesis of Steroids

Objectives

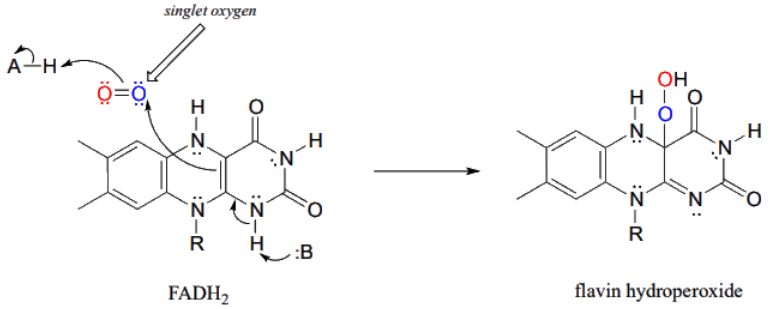
After completing this section, you should be able to

- give an overview of how steroids are synthsized.
- describe changes to molecules through the biosynthesis of steroids.

Steroid biosynthesis is an anabolic metabolic pathway that produces steroids from simple precursors. A unique biosynthetic pathway is followed in animals compared to many other organisms, making the pathway a common target for antibiotics and other anti-infective drugs. In humans and other animals, the biosynthesis of steroids follows the **mevalonate pathway** that uses acetyl-CoA as building blocks to form dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP). These two compounds are coupled to form geranyl pyrophosphate (GPP) which is then converted to the hydrocarbon polyene squalene. After an oxidation and multiple rearrangements, lanosterol the first steroid in the pathway is formed. Further conversions can yield different steroids.

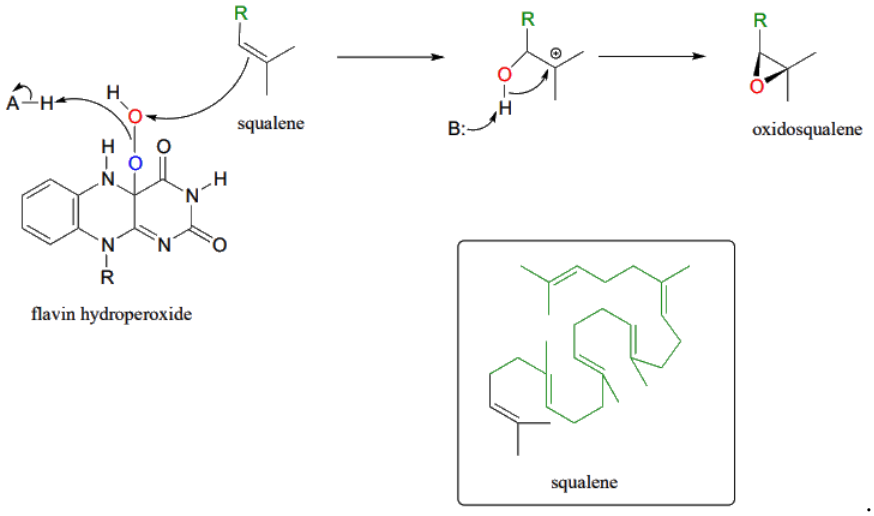


The key step in the biosynthesis of lanosterol is the regioselective epoxidation of squalene to give (3*S*)-2,3-oxidosqualene. This reaction is catalyzed by the monooxygenase enzyme squalene epoxidase. In this step, flavin hydroperoxide serves as the direct oxidizing agent. In flavin hydroperoxide, the peroxide group is linked to one of the carbons of the reactive triple-ring system of the coenzyme. A possible mechanism for the formation of flavin peroxide from $FADH_2$ and molecular oxygen is shown below.

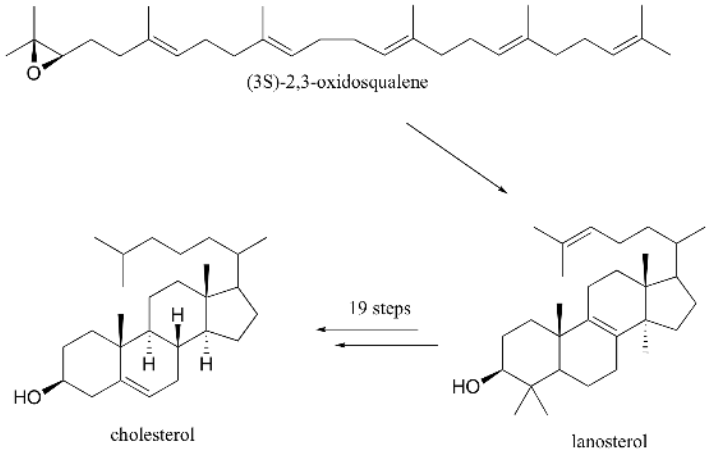


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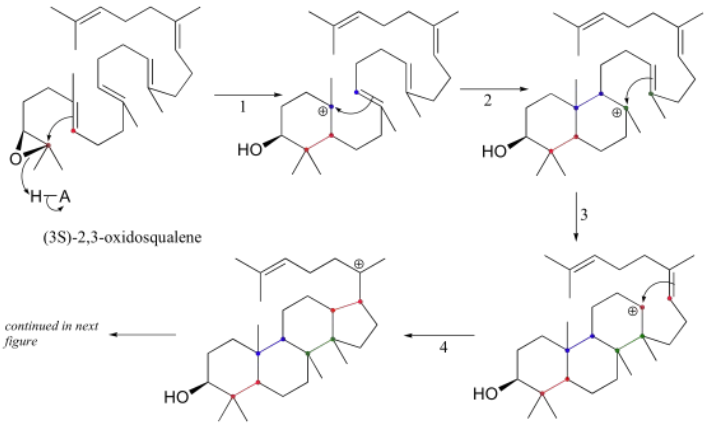
The mechanism for the flavin-hydroperoxide-dependent epoxidation of squalene is initiated by the nucleophilic attack of the pi electrons of a squalene double bond on the electrophilic terminal hydroperoxide oxygen.



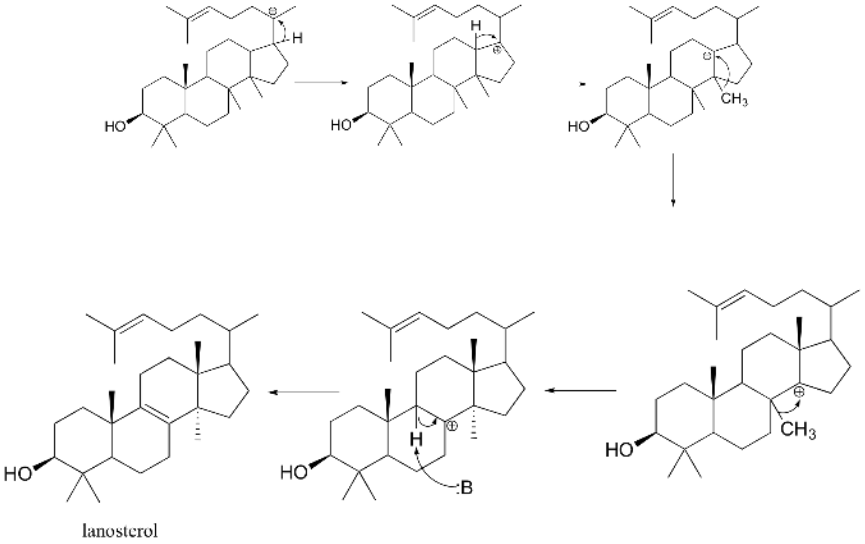
Oxidosqualene goes on to cyclize to lanosterol in a complex and fascinating electrophilic reaction which catalyzed by oxidosqualene-lanosterol cyclase. This reaction has two phases. The first phase, in which the actual cyclization takes place, is a series of electrophilic addition steps. The second phase is a series of hydride and methyl shifts. There is some argument about whether these processes occur in a stepwise fashion (with discreet carbocation intermediates) or in a concerted manner. For the sake of clarity, we will show the reaction proceeding stepwise. After lanosterol is formed the pathway continued to form cholesterol which is the precursor that all other steroids are derived.



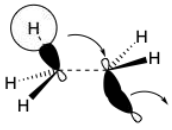
The cyclization phase begins with attack by pi electrons on an epoxide electrophile. The epoxide ring opens to form an alcohol after protonation. A relatively stable tertiary carbocation is also formed. Steps 2, 3, and 4 are simply successive attacks by pi electrons on the carbocation generated by the previous attack. The overall result of this electrophilic cascade is the opening of the epoxide ring, and closure of three six-membered and one five-membered ring.

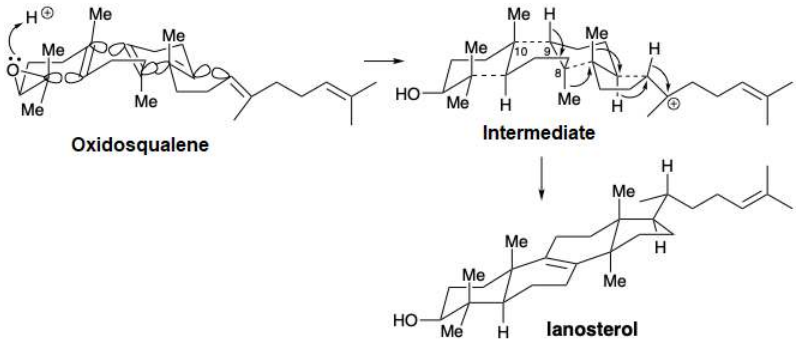


Next comes the rearrangement phase of the reaction in which a series of two 1,2-hydride and two 1,2-methyl shifts to give lanosterol after proton loss from the 9 position.



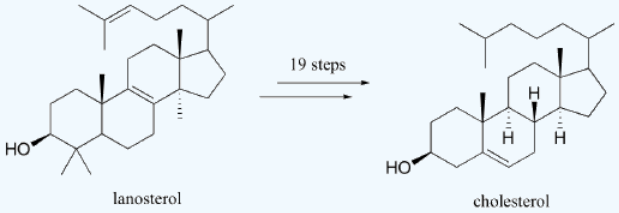
Especially interesting are the stereochemical details of the polyene cyclization and subsequent rearrangement. The polyene cyclization involves stereospecific **anti-periplanar** addition across three C=C bonds in oxidosqualene (see below). The folded conformation of oxidosqualene, required for cyclization is probably imposed by the enzyme involved since appreciable steric congestion is present in both oxidosqualene and the intermediate. Relief of steric strain provides a large driving force for the rearrangements to lanosterol that involves stereospecific inversion of configuration at each stereocenter during 1,2-hydrogen or methyl shifts. Thus, each 1,2-hydride or 1,2-methyl shift occurs to the backside of the orbital connected to the leaving group in what can be viewed as a series of nucleophilic substitution reactions – where σ-bonding electron pairs serve as the nucleophiles.





? Exercise 13.7.1

What changes must be made to the structure of lanosterol to convert it to cholesterol?



Answer

Three methyl groups and a double bond are removed. Another double bond is moved to the other side of a six-membered ring.

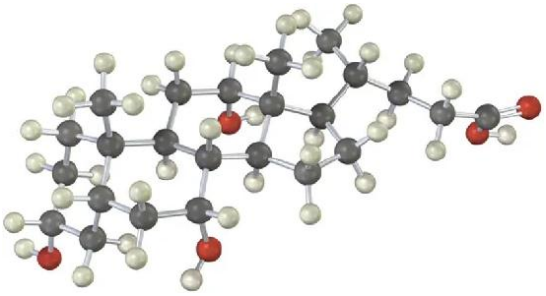
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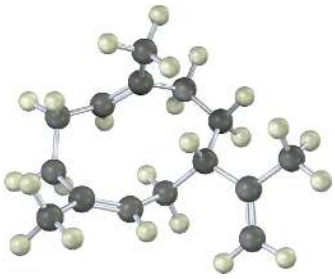
14.9: Additional Problems

Visualizing Chemistry

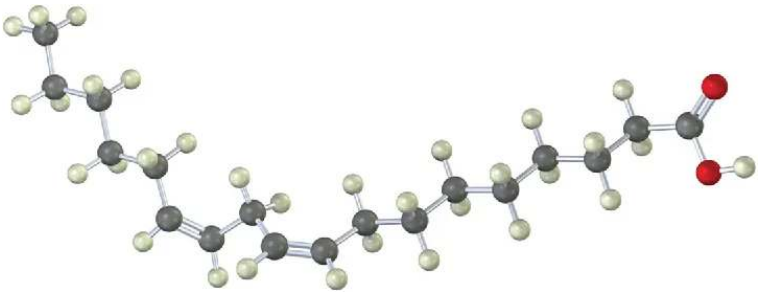
PROBLEM 14.11 The following model is that of cholic acid, a constituent of human bile. Locate the three hydroxyl groups, and identify each as axial or equatorial. Is cholic acid an A–B trans steroid or an A–B cis steroid?



PROBLEM 14.12 The following model is the sesquiterpenoid helminthogermacrene. Identify each isoprene unit.

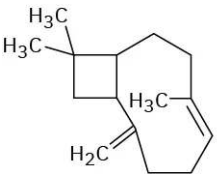


PROBLEM 14.13 Identify the following fatty acid, and tell whether it is more likely to be found in peanut oil or in red meat:



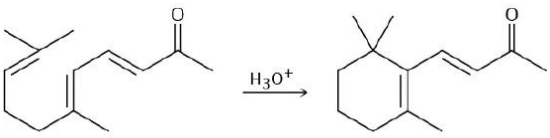
Mechanism Problems

PROBLEM 14.14 Propose a mechanistic pathway for the biosynthesis of caryophyllene, a substance found in clove oil.



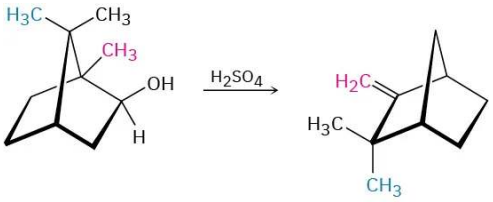
Caryophyllene

PROBLEM 14.15 Suggest a mechanism by which ψ-ionone is transformed into β-ionone on treatment with acid.



ψ-Ionone **β-Ionone**

PROBLEM 14.16 Isoborneol is converted into camphene on treatment with dilute sulfuric acid. Propose a mechanism for the reaction, which involves a carbocation rearrangement.



Isoborneol **Camphene**

Fats, Oils, and Related Lipids

PROBLEM 14.17 Fatty fish like salmon and albacore are rich in *omega-3* fatty acids, which have a double bond three carbons in from the noncarboxyl end of the chain and have been shown to lower blood cholesterol levels. Draw the structure of 5,8,11,14,17-eicosapentaenoic acid, a common example. (Eicosane = $C_{20}H_{42}$.)

PROBLEM 14.18 Fats can be either optically active or optically inactive, depending on their structure. Draw the structure of an optically active fat that yields 2 equivalents of stearic acid and 1 equivalent of oleic acid on hydrolysis. Draw the structure of an optically inactive fat that yields the same products.

PROBLEM 14.19 Spermaceti, a fragrant substance from sperm whales, was widely used in cosmetics until it was banned in 1976 to protect whales from extinction. Chemically, spermaceti is cetyl palmitate, the ester of cetyl alcohol (n-$C_{16}H_{33}OH$) with palmitic acid. Draw its structure.

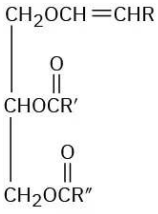
PROBLEM 14.20 Show the products you would expect to obtain from reaction of glyceryl trioleate with the following reagents:

(a) Excess Br_2 in CH_2Cl_2 (b) H_2/Pd (c) NaOH/H_2O (d) O_3, then Zn/CH_3CO_2H (e) $LiAlH_4$, then H_3O^+ (f) CH_3MgBr, then H_3O^+

PROBLEM 14.21 How would you convert oleic acid into the following substances?

(a) Methyl oleate (b) Methyl stearate (c) Nonanal (d) Nonanedioic acid (e) 9-Octadecynoic acid (stearolic acid) (f) 2-Bromostearic acid (g) 18-Pentatriacontanone, $CH_3(CH_2)_{16}CO(CH_2)_{16}CH_3$

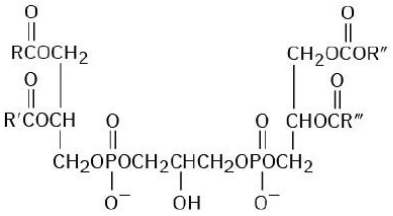
PROBLEM 14.22 *Plasmalogens* are a group of lipids found in nerve and muscle cells. How do plasmalogens differ from fats?



A plasmalogen

PROBLEM 14.23 What products would you obtain from hydrolysis of a plasmalogen (Problem 14-22) with aqueous NaOH? With H_3O^+?

PROBLEM 14.24 *Cardiolipins* are a group of lipids found in heart muscles. What products would be formed if all ester bonds, including phosphates, were saponified by treatment with aqueous NaOH?



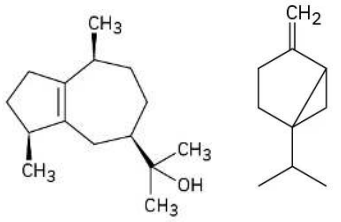
A cardiolipin

PROBLEM 14.25 Stearolic acid, $C_{18}H_{32}O_2$, yields stearic acid on catalytic hydrogenation and undergoes oxidative cleavage with ozone to yield nonanoic acid and nonanedioic acid. What is the structure of stearolic acid?

PROBLEM 14.26 How would you synthesize stearolic acid (Problem 14-25) from 1-decyne and 1-chloro-7-iodoheptane?

Terpenoids and Steroids

PROBLEM 14.27 Without proposing an entire biosynthetic pathway, draw the appropriate precursor, either geranyl diphosphate or farnesyl diphosphate, in a conformation that shows a likeness to each of the following terpenoids:



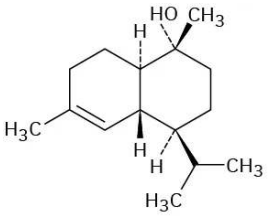
(a) **Guaiol** (b) **Sabinene**

Problem 14.28 Indicate by asterisks the chirality centers present in each of the terpenoids shown in Problem 14.27. What is the maximum possible number of stereoisomers for each?

PROBLEM 14.29 Assume that the three terpenoids in Problem 27-27 are derived biosynthetically from isopentenyl diphosphate and dimethylallyl diphosphate, each of which was isotopically labeled at the diphosphate-bearing carbon atom (C1). At what positions would the terpenoids be isotopically labeled?

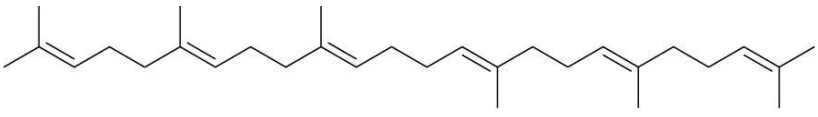
PROBLEM 14.30 Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material for the biosynthesis of mevalonate, as shown in Figure 14.8. At what positions in mevalonate would the isotopic label appear?

PROBLEM 14.31 Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material and that the mevalonate pathway is followed. Identify the positions in α-cadinol where the label would appear.



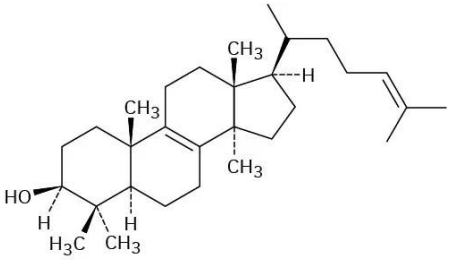
α-Cadinol

PROBLEM 14.32 Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material and that the mevalonate pathway is followed. Identify the positions in squalene where the label would appear.



Squalene

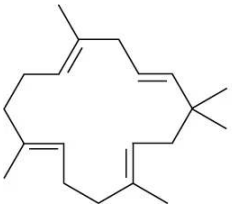
PROBLEM 14.33 Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material and that the mevalonate pathway is followed. Identify the positions in lanosterol where the label would appear.



Lanosterol

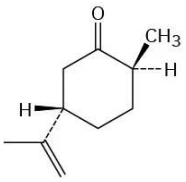
General Problems

PROBLEM 14.34 Flexibilene, a compound isolated from marine coral, is the first known terpenoid to contain a 15-membered ring. What is the structure of the acyclic biosynthetic precursor of flexibilene? Show the mechanistic pathway for the biosynthesis.



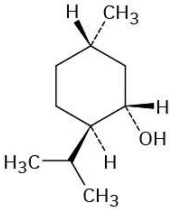
Flexibilene

PROBLEM 14.35 Draw the most stable chair conformation of dihydrocarvone.



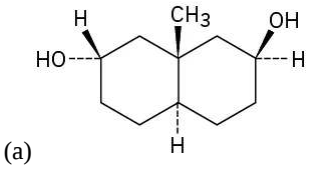
Dihydrocarvone

PROBLEM 14.36 Draw the most stable chair conformation of menthol, and label each substituent as axial or equatorial.

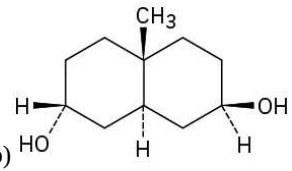


Menthol (from peppermint oil)

PROBLEM 14.37 As a general rule, equatorial alcohols are esterified more readily than axial alcohols. What product would you expect to obtain from the reaction of the following two compounds with 1 equivalent of acetic anhydride?

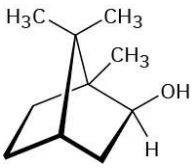


(a)



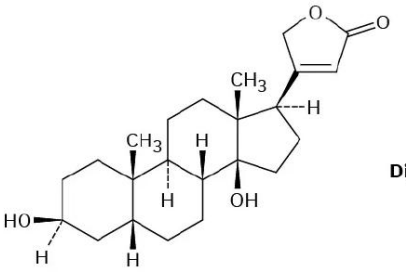
(b)

PROBLEM 14.38 Propose a mechanistic pathway for the biosynthesis of isoborneol. A carbocation rearrangement is needed at one point in the scheme.



Isoborneol

PROBLEM 14.39 Digitoxigenin is a heart stimulant obtained from the purple foxglove *Digitalis purpurea* and used in the treatment of heart disease. Draw the three-dimensional conformation of digitoxigenin, and identify the two –OH groups as axial or equatorial.



Digitoxigenin

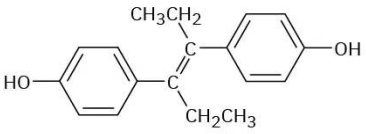
PROBLEM 14.40 What product would you obtain by reduction of digitoxigenin (Problem 14-39) with $LiAlH_4$? By oxidation with the Dess–Martin periodinane?

PROBLEM 14.41 Vaccenic acid, $C_{18}H_{34}O_2$, is a rare fatty acid that gives heptanal and 11-oxoundecanoic acid [$OHC(CH_2)_9CO_2H$] on ozonolysis followed by zinc treatment. When allowed to react with CH_2I_2/Zn(Cu), vaccenic acid is converted into lactobacillic acid. What are the structures of vaccenic and lactobacillic acids?

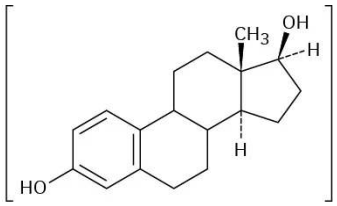
PROBLEM 14.42 Eleostearic acid, $C_{18}H_{30}O_2$, is a rare fatty acid found in the tung oil used for finishing furniture. On ozonolysis followed by treatment with zinc, eleostearic acid furnishes one part pentanal, two parts glyoxal (OHC–CHO), and one part 9-oxononanoic acid [$OHC(CH_2)_7CO_2H$]. What is the structure of eleostearic acid?

PROBLEM 14.43 Diterpenoids are derived biosynthetically from geranylgeranyl diphosphate (GGPP), which is itself biosynthesized by reaction of farnesyl diphosphate with isopentenyl diphosphate. Show the structure of GGPP, and propose a mechanism for its biosynthesis from FPP and IPP.

PROBLEM 14.44 Diethylstilbestrol (DES) has estrogenic activity even though it is structurally unrelated to steroids. Once used as an additive in animal feed, DES has been implicated as a causative agent in several types of cancer. Show how DES can be drawn so that it is sterically similar to estradiol.

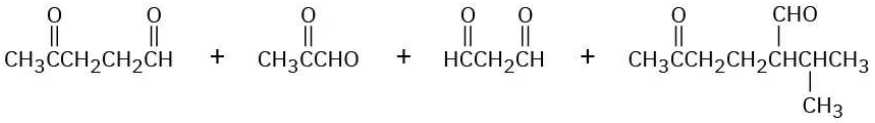


Diethylstilbestrol



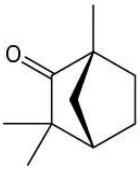
Estradiol

PROBLEM 14.45 Cembrene, $C_{20}H_{32}$, a diterpenoid hydrocarbon isolated from pine resin, has a UV absorption at 245 nm, but dihydrocembrene ($C_{20}H_{34}$), the product of hydrogenation with 1 equivalent of H_2, has no UV absorption. On exhaustive hydrogenation, 4 equivalents of H_2 react, and octahydrocembrene, $C_{20}H_{40}$, is produced. On ozonolysis of cembrene, followed by treatment of the ozonide with zinc, four carbonyl-containing products are obtained:



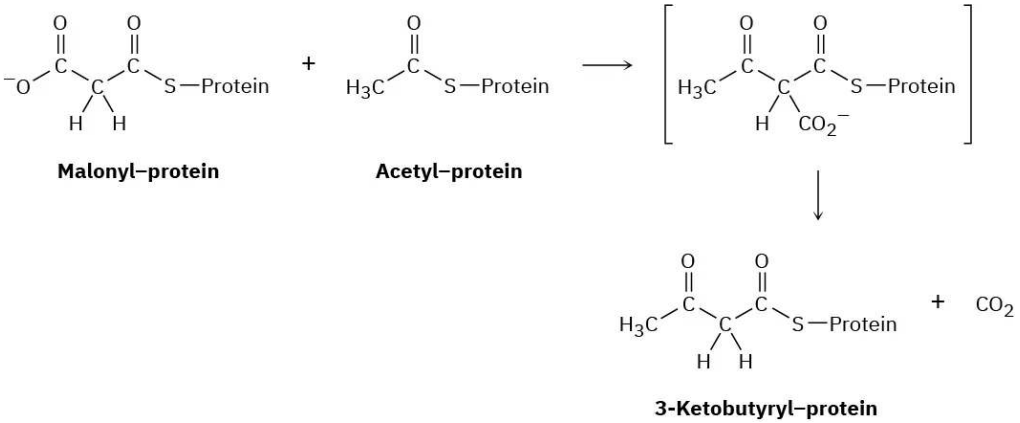
Propose a structure for cembrene that is consistent with its formation from geranylgeranyl diphosphate.

PROBLEM 14.46 α-Fenchone is a pleasant-smelling terpenoid isolated from oil of lavender. Propose a pathway for the formation of α-fenchone from geranyl diphosphate. A carbocation rearrangement is required.



α-Fenchone

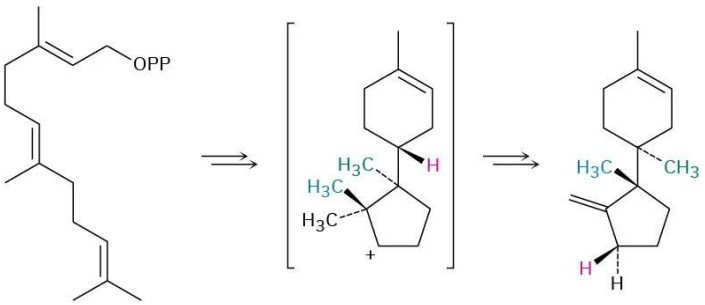
PROBLEM 14.47 Fatty acids are synthesized by a multistep route that starts with acetate. The first step is a reaction between protein-bound acetyl and malonyl units, yielding a protein-bound 3-ketobutyryl unit. Show the mechanism, and tell what kind of reaction is occurring.



Malonyl–protein **Acetyl–protein**

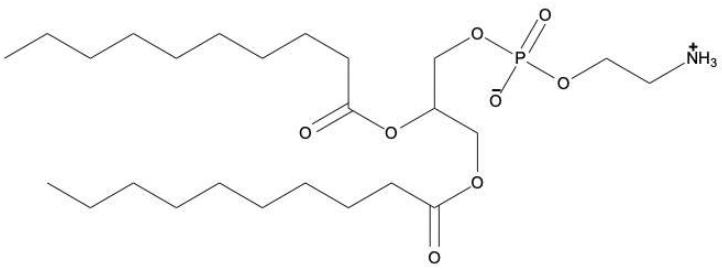
3-Ketobutyryl–protein

PROBLEM 14.48 Propose a mechanism for the biosynthesis of the sesquiterpenoid trichodiene from farnesyl diphosphate. The process involves cyclization to give an intermediate secondary carbocation, followed by several carbocation rearrangements.

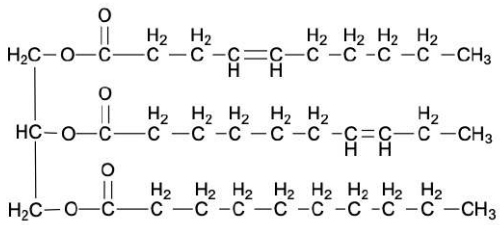


Farnesyl diphosphate (FPP) **Trichodiene**

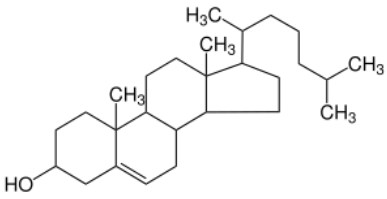
PROBLEM 14.47 Classify each structure as a fatty acid, phospholipid, triacylglycerol, or steroid.



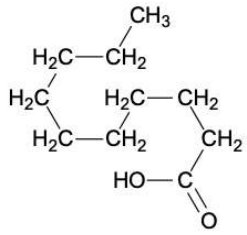
(a)



(b)



(c)



(d)

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14.S: Biomolecules - Lipids (Summary)

Concepts & Vocabulary

- fulfill all of the detailed objectives listed under each individual section.
- define, and use in context, any of the key terms introduced in this chapter: anabolic steroid; androgen; eicosanoid; estrogen; fatty acid; hormone; lipid; lipid bilayer; lipoprotein; micelle; mineralocorticoid; omega-3 fatty acid; phospholipid; polyunsaturated fatty acid; progestin; prostaglandin; saponification; steroid; terpenoid; triacylglycerol; wax.

Summary

Lipids are the naturally occurring materials isolated from plants and animals by extraction with a nonpolar organic solvent. Animal fats and vegetable oils are the most widely occurring lipids. Both are **triacylglycerols**—triesters of glycerol with long-chain **fatty acids**. Animal fats are usually saturated, whereas vegetable oils usually have unsaturated fatty acid residues.

Phospholipids are important constituents of cell membranes and are of two kinds. *Glycerophospholipids*, such as phosphatidylcholine and phosphatidylethanolamine, are closely related to fats in that they have a glycerol backbone esterified to two fatty acids (one saturated and one unsaturated) and to one phosphate ester. *Sphingomyelins* have the amino alcohol sphingosine for their backbone.

Eicosanoids and **terpenoids** are still other classes of lipids. Eicosanoids, of which prostaglandins are the most abundant kind, are derived biosynthetically from arachidonic acid, are found in all body tissues, and have a wide range of physiological activity. Terpenoids are often isolated from the essential oils of plants, have an immense diversity of structure, and are produced biosynthetically from the five-carbon precursor isopentenyl diphosphate (IPP). Isopentenyl diphosphate is itself biosynthesized from 3 equivalents of acetate in the mevalonate pathway.

Steroids are plant and animal lipids with a characteristic tetracyclic carbon skeleton. Like the eicosanoids, steroids occur widely in body tissues and have a large variety of physiological activities. Steroids are closely related to terpenoids and arise biosynthetically from the triterpenoid lanosterol. Lanosterol, in turn, arises from cationic cyclization of the acyclic hydrocarbon squalene.

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CHAPTER OVERVIEW

15: Orbitals and Organic Chemistry - Pericyclic Reactions

Pericyclic reactions are of significant synthetic importance in organic chemistry due to their high stereo- and regioselectivity, mild reaction conditions, and the formation of multiple bonds in a single step. They find applications in the synthesis of complex organic molecules, natural product synthesis, and the construction of functional materials. Understanding the principles governing pericyclic reactions is essential for synthetic chemists to design and control reactions with precision.

15.0: Chapter Overview
15.1: Molecular Orbitals of Conjugated Pi Systems
15.2: Electrocyclic Reactions
15.3: Stereochemistry of Thermal Electrocyclic Reactions
15.4: Photochemical Electrocyclic Reactions
15.5: Cycloaddition Reactions
15.6: Stereochemistry of Cycloadditions
15.7: Sigmatropic Rearrangements
15.8: Some Examples of Sigmatropic Rearrangements
15.9: Additional Problems
15.S: A Summary of Rules for Pericyclic Reactions

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15.0: Chapter Overview

Learning Objectives

- Define pericyclic reactions as concerted processes involving cyclic movement of electrons.
- Explain the Woodward-Hoffmann Rules for predicting outcomes based on molecular orbital symmetry.
- Outline subclasses like cycloadditions, electrocyclic reactions, and sigmatropic rearrangements.
- Describe how pericyclic reactions proceed through cyclic transition states and molecular orbitals.
- Provide key examples like Diels-Alder, electrocyclic ring closures, and Claisen rearrangements.
- Discuss how pericyclic reactions are used in synthesis of complex molecules and materials.

Pericyclic reactions represent a fascinating class of organic reactions characterized by the concerted movement of electrons around a cyclic array of atoms. These reactions involve a cyclic transition state where bonding changes occur with the involvement of π electrons. The term "pericyclic" stems from the Greek roots "peri," meaning around, and "cyclo," referring to cycle or ring, encapsulating the cyclic nature of these reactions.

Key features of pericyclic reactions include their stereospecificity, concertedness, and often high regio- and stereochemical control. They are governed by orbital symmetry rules, primarily the Woodward-Hoffmann rules, which provide a theoretical framework for predicting the outcome of these reactions based on the symmetry properties of the molecular orbitals involved.

Pericyclic reactions encompass several important subclasses, including:

1. **Cycloadditions**: In cycloaddition reactions, two or more unsaturated molecules combine to form a cyclic product. Diels-Alder reaction is a classic example, where a conjugated diene reacts with a dienophile to form a cyclohexene ring.
2. **Electrocyclic Reactions**: These reactions involve the reorganization of π electrons in a conjugated system to form a cyclic compound. Examples include the ring-opening and ring-closing reactions of cyclobutene and cyclohexadiene systems.
3. **Sigmatropic Rearrangements**: Sigmatropic rearrangements involve the migration of a σ-bond (a single bond) along a conjugated system. The Claisen rearrangement and the Cope rearrangement are prominent examples of sigmatropic shifts.
4. **[2+2] Cycloadditions**: These reactions involve the formation of a four-membered ring from two unsaturated reactants.

Pericyclic reactions find wide applications in organic synthesis due to their efficiency, selectivity, and the ability to form multiple bonds stereospecifically in a single step. Moreover, their predictable nature based on orbital symmetry principles makes them valuable tools for designing complex molecular architectures. Understanding and mastering pericyclic reactions are essential for synthetic chemists aiming to construct intricate organic molecules efficiently and with precision.

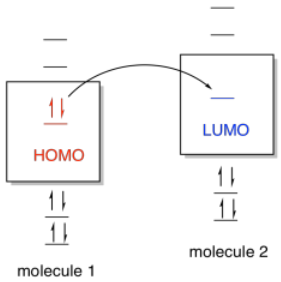
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15.1: Molecular Orbitals of Conjugated Pi Systems

Frontier Molecular Orbital Theory

Prior to 1965, pericyclic reactions were known as "no mechanism reactions" since no one could adequately explain why reaction outcomes changed depending on whether reactants were exposed to heat or light. In 1965 Robert Burns Woodward and Roald Hoffmann used **Frontier Molecular Orbital Theory**, initially proposed by Kenichi Fukui, to develop their **Theory of Conservation of Orbital Symmetry** where outcomes of pericyclic reactions are explained by examining the **Highest Occupied Molecular Orbital (HOMO)** or **Lowest Unoccupied Molecular Orbital (LUMO)** of the reacting system. Their analysis of cycloadditions, electrocyclic reactions, and sigmatropic rearrangements is commonly referred to as the Woodward-Hoffmann Rules. A detailed analysis of three reaction types is provided in the subsequent sections of this chapter.

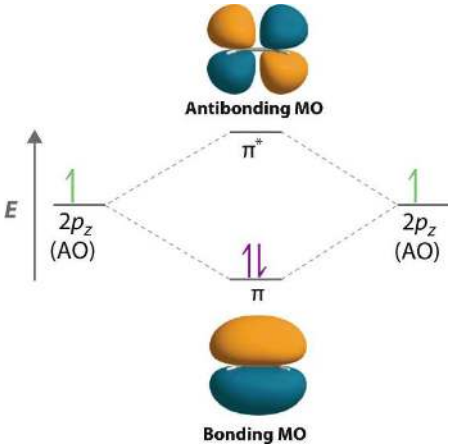
HOMO and LUMO are often referred to as **frontier orbitals** and their energy difference is termed the **HOMO–LUMO gap**. One common way of thinking about reactions in this way is through the concept of frontier orbitals. This idea says that if one species is going to donate electrons to another in order to form a new bond, then the donated electrons are most likely going to come from the highest occupied energy level. In this level, called the highest occupied molecular orbital (HOMO), the electrons are further from the nucleus and therefore less tightly held by the protons in the nucleus. The electrons would be donated, in turn, to the lowest empty energy level on the other species, called the lowest unoccupied molecular orbital (LUMO).



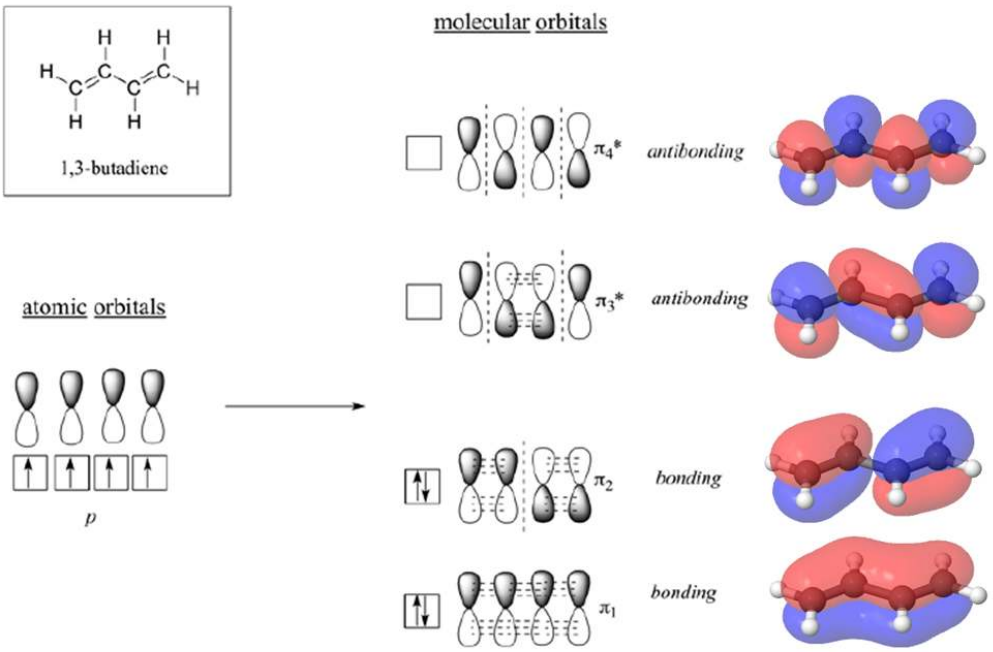
Molecular orbital interaction between frontier orbitals.

Molecular Orbitals

According to MO theory discussed in **Section 1-11**, when a double bond is non-conjugated, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy π bonding orbital and one a high-energy **π-star (π*) anti-bonding molecular orbital**. These are sometimes denoted, in MO diagrams like the one below, with the Greek letter psi (Ψ) instead of π. In the bonding Ψ_1 orbital, the two (+) lobes of the $2p_z$ orbitals interact constructively with each other, as do the two (-) lobes. Therefore, there is increased electron density between the nuclei in the molecular orbital – this is why it is a bonding orbital. In the higher-energy anti-bonding Ψ_2* orbital, the (+) lobes of one $2p_z$ orbital interacts destructively with the (-) lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy $\Psi_1$orbital when the molecule is in the ground state.

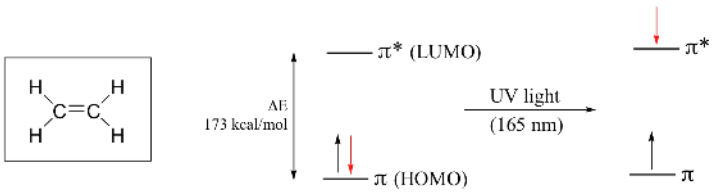


With a conjugated diene, such as 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two antibonding pi* orbitals. The combination of four pi molecular orbitals allow for the formation of a bonding molecular orbital that is lower in energy than those created by an unconjugated alkene. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.

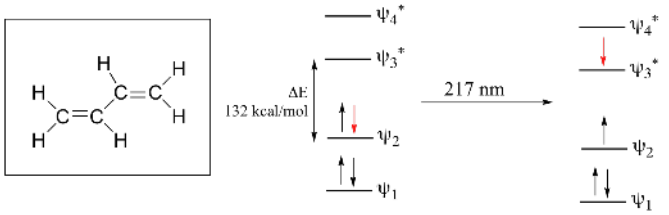


Electronic Transitions

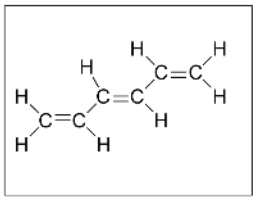
When a double-bonded molecule such as ethene (common name ethylene) absorbs 165 nm light, it undergoes a **π - π* transition**. An electron is moved from the HOMO of ethene to the LUMO placing the molecule in an **excited state**.

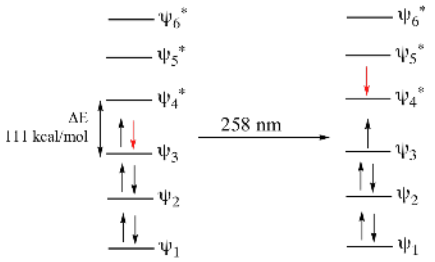


Where electronic transition becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the HOMO–LUMO gap energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. The MO diagram for 1,3-butadiene, the simplest conjugated system. Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are pi bonding, while the upper two are pi antibonding. Comparing this MO picture to that of ethene, our isolated pi-bond example the HOMO would be psi 2 and the LUMO would be psi 3. The HOMO-LUMO energy gap is smaller for the conjugated 1,3-butadiene system which absorbs UV light with a wavelength of 217 nm.



As conjugated pi systems become larger, the HOMO–LUMO gap energy gap for a π - π* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the π - π* transition in 1,3,5-hexatriene, for example, occurs at 258 nm.





Woodward-Hoffmann Rules

Much of what we have said about the electronic factors controlling pericyclic reaction was formulated in the mid 1960's by the American chemists R. B. Woodward and R. Hoffmann, in terms of what came to be called the **orbital symmetry** principles, or the **Woodward-Hoffmann rules**. This is a particularly simple approach says that many details of pericyclic reactions can explained by "conservation of orbital symmetry." This requires the symmetries of the molecular orbitals of reactants to be the same as the molecular orbitals of the products for a reaction to proceed.

The original approach of Woodward and Hoffmann involved construction of an "orbital correlation diagram" to see if the lobes of the reactant molecular orbitals match phases and allow for overlap required for bonding to occur. The symmetries of the appropriate reactant and product orbitals were matched to determine whether the transformation could proceed without a symmetry imposed conversion of bonding reactant orbitals to antibonding product orbitals. If the correlation diagram indicated that the reaction could occur without encountering such a **symmetry-imposed barrier**, it was termed **symmetry allowed**. If a symmetry barrier was present, the reaction was designated **symmetry-forbidden**.

? Exercise 15.1.1

Using the molecular orbital diagram for 1,3,5-hexatriene determine the HOMO and LUMO for both the ground and excited state.

Answer

For the ground state the HOMO is psi 3 and LUMO is psi 4.

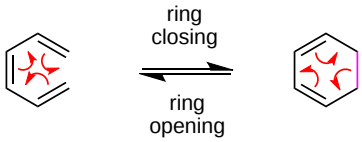
For the excited state the HOMO is psi 4 and LUMO is psi 5.

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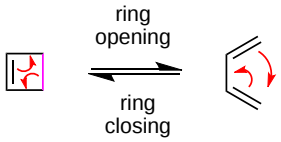
- **14.8: Interpreting Ultraviolet Spectra- The Effect of Conjugation** by Dietmar Kennepohl, Steven Farmer, Tim Soderberg, William Reusch is licensed CC BY-SA 4.0.
- **14.7: Structure Determination in Conjugated Systems - Ultraviolet Spectroscopy** by Dietmar Kennepohl, Steven Farmer, Tim Soderberg is licensed CC BY-SA 4.0.

15.2: Electrocyclic Reactions

An electrocyclic reaction is the concerted cyclization of a conjugated π-electron system by converting one π-bond to a ring forming σ-bond. The key sigma bond must be formed at the terminus of a pi system. These reactions classified by the number of pi electrons involved. Thus, 4 pi reactions form 4 membered rings, as in a conjugated diene can being converted into a cyclobutene. Also, 6 pi reactions form 6 membered rings as in a conjugated triene can be converted into a cyclohexadiene. These reactions are often reversible with the reverse reaction may be called *electrocyclic ring opening*. Although more more pi electrons can be used, the 4 pi and 6 pi variants are by far the most common and are illustrated below with the key sigma bond highlighted in magenta.

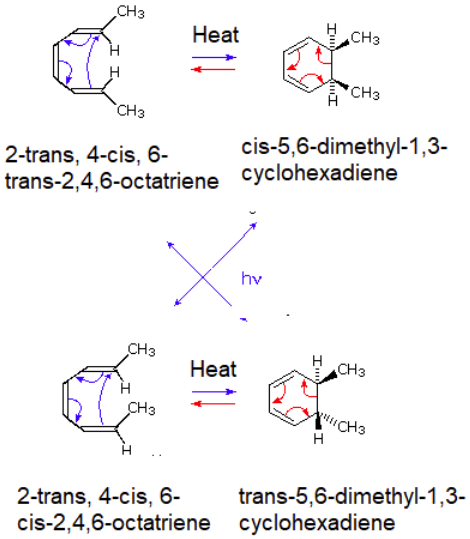


6 pi Electrocyclic Reaction

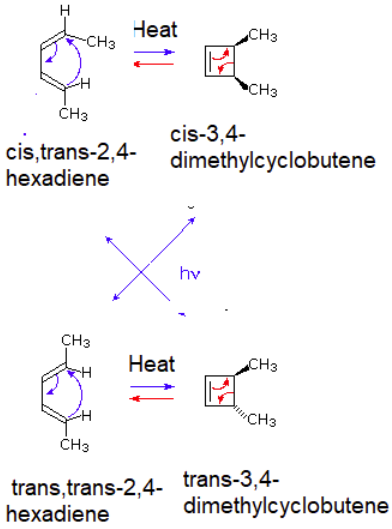


4 pi Electrocyclic Reaction

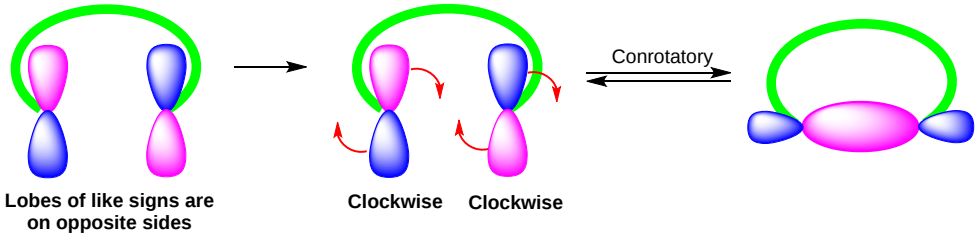
A striking feature of electrocyclic reactions that proceed by concerted mechanisms is their high degree of stereospecificity. For example, 2-*trans*, *4-cis*, *6-trans*-2,4,6-octatriene undergoes ring closure to *cis*-5,6-dimethyl-1,3-cyclohexadiene under thermal conditions i.e. when heated. Similarly the isomeric 2-*trans*, *4-cis*, *6-cis*-2,4,6-octatriene *produces trans*-5,6-dimethyl-1,3-cyclohexadiene, as noted below. However these results are completely reversed if the reaction is run under photochemical conditions (Irradiation with ultraviolet light). For example if 2-*trans*, *4-cis*, *6-cis*-2,4,6-octatriene is irradiated with UV light *cis*-5,6-dimethyl-1,3-cyclohexadiene would be produced.



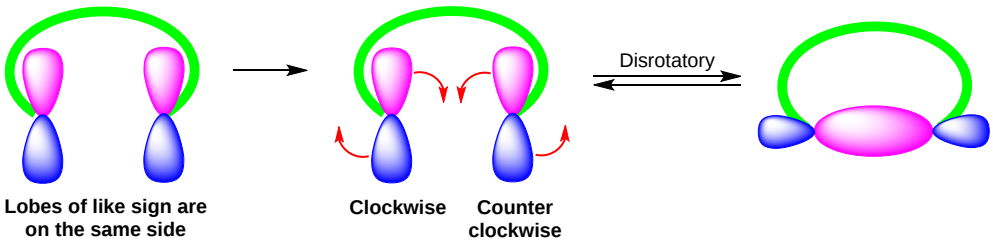
Similar results are seen with the 4 pi electrocyclic reaction of *cis*,*trans*-2,4-hexadiene being heated to exclusively form *cis*-3,4-dimethylcyclobutene and being irradiated with UV light to exclusively form *trans*-3,4-dimethylcyclobutene. Likewise, *trans*,*trans*-2,4-hexadiene forms *trans*-3,4-dimethylcyclobutene when heated and *cis*-3,4-dimethylcyclobutene when being irradiated with UV light.



The stereospecificity of electrocyclic reaction can be explained by considering the terminal lobes of the molecular orbital fo the conjugated π-electron system. For electrocyclic reactions of occur, molecular orbital lobes with the same sign from the HOMO of the molecule must rotate to form/break the key ring sigma bond. If the orbital lobes involved both rotate in the same direction (both counterclockwise or both clockwise), the process is called conrotatory. This typically occurs when orbital lobes of the same sign are on opposite sides of the molecule.



If the orbitals involved rotate in opposite directions (one clockwise and one counterclockwise), the process is called disrotatory. These differences in rotation are critically important when stereocenters are formed or broken. This typically occurs when orbital lobes of the same sign are on the same side of the molecule.

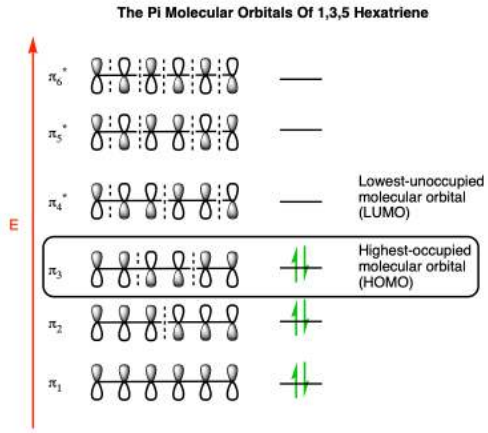


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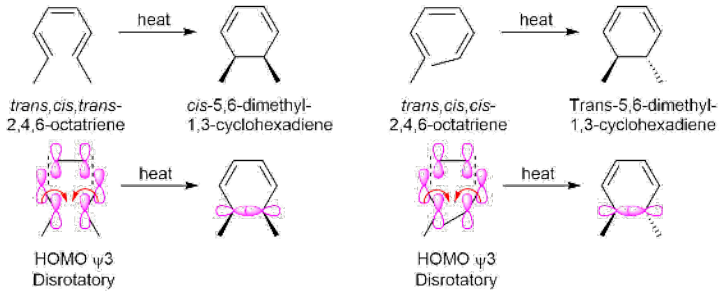
15.3: Stereochemistry of Thermal Electrocyclic Reactions

Frontier orbital theory can be used to predict the stereochemistry of electrocyclic reactions. Electrons in the HOMO are the highest energy and therefore the most easily moved during a reaction. A molecular orbital diagram can be used to determine the orbital symmetry of a conjugated polyene's HOMO. Thermal reactions utilize the HOMO from the ground-state electron configuration of the molecular orbital diagram while photochemical reactions utilize the HOMO in the excited-state electron configuration.

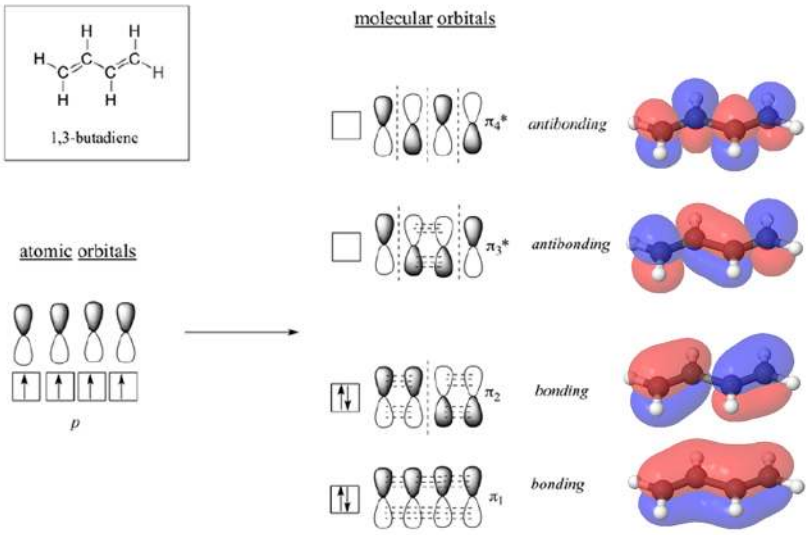
The molecular orbital of 1,3,5-hexatriene in its ground state electron configuration has psi three as its HOMO. The terminal molecular orbital lobes of the HOMO with the same sign are on the same side which predicts disrotatory ring closure under thermal conditions.



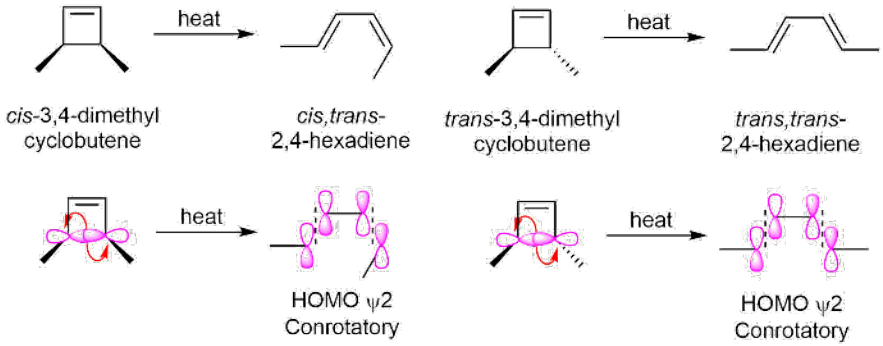
Disrotatory cyclization is observed during the electrocyclic reaction of 2,4,6-octatriene. The *trans,cis,cis*-2,4,6-octatriene isomer produces *cis*-5,6-dimethyl-1,3-cyclohexadiene as the product of thermal cyclization while the *trans,cis,cis*-2,4,6-octatriene isomer produces *trans*-5,6-dimethyl-1,3-cyclohexadiene.



The molecular orbital of a conjugated diene, such as 1,3-butadiene has psi two as the HOMO in its ground state electron configuration. The terminal molecular orbital lobes of the HOMO with the same sign are on opposite sides which predicts conrotatory ring closure under thermal conditions. However, the equilibrium of the electrocyclic reaction only allows for the ring opening to be observed.



Thus heating *cis*-3,4-dimethylcyclobutene causes the conrotatory ring opening to form *cis*,*trans*-2,4-hexadiene. Likewise, *trans*-3,4-dimethylcyclobutene forms *trans*,*trans*-2,4-hexadiene when heated.



A pattern begins to form revealing a relationship between the number of double bonds in the conjugated polyene and the rotation during electrocyclic reactions. For thermal electrocyclic reactions, polyenes with an odd number of double bonds undergo disrotation and those with an even number of double bond undergo conrotation.

? Exercise 15.3.1

1) The thermal electrocyclic ring opening of *trans*-3,4-dimethylcyclobutene could form *trans*,*trans*-2,4-hexadiene or *cis*,*cis*-2,4-hexadiene. However, the *trans*,*trans*-2,4-hexadiene is the isomer obtained from the reaction. Explain how it is possible to get both products and why the *trans*,*trans*-2,4-hexadiene is preferred.

2) If a conjugated tetraene were to undergo a thermal electrocylic reaction would the orbital nodes undergo con or disrotation?

Answer

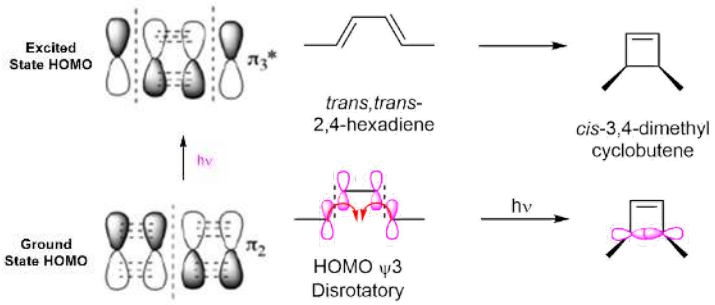
1) Dienes undergo conrotation during thermal electrocyclic ring opening. Conrotation means the orbital nodes both rotate in the same direction either both clock with or both counter clockwise. If the nodes both rotate counter clockwise the *trans*,*trans*-2,4-hexadiene isomers forms. If they both rotate clockwise the *cis*,*cis*-2,4-hexadiene isomer is formed. Trans double bonds are more stable than cis due to steric strain. The *trans*,*trans*-2,4-hexadiene is perferably formed because it is more stable.

2) A tetraene has an even number of double bonds so it would be expected to undergo conrotation.

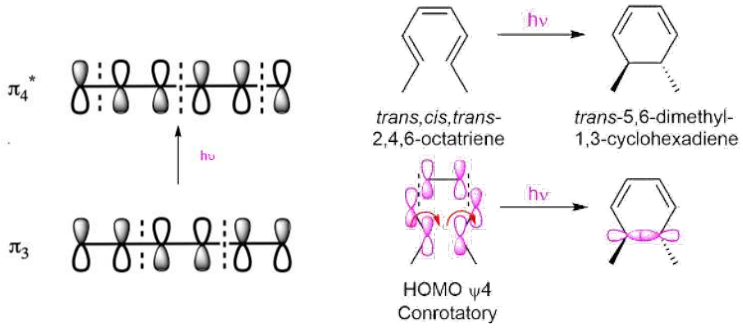
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15.4: Photochemical Electrocyclic Reactions

As discussed in **Section 30.1**, irradiation of a conjugated polyene with ultraviolet light causes an electron from the groude-state HOMO to be excited to the ground state LUMO. This creates a new higher energy HOMO in an electron configuration called the excited state. Electron excitation changes the symmetry of the new HOMO which has a corresponding effect on the reaction stereochemistry. Under photochemical reaction conditions conjugated dienes undergo disrotatory cyclization whereas under thermal conditions they underwent conrotatory cyclization. Likewise, conjugated triene undergo conrotatory photochemical cyclization while undergoing disrotatory thermal cyclization. For example, trans,trans-2,4-hexadiene undergoes conrotatory photochemical cyclization to form *cis*-3,4-dimethylcyclobutene.



The conjugated tirene, *trans*,*cis*,*trans*-2,4,6-octatriene undergoes conrotation to form *trans*-5,6-dimethyl-1,3-cyclohexadiene during photochemical cyclization.



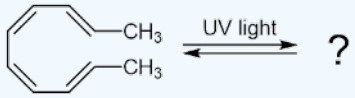
Generalized Statement of Woodward-Hoffmann Rules for Electrocyclic Reactions

Thermal and photochemical electrocyclic reactions always produce the opposite stereochemistry products due to the difference in symmetries in their HOMO frontier orbitals. This idea can be combined with the trend of even and odd polyenes to provide simple rules to predict the stereochemistry of electrocyclic reactions.

Number of Double Bonds	Thermal	Photochemical
Odd	Disrotatory	Conrotatory
Even	Conrotatory	Disrotatory

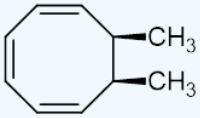
? Exercise 15.4.1

Would the following electrocyclic reaction be con or disrotatory? Please draw the expected product.



Answer

An even number of double bonds in photochemical conditions predicts a disrotatory reaction.

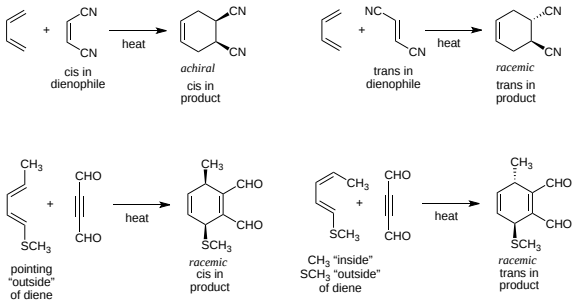


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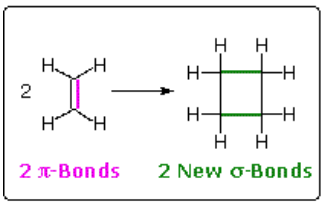
15.5: Cycloaddition Reactions

A concerted combination of two π-electron systems to form a ring of atoms having two new σ bonds and two fewer π bonds is called a **cycloaddition reaction**. The number of participating π-electrons in each component is given in brackets preceding the name of the reaction. The Diels-Alder reaction (**Section 14-4**) is the most useful cycloaddition reaction due to the ubiquity of 6-membered rings and its ability to reliably control stereochemistry in the product. In the Diels-Alder cycloaddition reaction, a conjugated diene, simply referred to as the **diene**, reacts with a double or triple bond coreactant called the **dienophile**, because it combines with (has an affinity for) the diene. The Diels-Alder reaction is a [4+2] cycloaddition (4 pi electrons from the diene and 2 pi electrons from the dienophile) that yields a functionalized 6-membered ring product. During the Diels-Alder reaction, two pi-bonds are converted to two sigma-bonds.

Due to the concerted mechanism for cycloaddition reactions, the geometry of atoms on the dienophile or the diene maintain their orientation in the product. This is a critical point for the 4 atoms (both dienophile atoms and the terminal atoms of the diene) that become sp^3 hybridized and thus are potential stereocenters in the product. (As a reminder, when chiral products are formed, we obtain a racemic mixture of enantiomers.) As highlighted below, cis dienophiles yield cis substituents in the product, while trans dienophiles yield trans product substituents. Substituents on the terminal atoms of the diene also can become stereocenters and this analysis is a little less straightforward than for dienophile substituents. The way to think about the diene substituents is whether the are pointing "outside" or "inside" the diene. These orientations are illustrated below. When groups are both pointing "outside" or "inside", we can consider them to be cis and they will end up cis in the product. When one group is pointing "outside" and one "inside", we can consider them as trans and they will be trans in the product.



Another important reaction is the [2+2] cycloaddition of two alkene containing molecules to form a 4-membered cyclobutane ring. The [2 + 2] cycloaddition of two alkenes does not occur by simply heating but can only be achieved by *irradiation* with ultraviolet light.



A [2+2] Cycloaddition

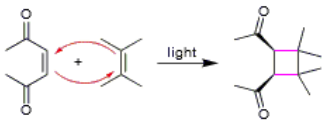
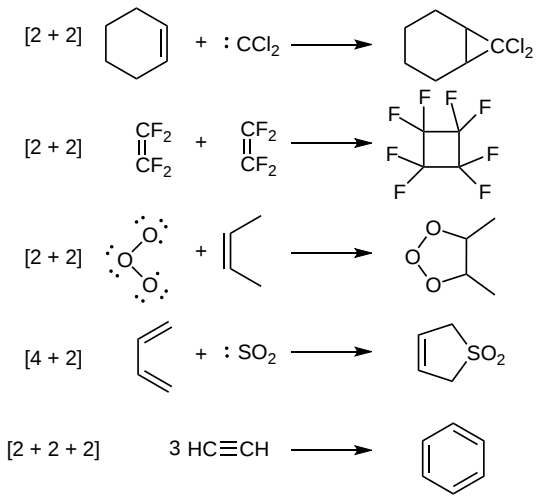
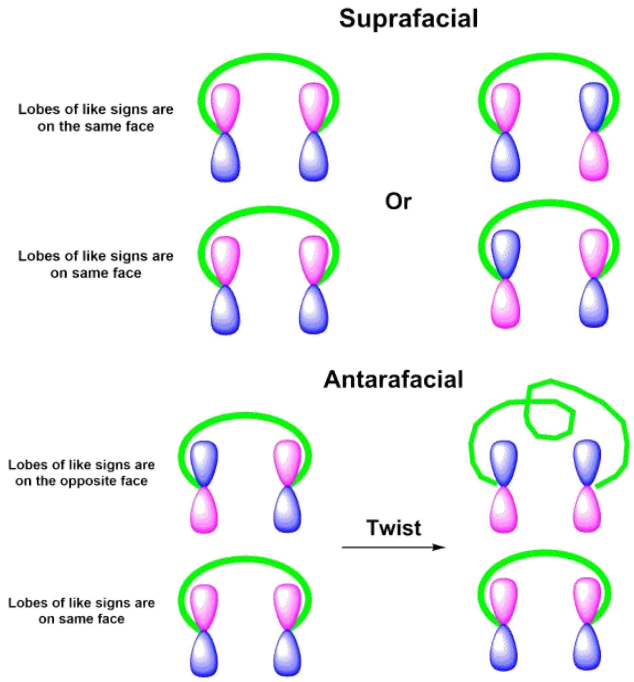


Photo [2+2] Cycloaddition

Many other cycloadditions are known, such as [2 + 2 + 2], and other types of [2 + 2], which give different size of rings. Some specific examples are shown below:



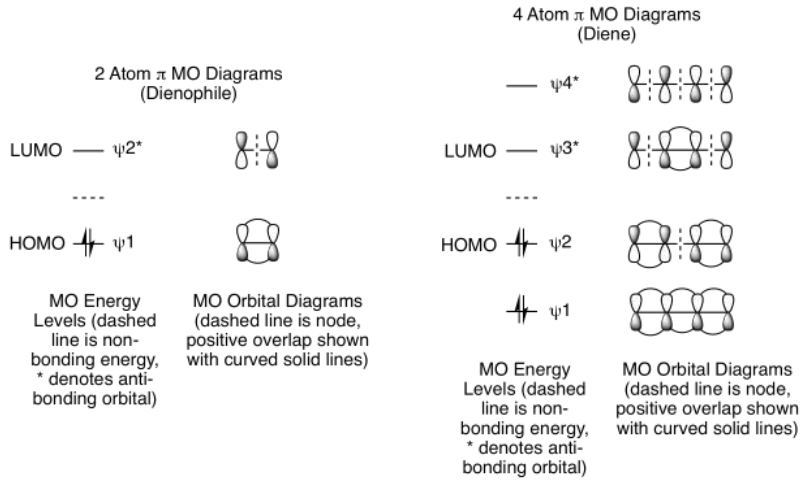
Like other pericyclic reactions, cycloadditions are determined by the orbital symmetry of the frontier orbitals of the reactants. For bonding to occur in a cycloaddition, the terminal lobes of the frontier orbitals of the two pi systems must have the correct symmetry. Correct symmetry can be obtained in two different ways. If the signs on the orbital lobes are the same on the faces of both reactants then the reaction undergoes a **suprafacial cycloaddition**. If the signs of the orbital lobes are the same on the face of one reactant but opposite on the other reactant then the reaction undergoes an **antarafacial cycloaddition**. Although both types are symmetry allowed, the fact that antarafacial cycloadditions require the twisting of a pi orbital system makes them more difficult to achieve.



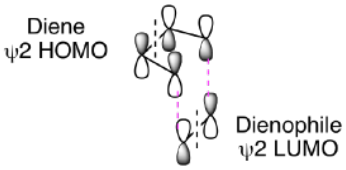
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15.6: Stereochemistry of Cycloadditions

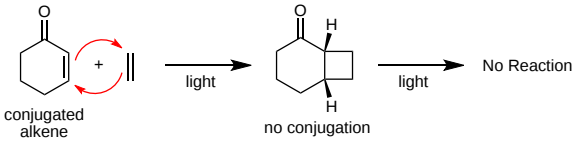
Frontier orbital theory can be used to predict if a given cycloaddition will occur with suprafacial or with antarafacial geometry. In a standard Diels-Alder reaction, bonding interactions are created when the electron containing HOMO of the diene donates electrons to the electron vacant LUMO of the other the dienophile. The dienophile has one pi bond, so it will use the pi MOs for a 2 atom system. The dienophile has 2 pi electrons which makes psi 2* its LUMO. The diene has two pi bonds, so it will use the pi MOs for a 4 atom system. The diene has has 4 pi electrons makes psi 2 its HOMO.



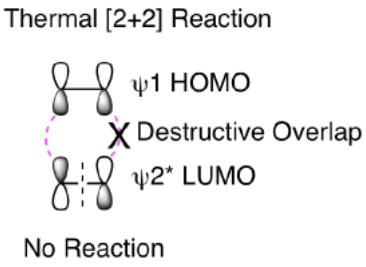
These MO diagrams show that the ground-state frontier orbitals of both reactants have terminal lobes with matching signs. The symmetry of these orbitals are such that bond formation will easily occur under thermal conditions with suprafacial geometry as shown below. (Note: The dashed black lines in the figure below represent nodes in the pi molecular orbitals of the diene and dienophile.) The two new sigma bonds, shown as dashed magenta lines below, are formed from constructive overlap of the terminal dienophile orbitals with the terminal orbitals of the diene.



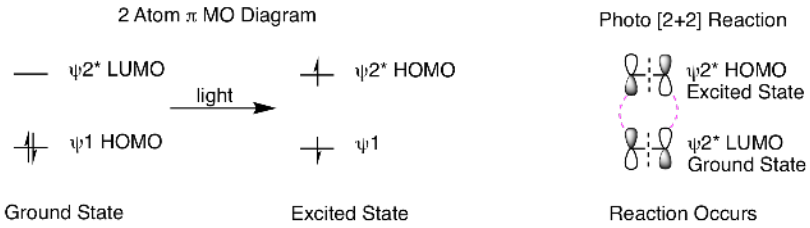
Photochemical [2+2] cycloadditions are excellent reactions for the synthesis of strained products containing 4-membered rings. One of the reaction partners must be conjugated so that it can absorb light and become an excited state molecule. These reactions produce strained 4-membered rings but are not reversible because the products lack conjugation and, thus, can't absorb light to facilitate a cycloreversion.



So, why won't this reaction happen thermally? How does our molecular orbital analysis help us understand the importance of this being a photochemical reaction? First, let's look at the orbital analysis if we tried to do a thermal [2+2] reaction. As shown below, we cannot get suprafacial overlap for both of the 2 pi reactants when trying to combine psi 1 HOMO with psi 2* LUMO. This means that it is not favorable to convert the two reactant pi bonds into two new product pi bonds.



What happens when we shine light on the reaction? Light creates an excited state molecule by promoting an electron in the HOMO to the LUMO, as shown below. This means the excited state HOMO is the ground state LUMO. We need to understand a few key points about photoreactions before doing our molecular orbital analysis. Excited state molecules are very short lived, relaxing back to the ground state very quickly. Therefore, it is practically impossible for two excited state molecules to find each other in a reaction. Instead, reactions occur between one excited state molecule and one ground state molecule. When only one molecule is conjugated, that is the molecule that will form the excited state. If both reactants are conjugated, either can form the excited state. The orbital analysis is shown below. First, we see the orbital picture when a ground state molecule absorbs light to form an excited state. Second, when we analyze the reaction, it is now psi 2* HOMO of the excited state molecule reacting with psi 2* LUMO of the ground state molecule. This gives suprafacial constructive overlap for both orbitals and the 2 reactant pi bonds can be converted into two product sigma bonds.



Cycloaddition reactions can be categorized based on the total number electrons involved in the rearrangement. The [4+2] Diels-Alder reaction involves 6 electrons and takes place using a suprafacial pathway under thermal conditions. The thermal [2+2] cycloaddtion of two alkenes involves 4 electrons and must take place by antarafacial pathway. However, the pathway is reversed for photochemical [2+2] cycloaddtions which take place by a supraficial pathway. These ideas can be generalized using the rules for cycloadditions below.

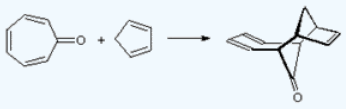
Generalized Statement of Woodward-Hoffmann Rules for Cycloadditions

Number of Electrons	Thermal	Photochemical
4n + 2	Suprafacial (Allowed)	Antarafacial (Forbidden)
4n	Antarafacial (Forbidden)	Suprafacial (Allowed)

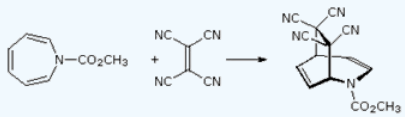
? Exercise 15.6.1

For the following reactions determine what type of cycloaddition is occurring, is the reaction supra or antarafacial, and would the reaction require thermal or photochemical conditions.

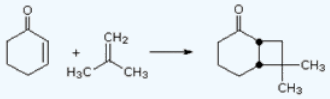
a)



b)



c)



Answer

a) [6+4], suprafacial, thermal

b) [4+2], suprafacial, thermal

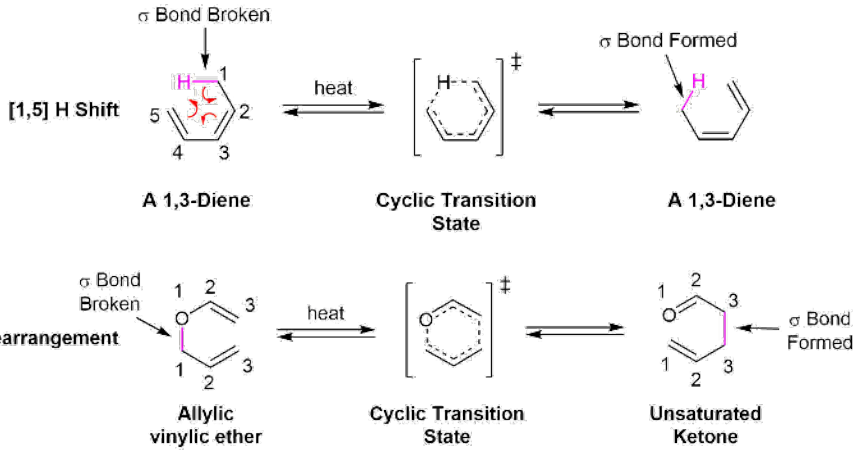
c) [2+2], antarafacial, photochemical

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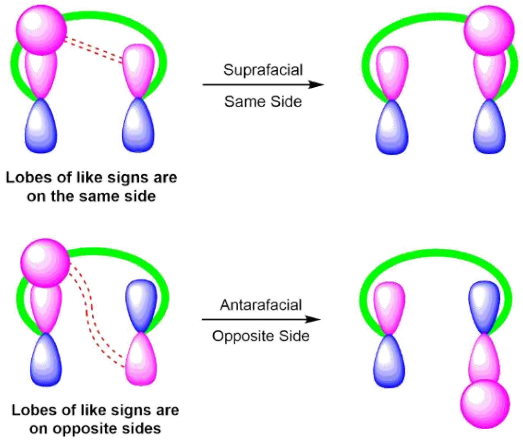
15.7: Sigmatropic Rearrangements

Molecular rearrangements in which a σ-bonded atom or group, flanked by one or more π-electron systems, shifts to a new location with a corresponding reorganization of the π-bonds are called **sigmatropic reactions**. The reactant and product have the same number and type of bonds, just different bond locations. These rearrangements are described by two numbers set in brackets, which refer to the position of the sigma bond in the reactant that is broken compared to the position of the sigma bond in the product that is formed. The most common examples include hydrogen shifts across a diene system (called a [1,5] H shift) and rearrangements of double allyl-type systems (called [3,3] rearrangements).

As shown in the examples below, the atoms on the sigma bond in the reactant that is broken (magenta bond) are both labeled "1", and the numbering of atoms on each side of that sigma bond continue until the atoms connected by the new sigma bond in the product (magenta) are reached. Thus, the H shift is [1,5] because the key sigma bond in both the reactant and product is to the H while the H moves from C-1 to C-5. For the [3,3] rearrangement, the broken sigma bond migrates across two allyl-type systems and forms between atoms "3" and "3" in the product. This particular example is a Claisen rearrangement since an allyl vinyl ether is transformed into a 1,4-carbonyl alkene.



The migration of a group during a sigmatropic rearrangement is controlled by the orbital symmetries of the alkenes involved. Sigmatropic rearrangements can occur on one face of the molecule (think top or bottom, like a syn addition to an alkene) which is called a **suprafacial** reaction or from one face to the other (think from top to bottom or vice versa, like an anti addition to an alkene) which is called **antarafacial**. We will explore this idea further in the next section.



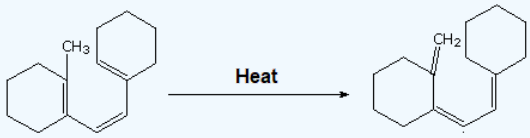
Generalized Statement of Woodward-Hoffmann Rules for Sigmatropic Rearrangements

Suprafacial and antarafacial sigmatropic rearrangements are considered symmetry-allowed by the Woodward-Hoffmann rules. However, suprafacial reactions are much more common. Note! These rules for sigmatropic rearrangements are the same as those given for cycloaddition reactions in **Section 30-3**.

Number of Double Bonds	Thermal	Photochemical
Odd	Suprafacial	Antarafacial
Even	Antarafacial	Suprafacial

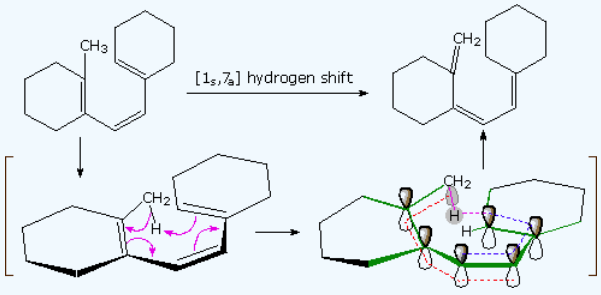
Exercise 15.7.1

For the following sigmatropic hydrogen shift please use braked number to describe the reaction. Predict if the hydrogen shift will be suprafacial and antarafacial. Lastly, draw in arrows to describe the mechanism for this reaction.



Answer

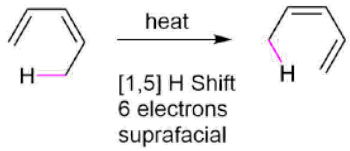
An example of an [1,7] hydrogen shift is shown in the following diagram. The conjugated alkene has three double bonds, which is an odd number, and the reaction is occuing under thermal conditions. This means the reaction is predicted to be suprafacial. The conjugated triene assumes a nearly planar coiled conformation in which a methyl hydrogen is oriented just above the end carbon atom of the last double bond. A [1_s,7_a] sigmatropic hydrogen shift may then take place, as described by the four curved arrows. With reference to the approximate plane of this π-electron system (defined by the green bonds), the hydrogen atom departs from the bottom face and bonds to the top face, so the transfer is antarafacial.



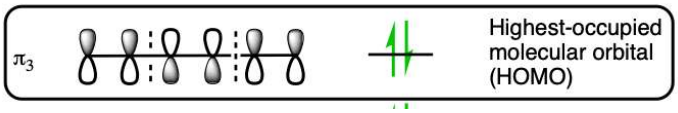
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15.8: Some Examples of Sigmatropic Rearrangements

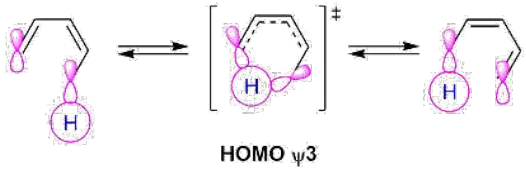
A sigmatropic rearrangement which involves a [1,5] hydrogen shift, like the one shown below illustrates, a hydrogen atom (s orbital) moving across a 5 atom system containing two conjugated double bonds. Since there are three curved arrows in the mechanism, this is a 6 pi reaction. The rules for sigmatropic rearrangements discussed in the last section predict the hydrogen atom will undergo a suprafacial shift. The C-H bond breaking and the C-H bond forming, magenta dashed lines, are both on the bottom face of the molecule's pi system.



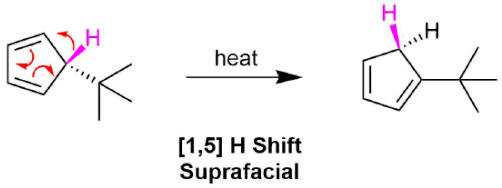
The suprafacial nature of this reaction comes from the orbital symmetry of the HOMO from a 6 pi electron molecular orbital. The orbital lobes on the terminal ends have the same sign on the same side.



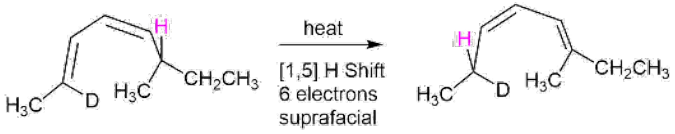
During the reaction mechanism the hydrogen atom, an s orbital, is passes from one molecular to another of the same sign on the same side of the molecule or suprafacial.



For example, 5-*t*-butyl-1,3-cyclopentadiene easily undergoes a [1,5] suprafacial shift of a hydrogen atom under thermal conditions to yield 1-*t*-butyl-1,3-cyclopentadiene as a rearranged product.



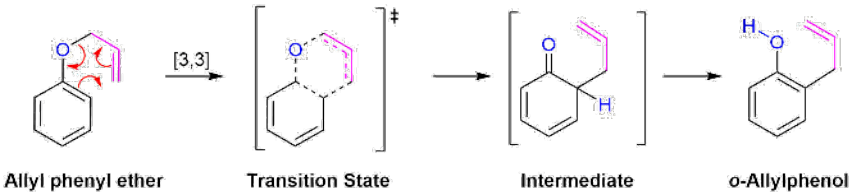
As another example, heating S-2-deuterio-6-methyl-(2E,4Z)-2,4-octadiene undergoes a thermal [1,5] suprafacial shift of a hydrogen to produce the product, R-2-deuterio-6-methyl-(2Z,4E)-3,5-octadiene with stereochemical control.



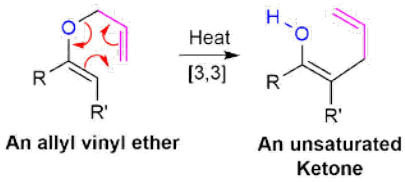
Claisen Rearrangement

A very important example of a [3,3] sigmatropic reaction is the **Claisen rearrangement** of an allyl aryl ether or an allyl vinyl ether (**Section 18-4**). Heating an allyl aryl ether to 250 ^{o}C causes an sigmatropic rearrangement to produce an *o*-allylphenol. This rearrangement initially produces the non-aromatic 6-allyl-2,4-cyclohexadienone intermediate which quickly undergoes a proton shift to reform the aromatic ring in the *o*-allylphenol product. Claisen rearrangement occurs in a six-membered, cyclic transition state involving the movement of six bonding electron.

https://chem.libretexts.org/@go/page/507260

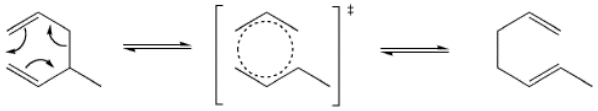


Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



Cope Rearrangement

Another important example of a [3,3] sigmatropic reaction is the **cope rearrangement**. This reaction converts between isomers of a 1,5-hexadiene through a cyclic transition state.

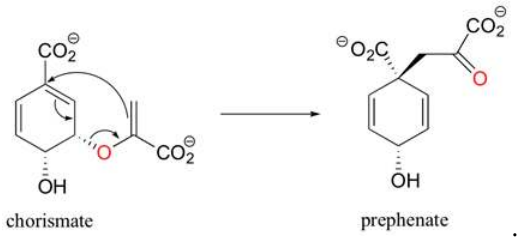


Both Cope and Claisen rearrangements involve the movement of six electrons which means they both react by suprafacial pathways under thermal conditions. These reactions can be considered to occur due to changes in overlap between orbitals around the cyclic transition state. Two orbitals which form the sigma bond being broken tilt away from each other while two orbitals that are pi bonding tilt toward each other to from a new sigma bond. After the change there are now two p orbitals parallel to each other on the left which then form new pi bonds.



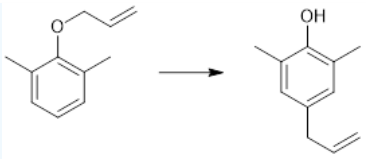
Orbital rearrangement in a Cope rearrangement

Sigmatropic rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.

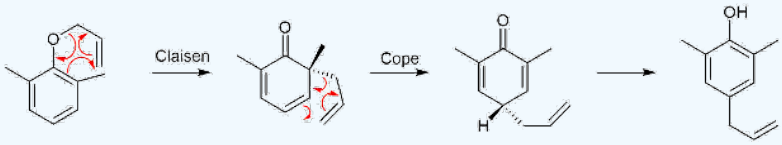


? Exercise 15.8.1

A Claisen rearrangement performed in the presence of ortho-substituents exclusively leads to para-substituted rearrangement products. This occurs via a Claisen rearrangement followed by a Cope rearrangement. Draw out the intermediates formed during this transformation and the mechanisms for both rearrangements.



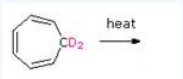
Answer



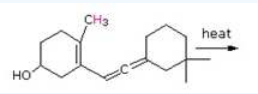
Exercise 15.8.2

Draw the expected products of the following [1,5] suprafacial shifts.

a)

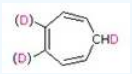


b)

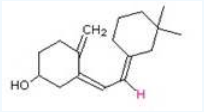


Answer

a)

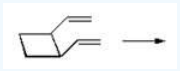


b)



Exercise 15.8.3

Draw the product of the following [3,3] suprafacial shifts.



Answer

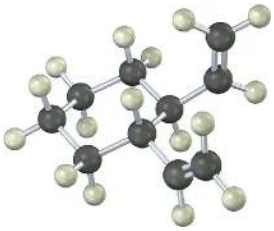


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15.9: Additional Problems

Visualizing Chemistry

PROBLEM 30.13 Predict the product obtained when the following substance is heated:

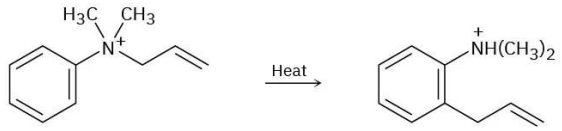


PROBLEM 30.14 The ^{13}C NMR spectrum of homotropilidene taken at room temperature shows only three peaks. Explain.



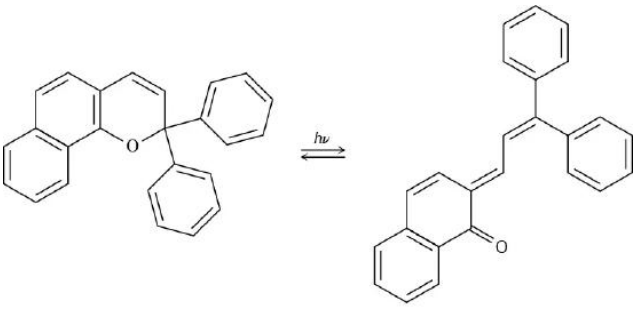
Mechanism Problems

PROBLEM 30.15 The following rearrangement of *N*-allyl-*N*,*N*-dimethylanilinium ion has been observed. Propose a mechanism.



***N*-Allyl-*N*,*N*-dimethylanilinium ion** **o-Allyl-*N*,*N*-dimethylanilinium ion**

PROBLEM 30.16 Plastic photochromic sunglasses are based on the following reversible rearrangement of a dye inside the lenses that occurs when the lenses are exposed to sunlight. The original dye absorbs UV light but not visible light and is thus colorless, while the rearrangement product absorbs visible light and is thus darkened.

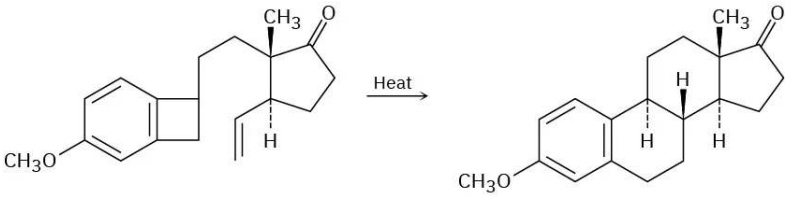


(Colorless) **(Dark)**

(a) Show the mechanism of the rearrangement.

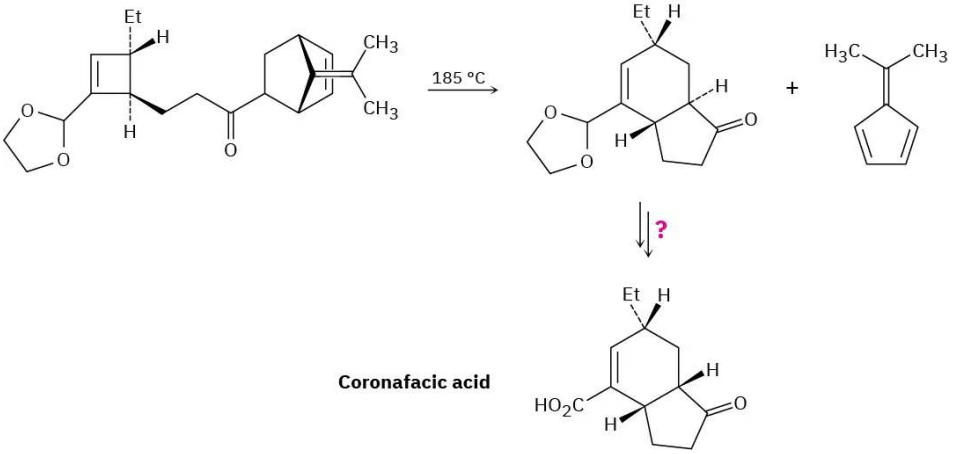
(b) Why does the rearrangement product absorb at a longer wavelength (visible light) than the original dye (UV)?

PROBLEM 30.17 The sex hormone estrone has been synthesized by a route that involves the following step. Identify the pericyclic reactions involved, and propose a mechanism.



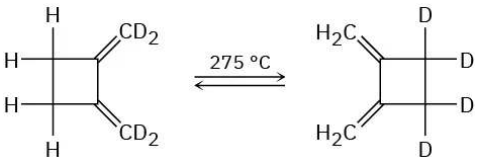
Estrone methyl ether

PROBLEM 30.18 Coronafacic acid, a bacterial toxin, was synthesized using a key step that involves three sequential pericyclic reactions. Identify them, and propose a mechanism for the overall transformation. How would you complete the synthesis?



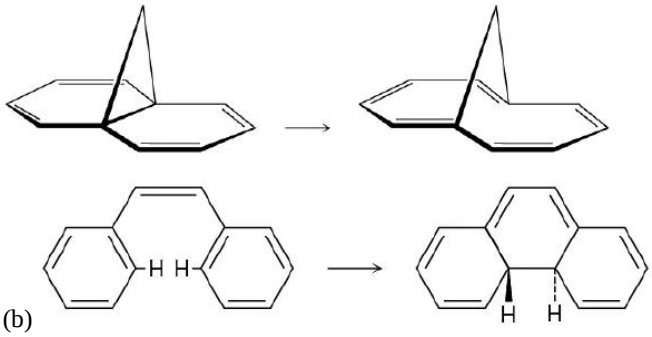
Coronafacic acid

PROBLEM 30.19 The following thermal rearrangement involves two pericyclic reactions in sequence. Identify them, and propose a mechanism to account for the observed result.



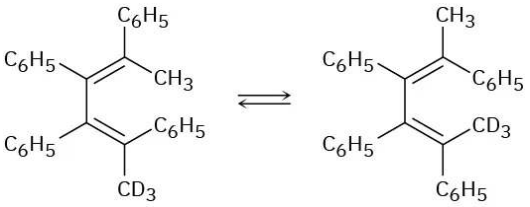
Electrocyclic Reactions

PROBLEM 30.20

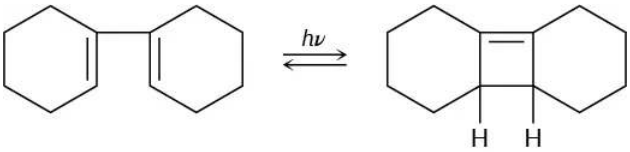


(b)

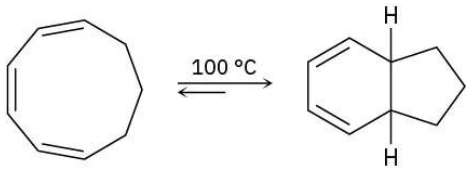
PROBLEM 30.21 The following thermal isomerization occurs under relatively mild conditions. Identify the pericyclic reactions involved, and show how the rearrangement occurs.



PROBLEM 30.22 Would you expect the following reaction to proceed in a conrotatory or disrotatory manner? Show the stereochemistry of the cyclobutene product, and explain your answer.



PROBLEM 30.23 Heating (1*Z*,3*Z*,5*Z*)-1,3,5-cyclononatriene to 100 °C causes cyclization and formation of a bicyclic product. Is the reaction conrotatory or disrotatory? What is the stereochemical relationship of the two hydrogens at the ring junctions, cis or trans?

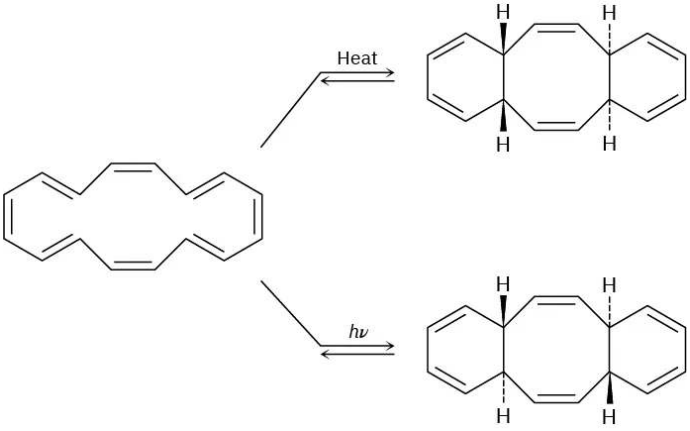


(1*Z*,3*Z*,5*Z*)-1,3,5-Cyclononatriene

PROBLEM 30.24 (2*E*,4*Z*,6*Z*,8*E*)-2,4,6,8-Decatetraene has been cyclized to give 7,8-dimethyl-1,3,5-cyclooctatriene. Predict the manner of ring-closure—conrotatory or disrotatory—for both thermal and photochemical reactions, and predict the stereochemistry of the product in each case.

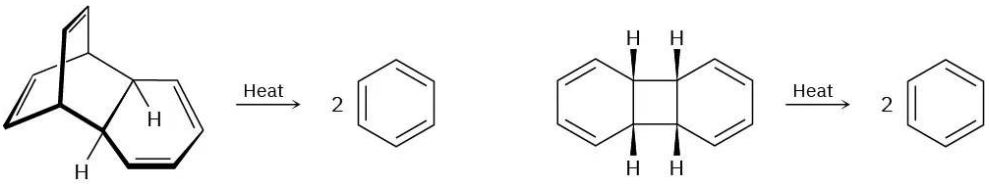
PROBLEM 30.25 Answer Problem 30-24 for the thermal and photochemical cyclizations of (2*E*,4*Z*,6*Z*,8*Z*)-2,4,6,8-decatetraene.

PROBLEM 30.26 The cyclohexadecaoctaene shown isomerizes to two different isomers, depending on reaction conditions. Explain the observed results, and indicate whether each reaction is conrotatory or disrotatory.

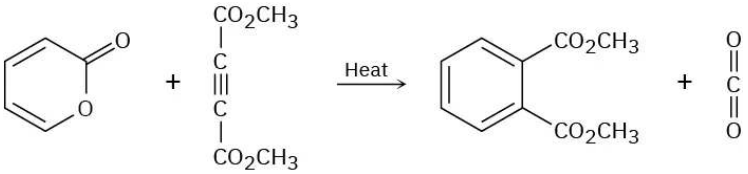


Cycloaddition Reactions

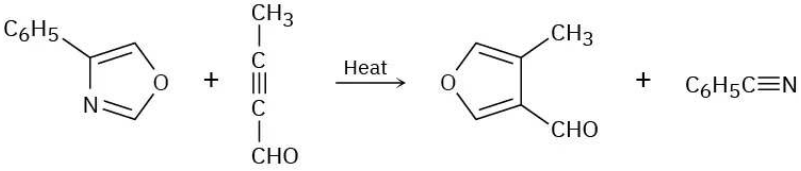
PROBLEM 30.27 Which of the following reactions is more likely to occur? Explain.



PROBLEM 30.28 The following reaction takes place in two steps, one of which is a cycloaddition while the other is a *reverse* cycloaddition. Identify the two pericyclic reactions, and show how they occur.

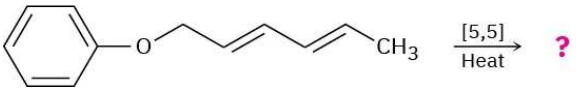


PROBLEM 30.29 Two sequential pericyclic reactions are involved in the following furan synthesis. Identify them, and propose a mechanism for the transformation.

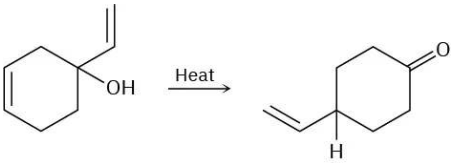


Sigmatropic Rearrangements

PROBLEM 30.30 Predict the product of the following pericyclic reaction. Is this [5,5] shift a suprafacial or an antarafacial process?



PROBLEM 30.31 Propose a pericyclic mechanism to account for the following transformation:

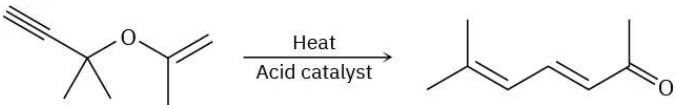


PROBLEM 30.32 Vinyl-substituted cyclopropanes undergo thermal rearrangement to yield cyclopentenes. Propose a mechanism for the reaction, and identify the pericyclic process involved.

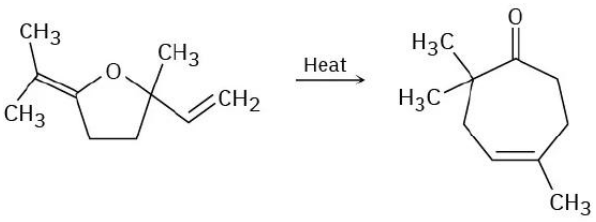


Vinylcyclopropane **Cyclopentene**

PROBLEM 30.33 The following synthesis of dienones occurs readily. Propose a mechanism to account for the results, and identify the kind of pericyclic reaction involved.



PROBLEM 30.34 Karahanaenone, a terpenoid isolated from oil of hops, has been synthesized by the thermal reaction shown. Identify the kind of pericyclic reaction, and explain how karahanaenone is formed.



Karahanaenone

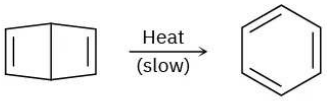
General Problems

PROBLEM 30.35

A photochemical [1,5] sigmatropic rearrangement

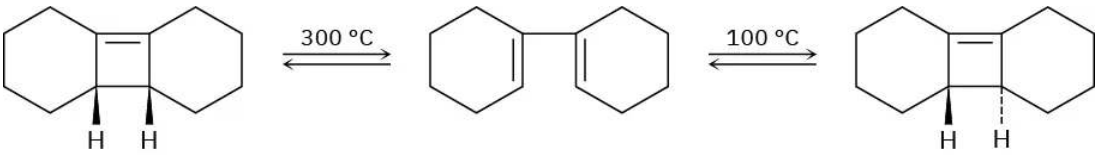
(b) A thermal [4 + 6] cycloaddition (c) A thermal [1,7] sigmatropic rearrangement (d) A photochemical [2 + 6] cycloaddition

PROBLEM 30.36 Bicyclohexadiene, also known as *Dewar benzene*, is extremely stable despite the fact that its rearrangement to benzene is energetically favored. Explain why the rearrangement is so slow.

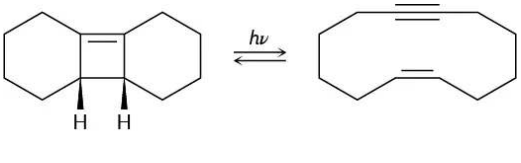


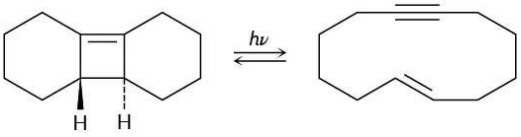
Dewar benzene **Benzene**

PROBLEM 30.37 Ring-opening of the *trans*-cyclobutene isomer shown takes place at much lower temperature than a similar ring-opening of the *cis*-cyclobutene isomer. Explain the temperature effect, and identify the stereochemistry of each reaction as either conrotatory or disrotatory.

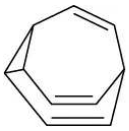


PROBLEM 30.38 Photolysis of the *cis*-cyclobutene isomer in Problem 30-37 yields *cis*-cyclododecaen-7-yne, but photolysis of the trans isomer yields *trans*-cyclododecaen-7-yne. Explain these results, and identify the type and stereochemistry of the pericyclic reaction.



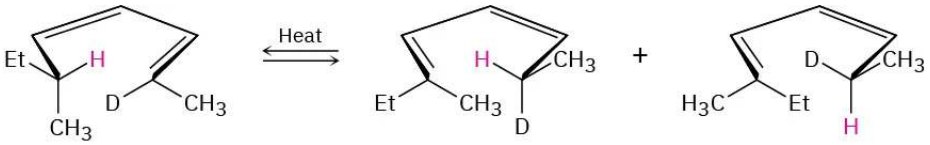


PROBLEM 30.39 The ^{1}H NMR spectrum of bullvalene at 100 °C consists only of a single peak at 4.22 δ. Explain.

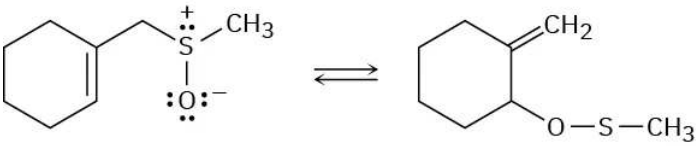


Bullvalene

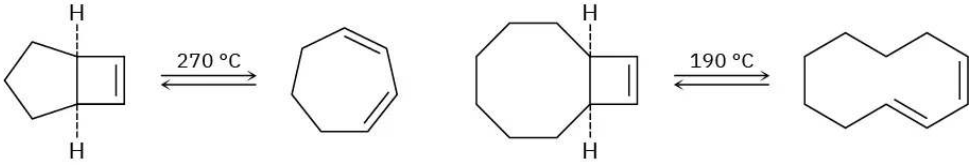
PROBLEM 30.40 The following rearrangement was devised and carried out to prove the stereochemistry of [1,5] sigmatropic hydrogen shifts. Explain how the observed result confirms the predictions of orbital symmetry.



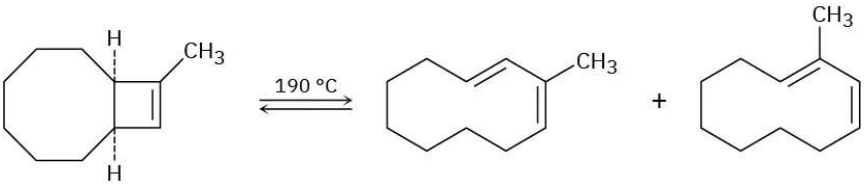
PROBLEM 30.41 The following reaction is an example of a [2,3] sigmatropic rearrangement. Would you expect the reaction to be suprafacial or antarafacial? Explain.



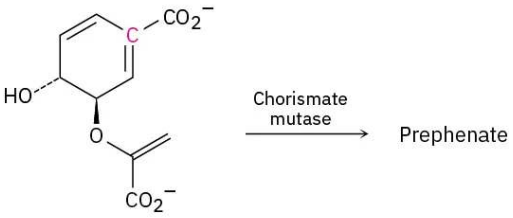
PROBLEM 30.42 When the compound having a cyclobutene fused to a five-membered ring is heated, (1*Z*,3*Z*)-1,3-cycloheptadiene is formed. When the related compound having a cyclobutene fused to an eight-membered ring is heated, however, (1*E*,3*Z*)-1,3-cyclodecadiene is formed. Explain these results, and suggest a reason why opening of the eight-membered ring occurs at a lower temperature.



PROBLEM 30.43 In light of your answer to Problem 30-42, explain why a mixture of products occurs in the following reaction:

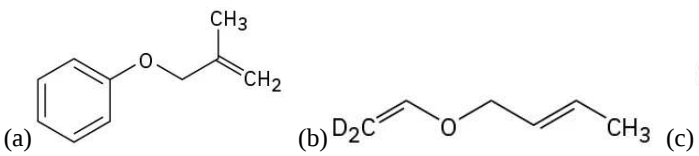


PROBLEM 30.44 In nature, the enzyme chorismate mutase catalyzes a Claisen rearrangement of chorismate that involves both the terminal double bond and the double bond with the highlighted carbon. What is the structure of prephenate, the biological precursor to the amino acids phenylalanine and tyrosine?



Chorismate

PROBLEM 30.45 Predict the product(s) if the starting materials underwent a Claisen rearrangement. Draw arrows to illustrate the rearrangement of electrons.



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15.S: A Summary of Rules for Pericyclic Reactions

Before pericyclic reactions can be put to use in a predictable and controlled manner, a broad mechanistic understanding of the factors that influence these concerted transformations must be formulated. The simplest, albeit least rigorous, method for predicting the configurational path favored by a proposed pericyclic reaction is based upon a transition state electron count. In most of the earlier examples, pericyclic reactions were described by a cycle of curved arrows, each representing a pair of bonding electrons. The total number of electrons undergoing reorganization is always even, and is either a **4n+2** or **4n** number (where n is an integer). Once this electron count is made, the following table may be used for predictions. It is important to remember that going from thermal to photochemical conditions or going from 4n to 4n+2 reaction electrons changes the outcome of the reaction.

	Electron Count	**Stereochemistry**
Thermal Reactions (Ground State)	**4n + 2**	Suprafacial or Disrotatory
	4n	Antarafacial or Conrotatory
	Electron Count	**Stereochemistry**
Photochemical Reactions (Excited State)	**4n + 2**	Antarafacial or Conrotatory
	4n	Suprafacial or Disrotatory

? Exercise 15.S.1

Predict the stereochemistry of the following reactions:

a. The photochemical cyclization of a conjugated tetraene.
b. The thermal cyclization of a conjugated tetraene
c. A thermal [4+4] cycloaddition
d. A photochemical [2+5] cycloaddition
e. A thermal [3,5] sigmatropic rearrangement

Answer

1)a) Disrotatory

b) Conrotatory

c) Antarafacial

d) Suprafacial

e) Antarafacial

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CHAPTER OVERVIEW

16: Synthetic Polymers

Synthetic polymer are man-made polymer that is not a biopolymer (e..g, proteins or complex carbohydrates). Synthetic polymers are mostly non-biodegradable and often synthesized from petroleum. The eight most common types of synthetic organic polymers are: Low-density polyethylene (LDPE), High-density polyethylene (HDPE), Polypropylene (PP), Polyvinyl chloride (PVC), Polystyrene (PS), Nylon, nylon 6, nylon 6,6, Teflon (Polytetrafluoroethylene) and Thermoplastic polyurethanes (TPU).

16.0: Chapter Objectives
16.1: Chain-Growth Polymers
16.2: Stereochemistry of Polymerization - Ziegler-Natta Catalysts
16.3: Copolymers
16.4: Step-Growth Polymers
16.5: Olefin Metathesis Polymerization
16.6: Polymer Structure and Physical Properties
16.7: Additional Problems
16.S: Synthetic Polymers (Summary)

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16.0: Chapter Objectives

Learning Objectives

By the end of this chapter, students should be able to:

- Explain how synthetic polymers are formed through various polymerization reactions.
- Identify how the molecular structure of polymers influences their macroscopic properties.
- Categorize synthetic polymers based on their structure, properties, and applications.
- Describe experimental techniques used to analyze and characterize polymers.
- Examine the diverse applications of synthetic polymers in different industries.

Synthetic polymers constitute a vast class of materials that play an indispensable role in numerous aspects of modern life. These polymers are engineered in laboratories and industrial settings through chemical processes, wherein small molecules known as monomers are repetitively linked together to form long chains or networks. The resulting macromolecules exhibit a wide range of properties and functionalities tailored to specific applications, making them ubiquitous in everyday products and industrial processes.

The synthesis of synthetic polymers typically involves polymerization reactions, where monomers undergo chemical bonding to form polymer chains. This can occur through various mechanisms, including addition polymerization, condensation polymerization, and ring-opening polymerization, each yielding polymers with distinct structures and properties (Figure 16.0.1).

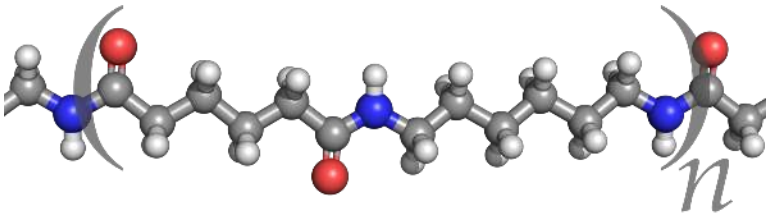


Figure 16.0.1: Nylon 6,6 chemical structure (CC BY 3.0; YassineMrabet via Wikipedia)

One of the most significant advantages of synthetic polymers is their versatility. By selecting different monomers and adjusting reaction conditions, polymer chemists can precisely control the molecular architecture, composition, and properties of the resulting polymers. This versatility enables the design of materials with tailored characteristics such as mechanical strength, flexibility, thermal stability, conductivity, and biocompatibility.

Synthetic polymers find applications across diverse industries and sectors. Plastics, for example, are ubiquitous in packaging, construction, electronics, automotive components, and consumer goods due to their lightweight, moldability, and durability. Synthetic fibers such as polyester, nylon, and acrylics are widely used in textiles, apparel, and industrial materials. Polymers also play critical roles in adhesives, coatings, biomedical implants, drug delivery systems, and advanced composites.

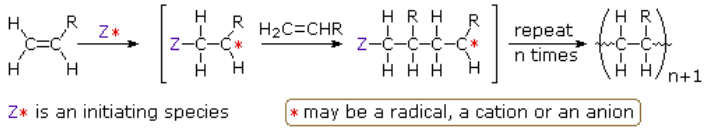
Understanding the structure-property relationships of synthetic polymers is essential for optimizing their performance and developing new materials with enhanced characteristics. Researchers continue to explore innovative polymerization techniques, advanced characterization methods, and sustainable alternatives to traditional polymers to address environmental concerns associated with plastic waste and pollution.

In summary, synthetic polymers represent a cornerstone of modern materials science and technology, providing tailored solutions to a myriad of societal challenges and driving innovation in various industries. Their versatility, tunable properties, and wide-ranging applications underscore their importance in shaping the world we live in today.

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16.1: Chain-Growth Polymers

Polymers resulting from additions to alkenes monomers are chain-growth polymers. In these processes each addition step results in a longer chain which ends in a reactive site. The mechanism of each addition step is the same, and each addition step adds another monomer to extend the chain by one repeating unit. The most common and thermodynamically favored chemical transformations of alkenes are addition reactions. Many of these addition reactions are known to proceed in a stepwise fashion by way of reactive intermediates, and this is the mechanism followed by most polymerizations. A general diagram illustrating this assembly of linear macromolecules, which supports the name chain growth polymers, is presented here. Since a pi-bond in the monomer is converted to a sigma-bond in the polymer, the polymerization reaction is usually exothermic by 8 to 20 kcal/mol. Indeed, cases of explosively uncontrolled polymerizations have been reported.

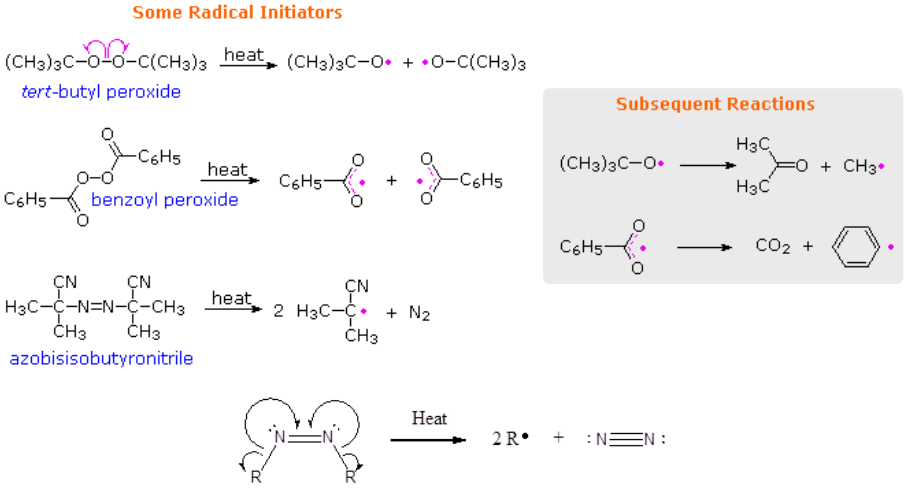


It is useful to distinguish four polymerization procedures fitting this general description.

• Radical Polymerization: The initiator is a radical, and the propagating site of reactivity (*) is a carbon radical.
• Cationic Polymerization: The initiator is an acid, and the propagating site of reactivity (*) is a carbocation.
• Anionic Polymerization: The initiator is a nucleophile, and the propagating site of reactivity (*) is a carbanion.
• Coordination Catalytic Polymerization: The initiator is a transition metal complex, and the propagating site of reactivity (*) is a terminal catalytic complex.

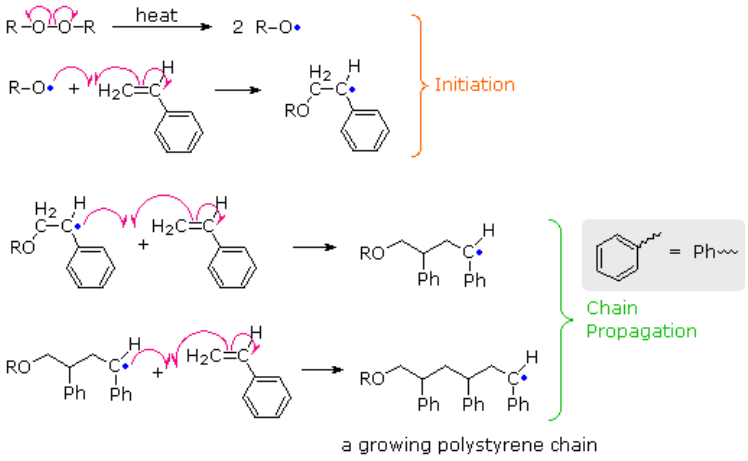
Radical Chain-Growth Polymerization

Virtually all of the monomers described above are subject to radical polymerization. Since this can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization is desired, it must be started by using a radical initiator, such as a peroxide or certain azo compounds. The formulas of some common initiators, and equations showing the formation of radical species from these initiators are presented below.

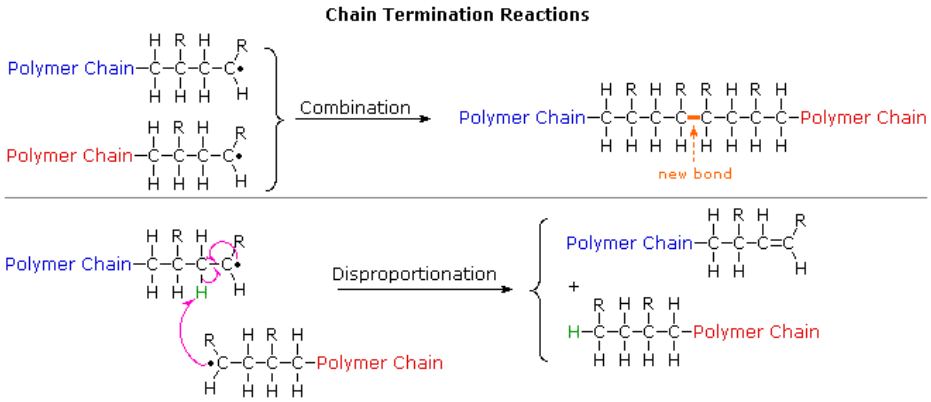


By using small amounts of initiators, a wide variety of monomers can be polymerized. One example of this radical polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples of chain propagation. Each monomer unit adds to the growing chain in a manner that generates the most stable radical. Since carbon radicals are stabilized by substituents of many kinds, the preference for head-to-tail regioselectivity in most addition polymerizations is understandable. Because radicals are tolerant of many functional groups and solvents (including water), radical polymerizations are widely used in the chemical industry.

Each step in this polymer formation is an addition to an alkene. The mechanism is in most cases a *free radical* addition. In free radical reactions the pi pair of electrons separates. One of these electrons pairs with an electron from the attacking reagent to form a sigma bond with one of the alkene carbons. and the other electron remains attached to the other alkene carbon. (Curved arrows with only one "barb" on a point are used to follow the path of a single electron in the same way that "double-headed" arrows follow the path of an electron pair.) Intermediates with an unpaired electron are called free radicals, so this step can be described as adding a free radical to an alkene to lengthen the chain by two carbons and generate a new free radical. In its turn this new free radical can add to another molecule of monomer and continue the process.

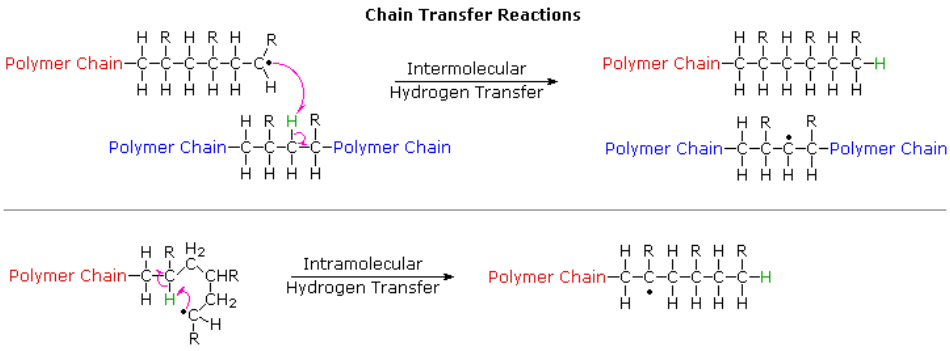


In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination processes are Radical Combination and Disproportionation. These reactions are illustrated by the following equations. The growing polymer chains are colored blue and red, and the hydrogen atom transferred in disproportionation is colored green. Note that in both types of termination two reactive radical sites are removed by simultaneous conversion to stable product(s). Since the concentration of radical species in a polymerization reaction is small relative to other reactants (e.g. monomers, solvents and terminated chains), the rate at which these radical-radical termination reactions occurs is very small, and most growing chains achieve moderate length before termination.



The relative importance of these terminations varies with the nature of the monomer undergoing polymerization. For acrylonitrile and styrene combination is the major process. However, methyl methacrylate and vinyl acetate are terminated chiefly by disproportionation.

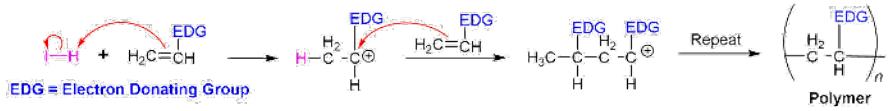
Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equations.



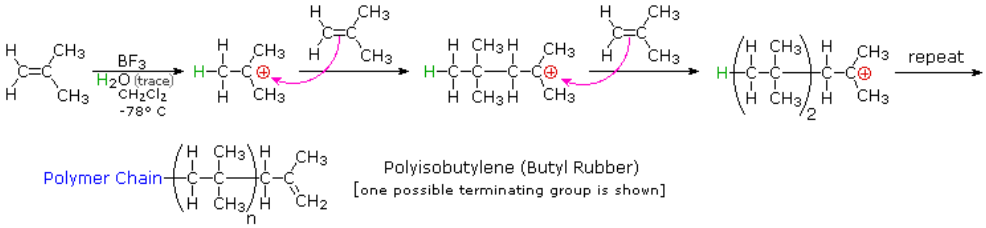
Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1º-radical at the end of a growing chain is converted to a more stable 2º-radical by hydrogen atom transfer. Further polymerization at the new radical site generates a side chain radical, and this may in turn lead to creation of other side chains by chain transfer reactions. As a result, the morphology of LDPE is an amorphous network of highly branched macromolecules.

Cationic Chain-Growth Polymerization

Cationic polymerizations are typically acid-catalyzed. Electrophilic addition of H^+ to a double bond forms a carbocation which is propagated by repeated reactions with addition alkene monomers. Alkene monomers bearing cation stabilizing groups, such as alkyl, phenyl or vinyl can be polymerized by cationic processes.

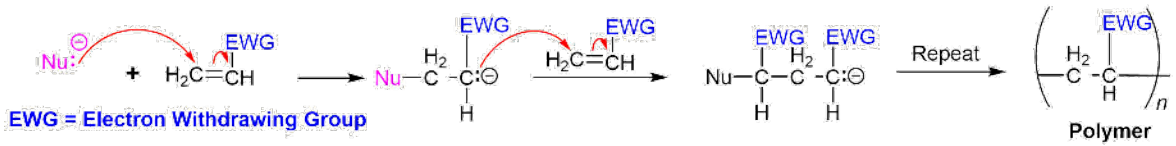


Polymerization of isobutylene (2-methylpropene) by traces of strong acids is an example of cationic polymerization. The initiation reagent cationic polymerization is commonly the Lewis acid, boron tribluoride (BF_3), along with traces of water to form the acidic $BF_3OH^-H^+$ catalyst. The polyisobutylene product is a soft rubbery solid, which is used for inner tubes. This process is similar to radical polymerization, as demonstrated by the following equations. Chain growth ceases when the terminal carbocation combines with a nucleophile or loses a proton, giving a terminal alkene (as shown here).



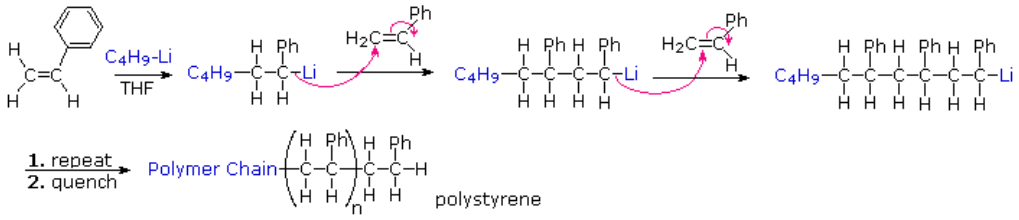
Anionic Chain-Growth Polymerization

Only monomers having anion stabilizing electron-withdrawing groups (EWG) substituents, such as phenyl, cyano or carbonyl can undergo anionic polymerization.

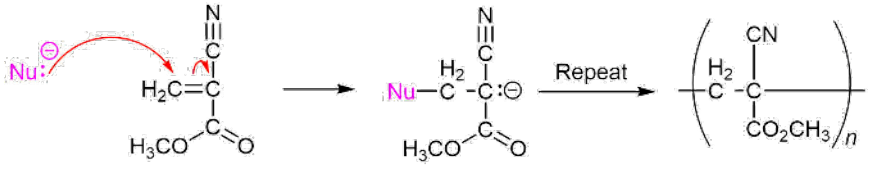


Species that have been used to initiate anionic polymerization include alkali metals, alkali amides, alkyl lithiums and various electron sources. The fundamental reaction for anion polymerization is a conjugate nucleophilic addition (**Section 18-13**) Treatment of a cold THF solution of styrene with 0.001 equivalents of n-butyllithium causes an immediate polymerization. This is

an example of anionic polymerization, the course of which is described by the following equations. Chain growth may be terminated by water or carbon dioxide, and chain transfer seldom occurs.

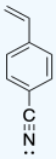


A practical application of anionic polymerization occurs in the use of superglue. This material is methyl 2-cyanoacrylate, CH_2=C(CN)CO_2CH_3. When exposed to water, amines or other nucleophiles, a rapid polymerization of this monomer takes place. Because the monomer has two electron withdrawing groups the polymerization particularly rapid.



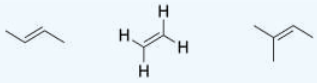
Exercise 16.1.1

1) Anionic polymerization of *p*-substituted styrene proceeds very well when the substituent is an electron-withdrawing group such as nitrile. Explain the reason for the success of this approach.

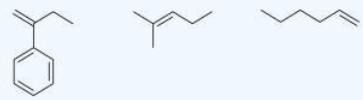


2) In each group, select the alkene monomer most suitable for cationic polymerization.

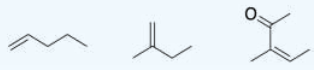
a)



b)

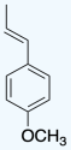


c)



3) Provide a mechanism for the formation of a protic initiator from the interaction of boron trifluoride with water.

4) Anethole in a naturally-occurring compound that has been used in cationic polymerizations. Show why anethole should be a good monomer for this method.



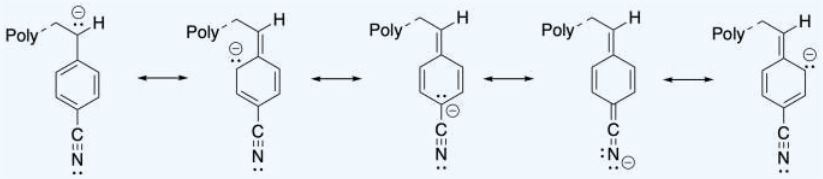
5) Show why radicals formed from the following monomers are relatively stable:

a) acrylonitrile, CH_2=CHCN

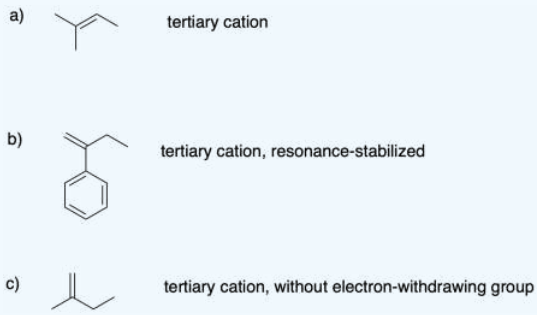
b) methyl acrylate, CH_2=$CHCO_2Me$

Answer

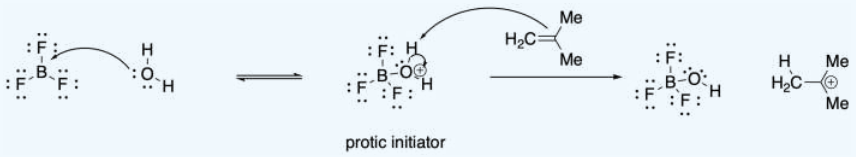
1) The additional resonance stabilization of the anion by the nitrile group makes anionic polymerization proceed smoothly.



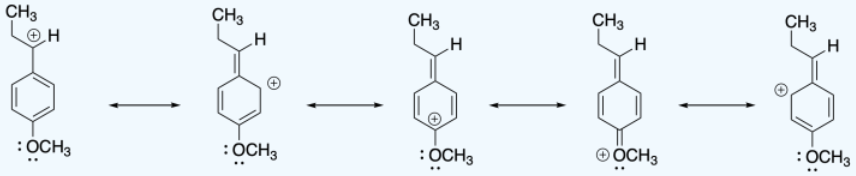
2)



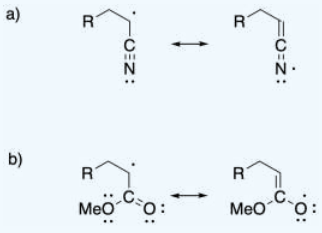
3)



4)



5)



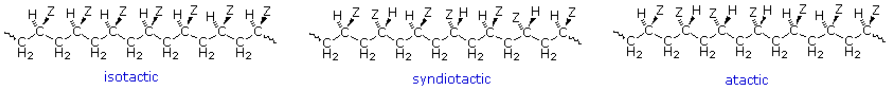
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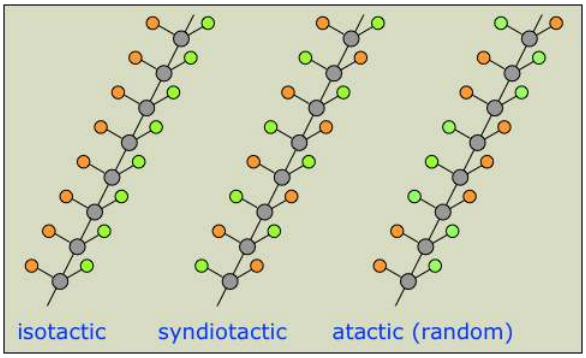
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16.2: Stereochemistry of Polymerization - Ziegler-Natta Catalysts

Ziegler-Natta Catalytic Polymerization

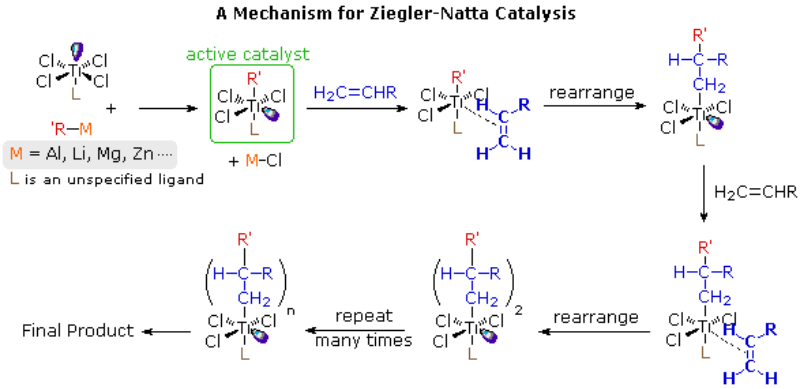
When propene is enchained into a polymer, a new chiral center is formed at every position where a methyl group branches from the backbone. Rather than trying to assign each of these chiral centers with stereochemical configurations (*R*) or (*S*), we instead describe the relative stereochemical relationships along the backbone. The term used to describe these relationships is "**tacticity**". If there is no apparent relationship between the projection of the methyl groups along the backbone, the polymer is termed "**atactic**". If the methyl groups alternate, pointing first one direction, then the other, all the way along the chain, then the polymer is termed "**syndiotactic**". If the methyl groups all project the same direction, the polymer is described as "isotactic".





An efficient and stereospecific catalytic polymerization procedure was developed by Karl Ziegler (Germany) and Giulio Natta (Italy) in the 1950's. Ziegler-Natta catalysts are prepared by reacting certain transition metal halides with organometallic reagents such as alkyl aluminum, lithium and zinc reagents. The catalyst formed by reaction of triethylaluminum with titanium tetrachloride is commonly used. Ziegler-Natta catalysts allowed for the first time, the stereochemically controlled synthesis of polymers with virtually no branching. By changing the catalyst, pure isotactic, syndiotactic, or atactic polymers could be created. For this important discovery, Ziegler and Natta received the 1963 Nobel Prize in chemistry. For example, the polymerization of ethylene, using a Ziegler-Natta catalyst produces a stronger (more crystalline) and more heat resistant product, called high-density polyethylene (HDPE), than typical radical polymerizations which produces low-density polyethlene (LDPE). HDPE is normally produced with molecular weights in the range of 200,000 to 500,000, but it can be made even higher. Polyethylene with molecular weights of three to six million is referred to as ultra-high molecular weight polyethylene, or UHMWPE. UHMWPE can be used to make fibers which are so strong they replaced Kevlar for use in bullet proof vests. Large sheets of it can be used instead of ice for skating rinks.

The following diagram presents one mechanism of the Ziegler-Natta polymerization. Formation of the Ziegler-Natta catalyst, adds an alkyl group ligand to create an organo transition metal compound with a vacant coordination site. An alkene ligand is then coordinated to the transition metal which is followed by a 1,2-insertion of the alkene into the metal-carbon bond. The insertion creates a vacant coordination site which can react with another alkene. These same elementary steps continue to occur to provide the polymerization.



Exercise 16.2.1

When the monomer vinylidene fluoride, $H_2C{=}CF_2$, is polymerized it does not create isotactic, syndiotactic, and atactic forms. Please explain

Answer

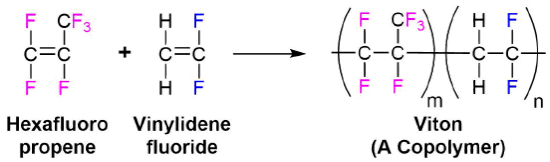
When vinylidene fluoride is polymerized it does not create a chiral center due to the symmetry created by the two fluorides. Chirality is necessary to create isotactic, syndiotactic, and atactic polymer forms.

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16.3: Copolymers

Homopolymers are made with a single monomer and are made up of identical repeating units. Copolymers is made when two or more different monomers are polymerized together to create a polymer with variable repeating units. For example the monomers hexafluoropropene and vinylidene fluoride can be polymerized together to create the copolymer vitron which is used to create durable gaskets.

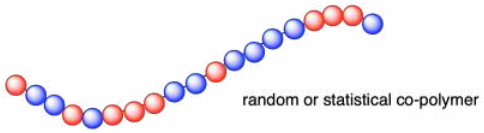


The synthesis of macromolecules composed of more than one repeating unit has been explored as a means of controlling the properties of the resulting material. In this respect, it is useful to distinguish several ways in which different monomeric units might be incorporated in a polymer. The following examples refer to a two component system, in which one monomer is designated A and the other B.

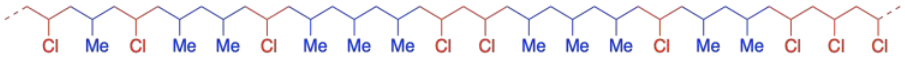
Statistical Copolymers

Also called random copolymers. Here the monomeric units are distributed randomly, and sometimes unevenly, in the polymer chain:

~ABBAAABAABBBABAABA~



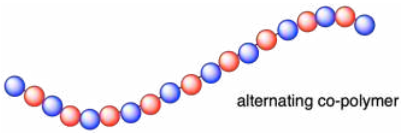
Most direct copolymerizations of equimolar mixtures of different monomers give statistical copolymers. If you take a mixture of alkenes that are capable of forming polymers and you polymerize them together, you may well get them randomly enchained into a growing polymer. For example, polymerizing propene and vinyl chloride together creates a polymer with random monmer unit.



Alternating Copolymers

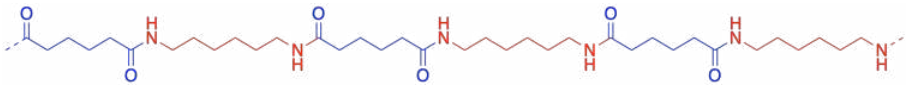
Here the monomeric units are distributed in a regular alternating fashion, with nearly equimolar amounts of each in the chain:

~ABABABABABABABAB~



Formation of alternating copolymers is favored when the monomers have different polar substituents (e.g. one electron withdrawing and the other electron donating), and both have similar reactivities toward radicals. For example, styrene and acrylonitrile copolymerize in a largely alternating fashion.

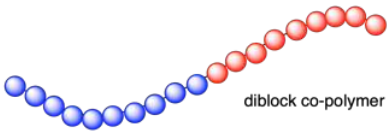
In some of the examples alternating copolymers, the chain is actually composed of two different monomers. This is the case in polyamides such as nylon-6,6, which is a chain is composed of difunctional amines alternating with difunctional carboxyloids (such as carboxylic acids or acid chlorides). Because of their complementary reactivity, the monomers have to alternate: an amine and then a carboxyloid, to form an amide, and so on. We can think of these polymers as "alternating co-polymers" because the two different monomers alternate with each other along the chain.



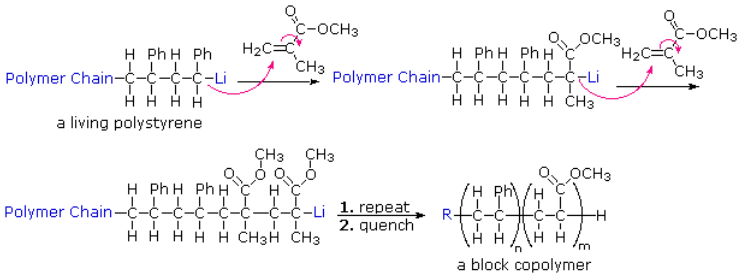
Block Copolymers

Instead of a mixed distribution of monomeric units, a long sequence or block of one monomer is joined to a block of the second monomer:

~AAAAA-BBBBBBB~AAAAAAA~BBB~



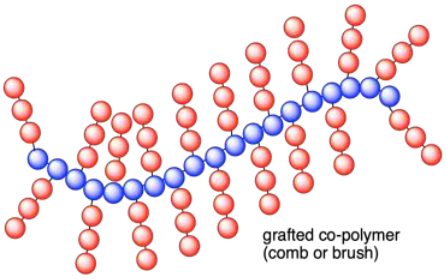
Several different techniques for preparing block copolymers have been developed, with a common example being anionic polymerization. In the anionic polymerization of styrene, a reactive site remains at the end of the chain until it is quenched. The unquenched polymer has been termed a living polymer because the polymerization can continue as long as monomer is present. If different suitable monomer, methyl methacrylate, is added the chain will continue grow by adding methyl methacrylate units and a block polymer will form. This is illustrated for in the following diagram.



Graft Copolymers

As the name suggests, side chains of a given monomer are "grafted" to the main chain of a different monomer:

~AAAAAAA(BBBBBBB~)AAAAAAA(BBBB~)AAA~.



Graft polymers can be made in great profusion by attaching chains of one kind of polymer to the middle of another. A particularly simple but uncontrollable way of doing this is to knock groups off a polymer chain with x-ray or alpha radiation in the presence of a monomer. The polymer radicals so produced then can grow side chains made of the new monomer. A more elegant procedure is to use a photochemical reaction to dissociate groups from the polymer chains and form radicals capable of polymerization with an added monomer.

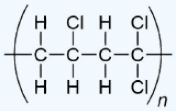
Some Useful Copolymers

Monomer A	Monomer B	Copolymer	Uses
$H_2C=CHCl$	$H_2C=CCl_2$	Saran	films & fibers
$H_2C=CHC_6H_5$	$H_2C=C-CH=CH_2$	SBR styrene butadiene rubber	tires
$H_2C=CHCN$	$H_2C=C-CH=CH_2$	Nitrile Rubber	adhesives hoses
$H_2C=C(CH_3)_2$	$H_2C=C-CH=CH_2$	Butyl Rubber	inner tubes
$F_2C=CF(CF_3)$	$H_2C=CHF$	Viton	gaskets

? Exercise 16.3.1

Draw the structure of an alternating segment of Saran, a copolymer of vinyl chloride (chloroethene) and vinylidene chloride (1,1-dichloroethene).

Answer



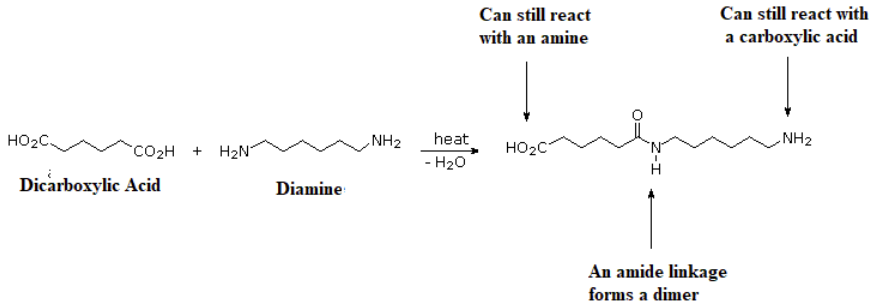
Saran

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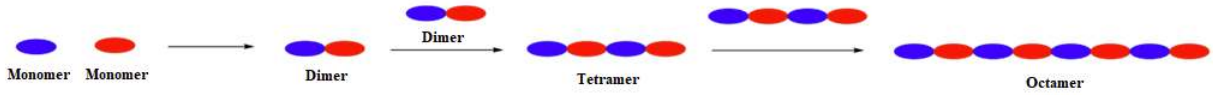
- **29.8: Block, Graft, and Ladder Polymers** by John D. Roberts and Marjorie C. Caserio is licensed CC BY-NC-SA 4.0.

16.4: Step-Growth Polymers

The process of step-growth polymerizations are fundamentally different than in chain-growth. In step-growth polymerizations, monomers are generally linked by a carbon-heteroatom bond (C-O & C-N) formed in non-sequential steps. Often, the reactions used to link these monomers include multiple nucleophilic acyl substitutions. Step-growth polymerizations usually use two different monomers, neither of which would undergo polymerization on its own. The two monomers are multifuntional and complementary to each other, such that each provides the other with a reactive partner. In this section, we will be focusing on monomers which are **difunctional**, meaning they contain two of the same reactive functional group. A step-growth polymerization starts with two complementary functional groups on different monomers reacting to form a dimer. Because both monomers were difunctional, each retains a reactive group and can react with additional complementary monomers.

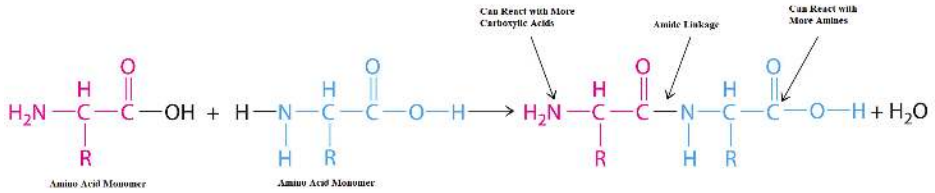


In fact the difuctionality of the monomers, allows step-growth polymers to grow in two directions at once. First, two complementary monomers react with each other to form a dimer. Assuming that monomers react at roughly similar rates, when one end of the dimer reacts again it will likely find another dimer and form a tetramer. Then when the tetramer goes to react again it will most likely find another tetramer and form an octamer. This process is repeated allowing the polymer to grow in two directions at the same time.



The Step-Growth Polymerization Process

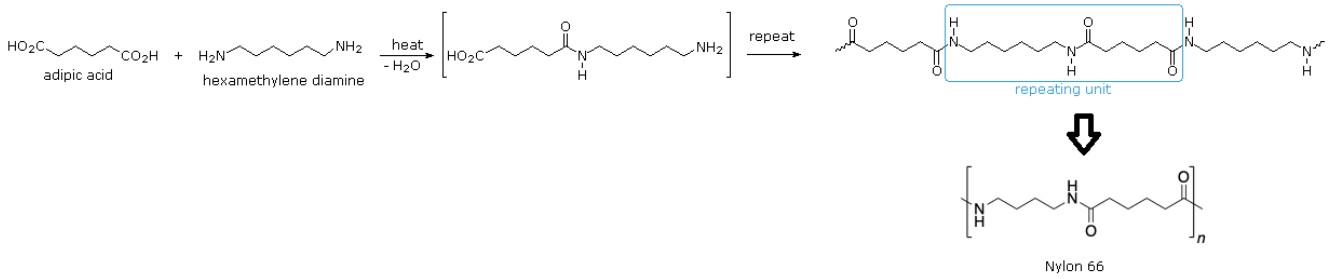
Virtually all fibers are made from some form of polymer. In particular, silk and wool are composed of a naturally occurring protein polymer. The monomers of proteins are called **amino acid residues**. These residues are connected by amide linkages which are also called **peptide bonds**. Many of the early efforts of polymer chemistry were to artificially create fibers which mimicked the properties of silk and wool.



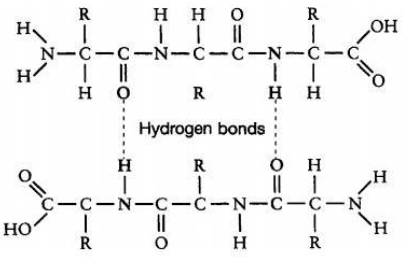
Polyamides

The first fully synthetic polymer fiber, nylon-6,6, was produced in 1938 by the company DuPont. The lead chemist of DuPont's work was Wallace H. Carothers, who reasoned that the properties of silk could be mimicked by constructing a polymer chain created with repeating amide bonds, just like the proteins in silk. Nylon-6,6 was created by first reacting 1,6-hexanedioic acid (adipic acid) and 1,6-hexanediamine to give a salt which was then heated creating multiple amide bonds through nucleophilic acyl substitution. The product of this particular reaction is a polyamide called nylon-6,6. The numbers of the name indicate how many

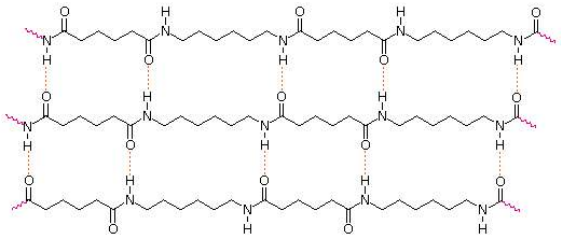
carbons are contained in each monomer. The first “6” stands for the number of carbons in the diamine monomer while the second number indicated the number of carbons in the dicarboxylic acid. Simply by varying the number of carbons in each monomer, a wide variety of nylon polymers can be made.



Nylons are among the most widely used synthetic fibers—for example, they are used in ropes, sails, carpets, clothing, tires, brushes, and parachutes. Known for their high strength and abrasion resistance, nylons can be molded into blocks for use in electrical equipment, gears, bearings, and valves. The strength of nylon fibers comes, in part, from their ability to form strong hydrogen bonding intermolecular forces with each other in much the same fashion as proteins.



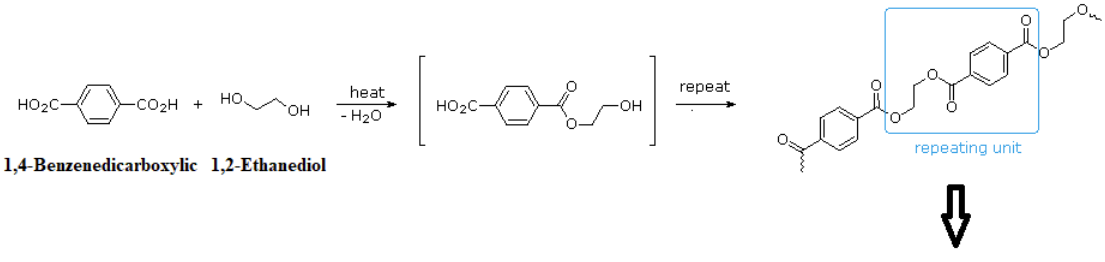
The Hydrogen Bonding between Proteins



The Hydrogen Bonding between Nylon Polyamides

Polyesters

Esterfication, via nucleophilic acyl substitutions, can also be used to form the primary linkages in step-growth polymers. A polyester is typically produced when a dicarboxylic acid and a diol are reacted together. After the initial reaction, the ester product contains a free (unreacted) carboxyl group at one end and a free alcohol group at the other. Further esterification using a step-growth polymerization, produces a polyester. The most important polyester, polyethylene terephthalate (PET), is made from the reaction of 1,4-benzenedicarboxylic (terephthalic acid) and 1,2-ethanediol (ethylene glycol) monomers.



1,4-Benzenedicarboxylic 1,2-Ethanediol

poly(ethyleneterephthalate)
(PET)
A Polyester

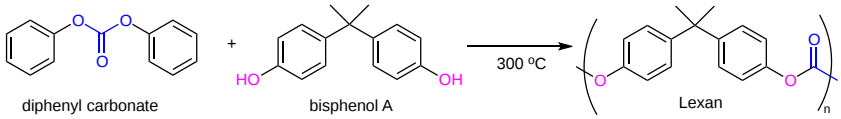
Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes.

Polycarbonates

Beyond carboxylic acid derivatives, virtually any reaction which involves reactive species on two different molecules can be used to perform a step-growth polymerization. A variation involves using a monomer containing a carbonate functional group (−O−(C=O)−O−). A carbonate acts like a double ester and can undergo a type of double transesterification reaction with two alcohols to form a new carbonate containing compound.



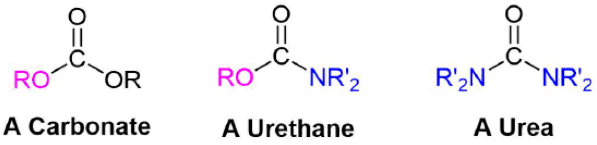
In effect, a carbonate is difunctional and can be reacted with a diol to form polymers containing repeated carbonate groups in their structure called polycarbonates. An example of a polycarbonate is the polymer, Lexan, which is created when diphenyl carbonate and bisphenol A (a diol) are reacted together.



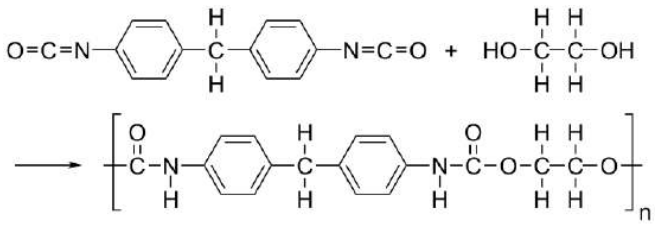
Bisphenol (BPA), primarily used to make polycarbonate, is one of the highest-volume chemicals produced in the world, with over six billion pounds made each year. Because polycarbonate is used to make plastic bottles, the lining for food cans, and the lining for beverage cans there has been much concern about trace amounts of BPA leaching from the containers and being ingested. A study conducted in 2003 and 2004 by the Center for Disease Control and Prevention found trace amounts BPA in the tissues of 93% of people in the United States. Consequently, this has led to many beverage companies switching to non-polycarbonate polymers.

Polyurethane

A urethane is a functional group similar to a carbonate and a urea. A urethane has an -OR and a -NR_2 group attached to the carbonyl carbon.



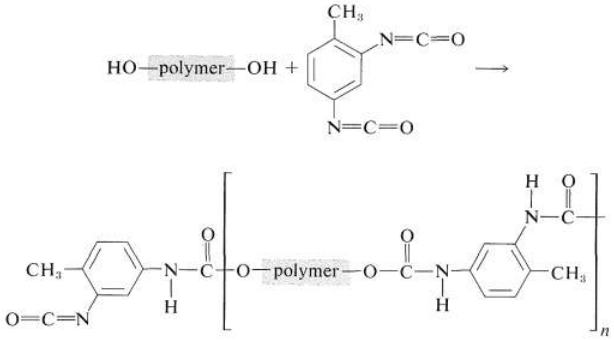
Polyurethane (**PUR** and **PU**) is a polymer composed of organic units joined by carbamate (urethane) links. Polyurethanes are produced by reacting an isocyanate containing two or more isocyanate groups per molecule ($R-(N=C=O)_n$) with a polyol containing on average two or more hydroxyl groups per molecule ($R'-(OH)_n$) in the presence of a catalyst or by activation with ultraviolet light.



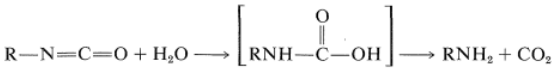
The very widely used polyurethane foams can be considered to be either block polymers or copolymers. The essential ingredients are a diisocyanate and a diol. The diisocyanate most used is 2,4-diisocyano-1-methylbenzene, and the diol can be a polyether or a

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polyester with hydroxyl end groups. The isocyano groups react with the hydroxyl end groups to form initially an addition polymer, which has polycarbamate (polyurethane) links, and isocyano end groups:



A foam is formed by addition of the proper amount of water. The water reacts with the isocyanate end groups to form carbamic acids which decarboxylate to give amine groups:

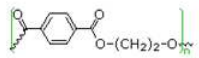
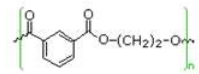
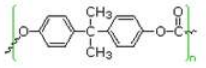
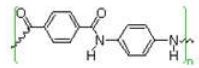
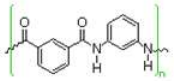


The carbon dioxide evolved is the foaming agent, and the amino groups formed at the same time extend the polymer chains by reacting with the residual isocyano end groups to form urea linkages:

$$\mathrm{R'N{=}C{=}O + RNH_2 \rightarrow R'NHCONHR}$$

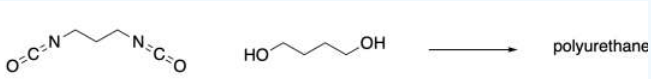
Polyurethanes are used in the manufacture of high-resilience foam seating, rigid foam insulation panels, microcellular foam seals and gaskets, durable elastomeric wheels and tires (such as roller coaster, escalator, shopping cart, elevator, and skateboard wheels), automotive suspension bushings, electrical potting compounds, high performance adhesives, surface coatings and surface sealants, synthetic fibers (e.g., Spandex), carpet underlay, hard-plastic parts (e.g., for electronic instruments), condoms,[1] and hoses.

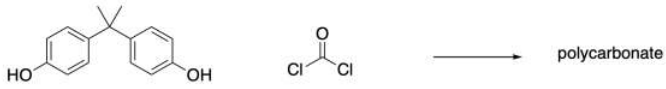
Common Step Growth Polymers

Formula	Type	Components	T_g ºC	T_m ºC
~[CO(CH$_2$)$_4$CO-OCH$_2$CH$_2$O]$_n$~	**polyester**	HO$_2$C-(CH$_2$)$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	< 0	50
	**polyester** Dacron, Mylar	para HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	70	265
	**polyester**	meta HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	50	240
	**polycarbonate** Lexan	(HO-C$_6$H$_4$-)$_2$C(CH$_3$)$_2$ (Bisphenol A) X$_2$C=O (X = OCH$_3$ or Cl)	150	267
~[CO(CH$_2$)$_4$CO-NH(CH$_2$)$_6$NH]$_n$~	**polyamide** Nylon 66	HO$_2$C-(CH$_2$)$_4$-CO$_2$H H$_2$N-(CH$_2$)$_6$-NH$_2$	45	265
~[CO(CH$_2$)$_5$NH]$_n$~	**polyamide** Nylon 6 Perlon		53	223
	**polyamide** Kevlar	para HO$_2$C-C$_6$H$_4$-CO$_2$H para H$_2$N-C$_6$H$_4$-NH$_2$	---	500
	**polyamide** Nomex	meta HO$_2$C-C$_6$H$_4$-CO$_2$H meta H$_2$N-C$_6$H$_4$-NH$_2$	273	390

? Exercise 16.4.1

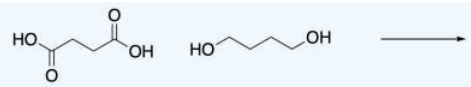
1) The following difunctional monomers would undergo polymerization together. Show the product that results.

a) 

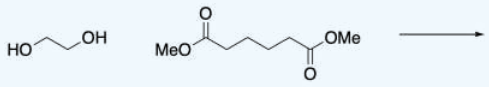
b) 

2) Provide structures of the polyesters made from the monomers as indicated.

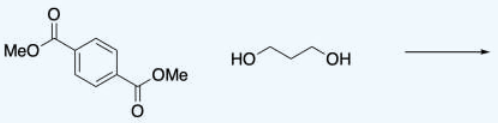
a)



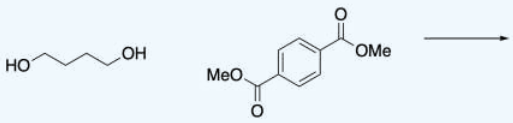
b)



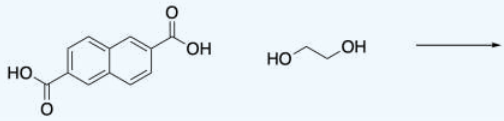
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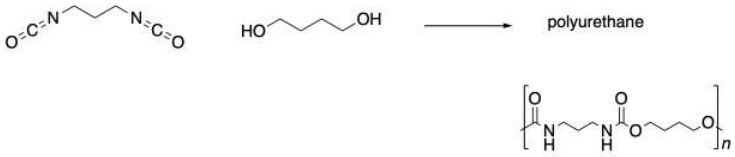
e)



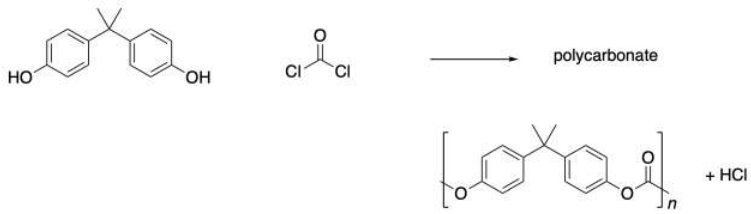
Answer

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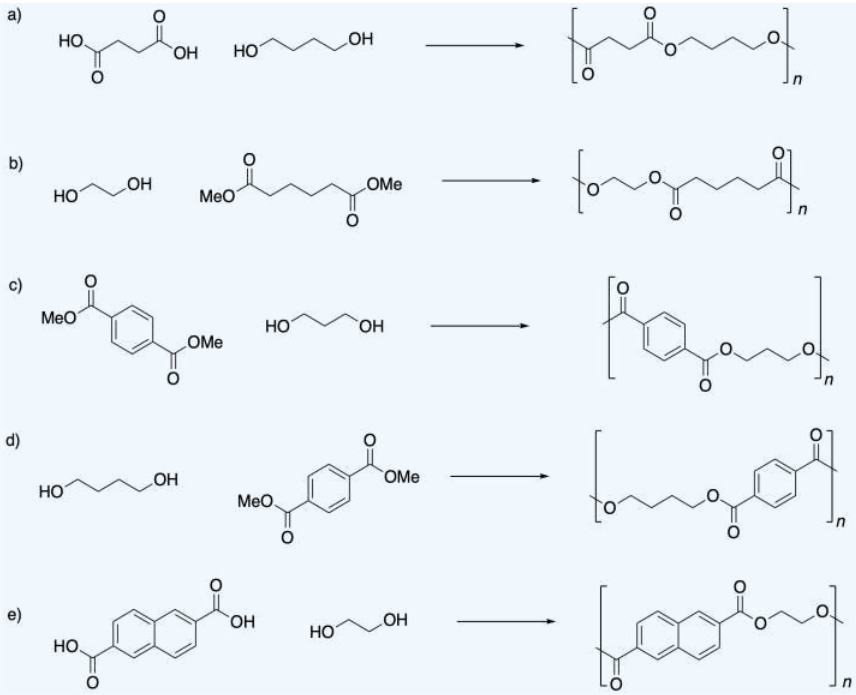
a)



b)



2)



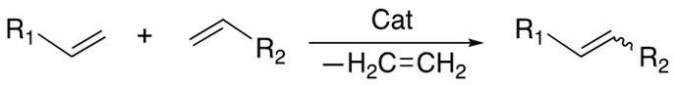
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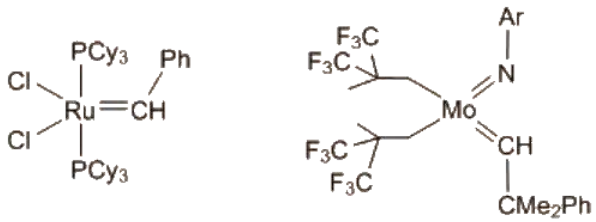
16.5: Olefin Metathesis Polymerization

Olefin Metathesis

The application of organometallic chemistry in homogenous catalysis is progressively increasing with the fast pace of discovery of new catalysts in the area. Alkene metathesis reactions are gaining wide popularity in synthesizing unsaturated olefinic compounds. Central to this catalysis is a metal carbene intermediate that reacts with olefins to give different olefinic compounds. When two different olefin substrates are used, the reaction is called the “cross metathesis” owing to the fact that the olefinic ends are exchanged. In a process called **olefin metathesis polymerization**, unsaturated olefinic polymers can be created by a metathesis reaction.



Olefin metathesis catalysts contain a metal carbon double bond with two of the most notable being are the **Grubbs Ru catalyst** and the **Schrock’s Mo catalyst**.



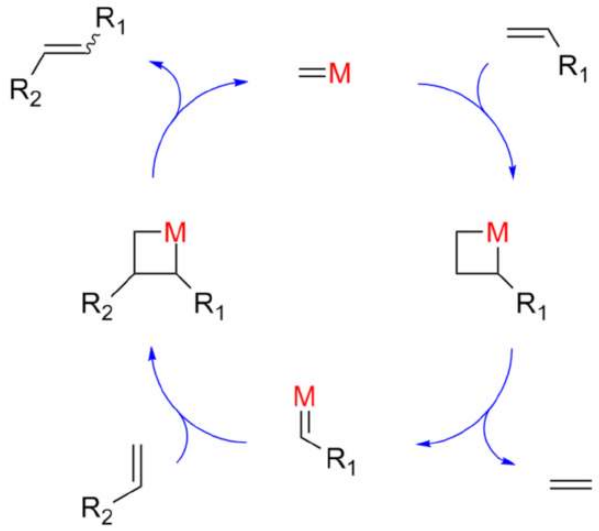
Grubbs catalyst

Schrock catalyst
(Ar = C_6H_3\{2,6-*i*-Pr\}$_2$)

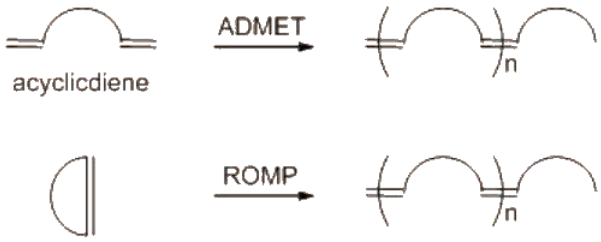
The Grubb’s and the Schrock’s Catalyst

Mechanism Cross Metathesis

An olefin metathesis catalyst is a transition metal compound that is capable of splitting the double bond of an alkene in half and putting the two pieces together with other alkenes. The key part of an olefin metathesis catalyst is a metal-carbon double bond. That is the group that is capable of switching the ends of alkenes around with different partners. The catalyst react reversibly with an alkene to produce a 4−membered metalacyclobutane intermediate called a metallacycle. The ring promptly opens to produce a different catalyst and alkene. The reaction of this new catalyst with the second alkene produces a second metallacycle intermediate. This ring opens to produce the metathesis product and yet another form of the catalyst. The ring opening and closing continues as the reaction moves forward.



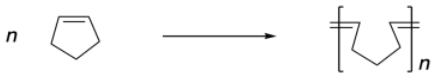
Olefin Metathesis Polymerization The variants of metathesis often used in producing polymers are: (*i*) the Acyclic Diene Metathesis (ADMET) and (*ii*) the Ring Opening Metathesis Polymerization (ROMP), both of which produce long chain polymers



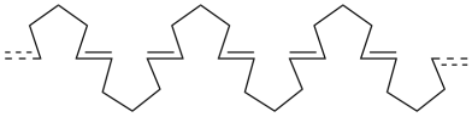
One method, called **ring-opening metathesis polymerization**, or ROMP, involves the use of a moderately strained cycloalkene, such as cyclopentene. The strain of the ring favors ring-opening, thereby driving formation of the open-chain product. The polymer that results has double bonds spaced regularly along the chain, allowing for either hydrogenation or further functionalization if desired.

Ring-opening metathesis polymerization (ROMP) takes a cyclic alkene, splits open its double bond, and knitting it together with other cyclic alkenes to produce a long polymer chain with regularly spaced double bonds. The ring-strain of the cycloalkenes favors the open-chain product and drives the polymerization reaction forward.

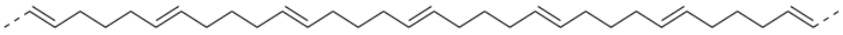
During a ROMP, a cyclopentene ring is opened up at the double bond and reaches out to join with other cyclopentene rings on either side of it.



The product polymer of a ROMP using cyclopentene rings would look something like this:

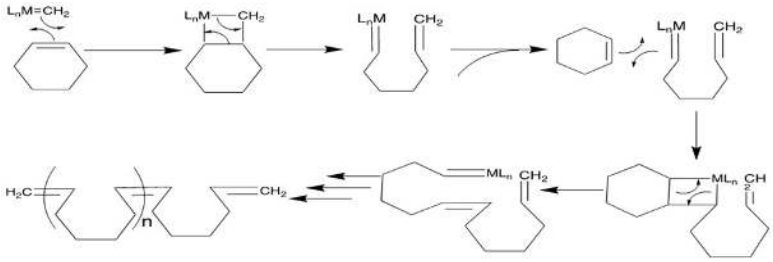


Which can draw it in an usual zig-zag conformation.

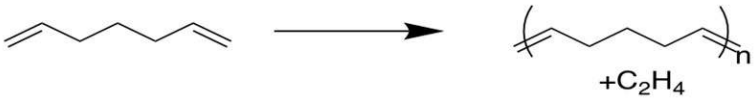


Mechanism

The mechanism starts with a cycloalkene and a metathesis catalyst reacting to form a four-member metallacycle. Opening of the metallacycle forms a new alkene and catalyst both of which are part of the same intermediate molecule. The catalyst end of the intermediate molecule can then react with a different cycloalkene to form a new metallacycle. This process is repeated causing the polymer chain to from.



The second method is called **acyclic diene metathesis** (ADMET) which uses long open-chain substrates, which contain a double bond at both ends of the main chain, such as 1,6-heptadiene. A byproduct of the reaction, gaseous ethylene ($H_2C=CH_2$), escapes which drives the equilibrium forward.



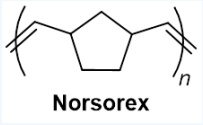
? Exercise 16.5.1

The ring opening metathesis polymerization of norborene produces a commercial polymer called Norsore which is used a sealing material. Please draw the structure of Norsore.



Norbornene

Answer



Norsorex

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16.6: Polymer Structure and Physical Properties

Polymer Crystallinity

To account for the physical differences between the different types of polymers, the nature of the aggregate macromolecular structure, or **morphology**, of each substance must be considered. Because polymer molecules are so large, they generally pack together in a non-uniform fashion, with ordered or crystalline-like regions, called **crystallites**, mixed together with disordered or amorphous domains. In some cases the entire solid may be amorphous, composed entirely of coiled and tangled macromolecular chains. Crystallinity occurs when linear polymer chains are structurally oriented in a uniform three-dimensional matrix. In the diagram on the right, crystalline domains are colored blue. Increased crystallinity is associated with an increase in rigidity, tensile strength and opacity (due to light scattering). Amorphous polymers are usually less rigid, weaker and more easily deformed. They are often transparent.

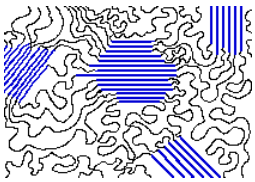


Figure 16.6.1: CSchematic diagram of crystallites (in blue) in a largely crystalline polymer.

Three factors that influence the degree of crystallinity are:

1. **Chain length:** Longer polymer chains tend to have greater van der Waals forces and increased crystallinity than do shorter chains (**Section 2-12**)
2. **Chain branching:** Polymer chains without branching can pack closely together. Lack of branching increases the crystallinity of polymers.
3. **Interchain interactions:** (Intermolecular forces and Crosslinking). Crystallinity increases as the strength of the intermolecular forces between polymer chains increases. Croslining between polymer chains tends to increase crystallinity.

The importance of the first two factors is nicely illustrated by the differences between LDPE and HDPE. As noted earlier (Section 31-2), HDPE is composed of very long unbranched hydrocarbon chains. These pack together easily in crystalline domains that alternate with amorphous segments, and the resulting material, while relatively strong and stiff, retains a degree of flexibility. In contrast, LDPE is composed of smaller and more highly branched chains which do not easily adopt crystalline structures. This material is therefore softer, weaker, less dense and more easily deformed than HDPE.

The forces between the chains in the crystallites of polyethene are the so-called **van der Waals** or **dispersion** forces, which are the same forces acting between smaller hydrocarbon molecules. Although these forces are relatively weak, they increase with the size of the molecule. Polymer chains are large enough that the van der Waals forces create a strong and stiff material.

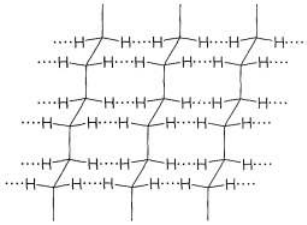


Figure 16.6.2: CRepresentation of attractive interactions between the hydrogens in a crystallite of polyethene

In other kinds of polymers, even stronger intermolecular forces can be produced by hydrogen bonding. This is especially important in the polyamides, such as the nylons, of which nylon 66 is most widely used. The increase strength of the interactions between polymer chains makes polyamides among some of the strongest polymer materials known.

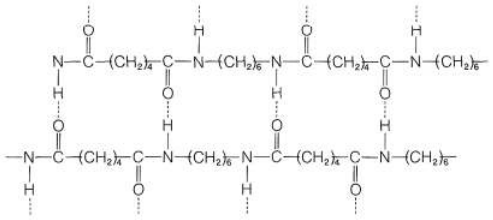


Figure 16.6.3: Possible hydrogen-bonded structure for crystallites of nylon 66, an amide-type polymer of hexanedioic acid and 1,6-hexanediamine.

Natural rubber is a completely amorphous polymer. Unfortunately, the potentially useful properties of raw latex rubber are limited by temperature dependence; however, these properties can be modified by chemical change. If the chains of rubber molecules are slightly cross-linked by sulfur atoms, a process called **vulcanization** which was discovered by Charles Goodyear in 1839, the desirable elastomeric properties of rubber are substantially improved. At 2 to 3% crosslinking a useful soft rubber, that no longer suffers stickiness and brittleness problems on heating and cooling, is obtained. At 25 to 35% crosslinking a rigid hard rubber product is formed. The following illustration shows a cross-linked section of amorphous rubber.

Glass Transition and Melt Transition Temperatures

The effect of temperature on the physical properties of polymers is very important to their practical uses. At low temperatures, polymers become hard and glasslike because the motions of the segments of the polymer chains with relation to each other are slow. The approximate temperature below which glasslike behavior is apparent is called the **glass transition temperature** and is symbolized by T_g. When a polymer containing crystallites is heated, the crystallites ultimately melt, and this temperature is usually called the **melt transition temperature** and is symbolized as T_m. As the amount of crystallinity in a polymer increases, so does T_m.

T_g often depends on the history of the sample, particularly previous heat treatment, mechanical manipulation and annealing. It is sometimes interpreted as the temperature above which significant portions of polymer chains are able to slide past each other in response to an applied force. The introduction of relatively large and stiff substituents (such as benzene rings) will interfere with this chain movement, thus increasing T_g (note polystyrene below). The introduction of small molecular compounds called **plasticizers** (discussed later in this section) into the polymer matrix increases the interchain spacing, allowing chain movement at lower temperatures. with a resulting decrease in T_g. T_m and T_g values for some common addition polymers are listed below.

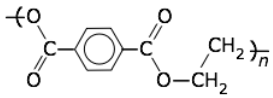
Polymer	LDPE	HDPE	PP	PVC	PS	PAN	PTFE	PMMA	Rubber
T_m (ºC)	110	130	175	180	175	>200	330	180	30
T_g (ºC)	–110	–100	–10	80	90	95	–110	105	–70

Polymer Categories

Thermoplastics

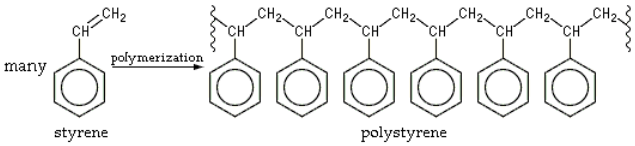
Most of the polymers described in this chapter are classified as **thermoplastic**s. Plastics that soften when heated and become firm again when cooled. This is the more popular type of plastic because the heating and cooling may be repeated and the thermoplastic may be reformed. These polymers tend to have high Tg so they are hard solids at room temperature, however, above Tg they they become malleable and may be shaped, pressed into molds, spun, or cast from melts.

Polyethylene (poly(ethylene terephthalate) or PET is the most common thermoplastic . In 2017, PET made up 34% of the total plastics market with over 100 million tones of polyethylene resins being produced. PET is partially crystalline and is used to create clear plastic bottles such as 2-liter beverage bottles, milk jugs, detergent bottles, and water bottles.



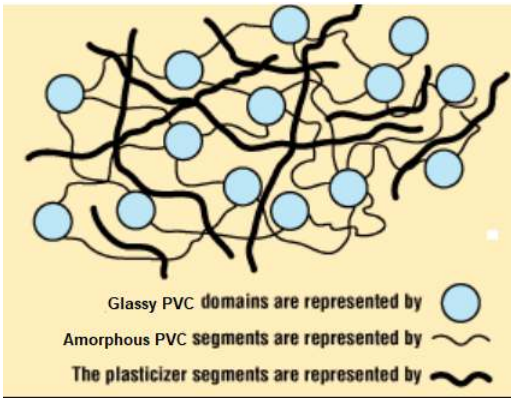
Polystyrene is also a common thermoplastic. The polymer is making it a solid but rather rather brittle at room temperature. Polystyrene is used to make hard clear plastic cups, foam cups, eating utensils, deli food containers, toy model kits, some packing

popcorn.

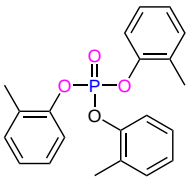


Plasticizers

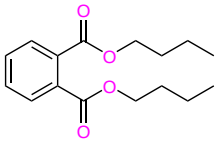
Plasticizers or **dispersants** are additives that increase the plasticity or decrease the viscosity of a material. These substances are compounded into certain types of plastics to render them more flexible by lowering the glass transition temperature. They accomplish this by taking up space between the polymer chains and acting as lubricants to enable the chains to more readily slip over each other. Many (but not all) are small enough to be diffusible and a potential source of health problems. Substantial concerns have been expressed over the safety of some plasticizers, especially because some low molecular weight ortho-phthalates have been classified as potential endocrine disruptors with some developmental toxicity reported.



Polyvinyl chloride (PVC) polymers are one of the most widely-plasticized types. PVC is usually is not very crystalline and is relatively brittle and glassy. The properties of polyvinyl chloride can be improved by blending it with substances of low volatility which tend to break down its glasslike structure. Common plasticizers used with PVC are tris-(2-methylphenyl) phosphate (tricresyl phosphate) and dibutyl benzene-1,2-dicarboxylate (dibutyl phthalate). Plasticized polyvinyl chloride is reasonably flexible and is widely used for flexible vinyl materials such as garden hoses, waterbeds, cheap shower curtains, raincoats and upholstery. The pungent oder associated with these products are a testament to the ability of plasticizers to migrate into the environment.



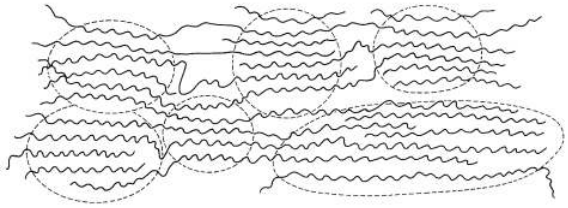
tris-(2-Methylphenyl) phosphate



Dibutyl phthalate

Fibers

Fibers are drawn into thin threads by forcing the melted or dissolved polymer through a spinneret to generate filaments that can be woven into fabrics. Part of this process, called **cold-drawing**, the polymer material is subjected to strong stress in one direction causing the material to elongate and the crystallites to be drawn together and oriented along the direction of the applied stress. Having the crystallites in a polymer oriented with respect to one another gives the polymer a much higher tensile strength than an unoriented polymer. Polymers such as nylon, which has strong intermolecular forces, has the crystallinity required to be drawn in oriented fibers.



Schematic representation of an oriented crystalline polymer produced by drawing the polymer in the horizontal direction. The crystalline regions are enclosed with dashed lines.

Elastomers

Elastomers usually are amorphous polymers which have the ability to be stretched. The key to this elastic behavior is polymer chains with weak forces between the chains and a sufficiently irregular structure to be unstable in the crystalline state. A useful elastomer needs to have some kind of cross-linking. The important difference between an elastomer and a crystalline polymer is the size of the amorphous regions. When tension is applied and the material elongates, the chains in the amorphous regions straighten out and become more nearly parallel. The forces between the chains are too weak to maintain the crystalline state in the absence of tension. Thus when tension is released, contraction occurs and the original, amorphous polymer is produced. The entropy of the chains is more favorable in the relaxed state than in the stretched state.

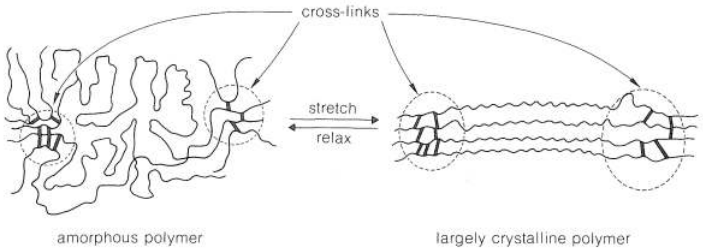
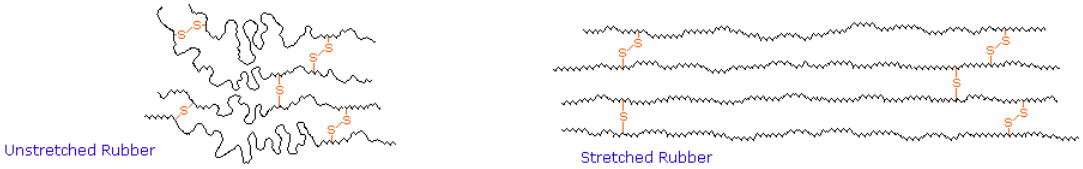
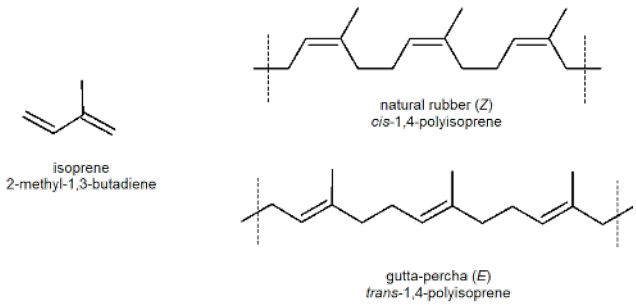


Figure 16.6.4: Schematic representation of an elastomer in relaxed and stretched configurations.

A good elastomer should not undergo plastic flow in either the stretched or relaxed state, and when stretched should have a "memory" of its relaxed state. These conditions are best achieved with natural rubber (*cis*-poly-2-methyl-1,3-butadiene, *cis*-polyisoprene) by curing (*vulcanizing*) with sulfur. Natural rubber (**Section 14-6)** is tacky and undergoes plastic flow rather readily, but when it is heated with elemental sulfur, sulfur cross-links are introduced between the chains. These cross-links reduce plastic flow and provide a reference framework for the stretched polymer to return to when it is allowed to relax. Also the double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation.



However, the gutta-percha (structure above) E-isomer of rubber adopts a uniform zig-zag conformation, which produces greater crystallinity making it not an elastomer.



Thermosets

Thermosets are plastics that soften when heated and can be molded, but harden permanently. In a thermoset, crosslinks connect the different chains in the material, forming bridges that span from chain to chain to chain, essentially uniting the material into one big molecule. If it is one big molecule, the chains can never move completely independently of each other, and the material cannot form a new shape.

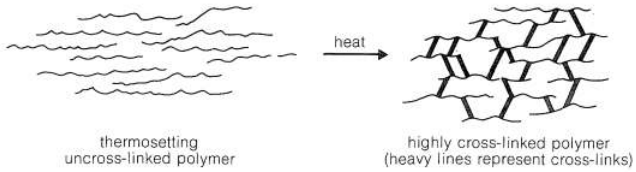
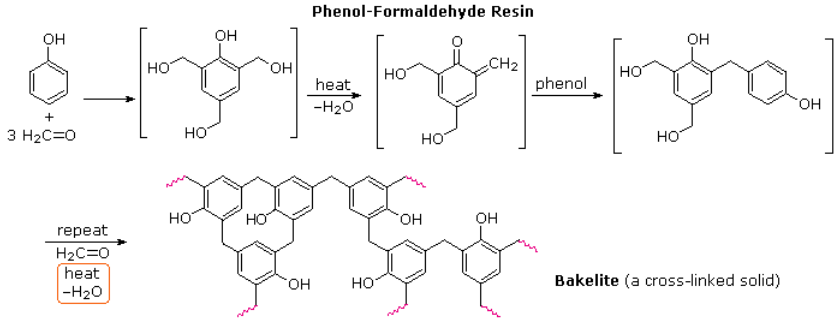


Figure 16.6.4: Schematic representation of the conversion of an uncross-linked thermosetting polymer to a highly cross-linked polymer. The cross-links are shown in a two-dimensional network, but in practice three-dimensional networks are formed.

One of the oldest known thermosetting synthetic polymers, **Bakelite**, is made by condensation of phenol with formaldehyde. During the thermoset process water is lost and many crosslinks are formed. produce (4-hydroxyphenyl)methanol. **Bakelite** was patented on December 7, 1909 and was revolutionary for its electrical nonconductivity and heat-resistant properties used in electrical insulators, radio and telephone casings and such diverse products as kitchenware, jewelry, pipe stems, and children's toys.

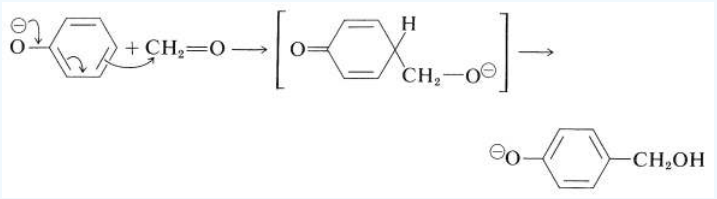


? Exercise 16.6.1

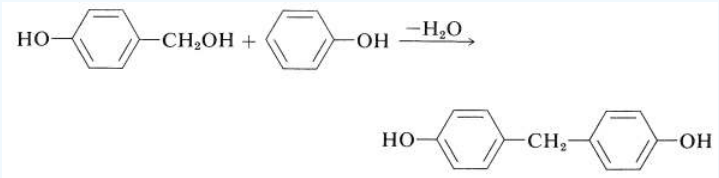
Propose a mechanism for the base-catalyzed polymerization of phenol and formaldehyde to form Bakelite.

Answer

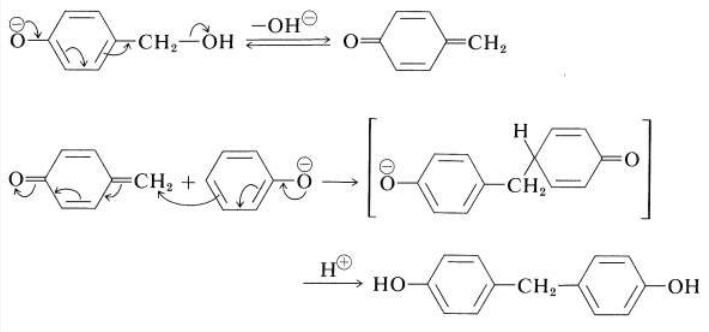
One of the oldest known thermosetting synthetic polymers is made by condensation of phenols with aldehydes using basic catalysts. The resins that are formed are known as **Bakelites**. The initial stage is the base-induced reaction of benzenol and methanal to give a (4-hydroxyphenyl)methanol, and this reaction closely resembles an aldol addition and can take place at either the 2- or the 4-position of the benzene ring:



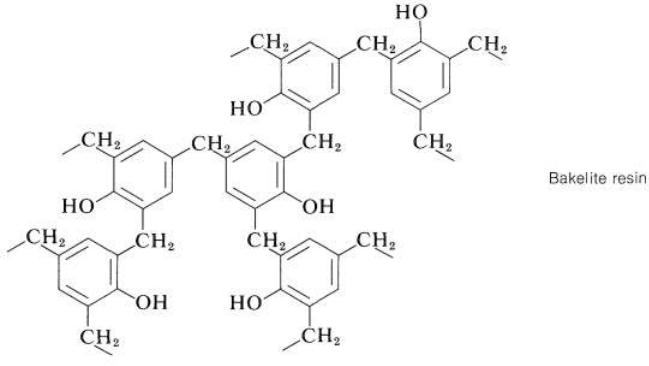
The next step in the condensation is formation of a bis(hydroxyphenyl)methane derivative, which for convenience is here taken to be the 4,4'-isomer:



This reaction is probably a Michael type of addition to a base-induced dehydration product of the (4-hydroxyphenyl)methanol:



Continuation of these reactions at the 2-, 4-, and 6-positions of the benzenol leads to the cross-linked three-dimensional Bakelite resin:

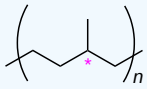


Exercise 16.6.2

Would you expect the catalytic hydrogenation of gutta-percha to produce a product that is syndiotactic, atactic, or isotactic?

Answer

Atactic. The methyl groups in gutta-percha lack stereochemistry because they are attached to double bond. Catalytic hydrogenation does not provide stereochemical control so H2 could attack from either side of the double bond to produce a chiral center involving the methyl group which is R or S.



Atactic

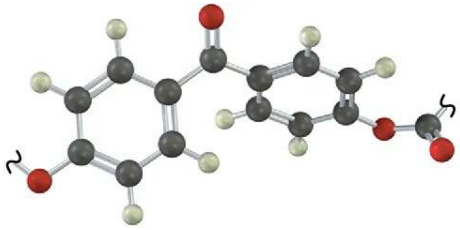
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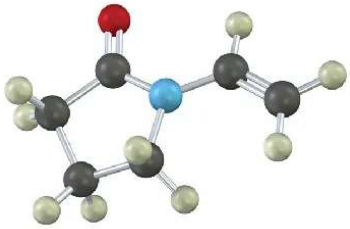
16.7: Additional Problems

Visualizing Chemistry

PROBLEM 31.13 Identify the structural class to which the following polymer belongs, and show the structure of the monomer units used to make it:



PROBLEM 31.14



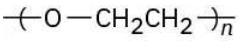
(a)



(b)

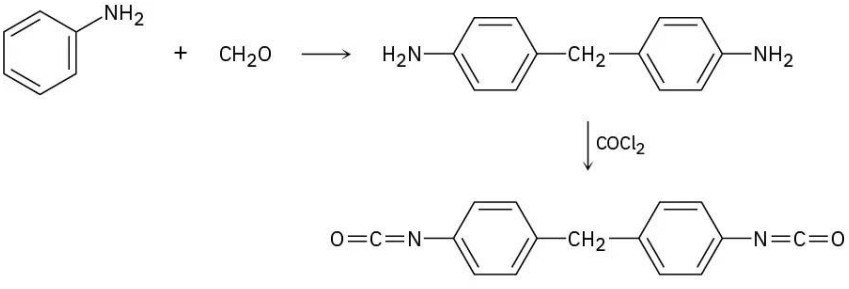
Mechanism Problems

PROBLEM 31.15 Poly(ethylene glycol), or Carbowax, is made by anionic polymerization of ethylene oxide using NaOH as catalyst. Propose a mechanism.



Poly(ethylene glycol)

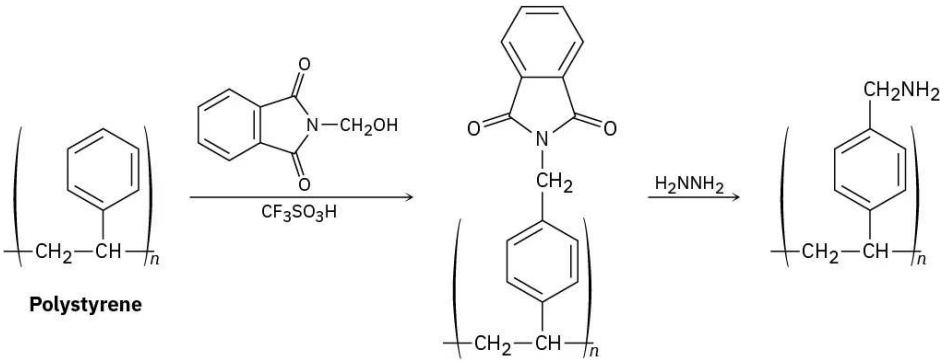
PROBLEM 31.16 The polyurethane foam used for home insulation uses methanediphenyldiisocyanate (MDI) as monomer. The MDI is prepared by acid-catalyzed reaction of aniline with formaldehyde, followed by treatment with phosgene, $COCl_2$. Propose mechanisms for both steps.



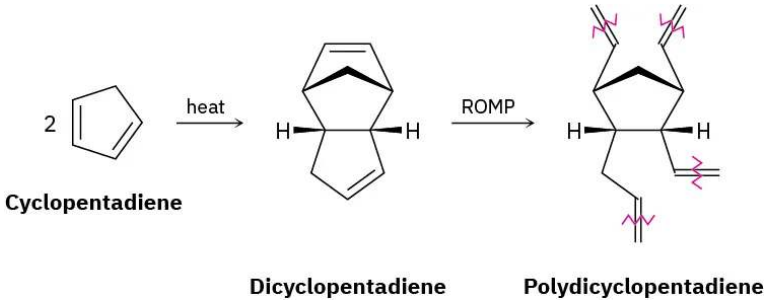
MDI

PROBLEM 31.17 Write the structure of a representative segment of polyurethane prepared by reaction of ethylene glycol with MDI (Problem 31.16).

PROBLEM 31.18 The polymeric resin used for Merrifield solid-phase peptide synthesis (Section 26.8) is prepared by treating polystyrene with *N*-(hydroxymethyl)phthalimide and trifluoromethanesulfonic acid, followed by reaction with hydrazine. Propose a mechanism for both steps.



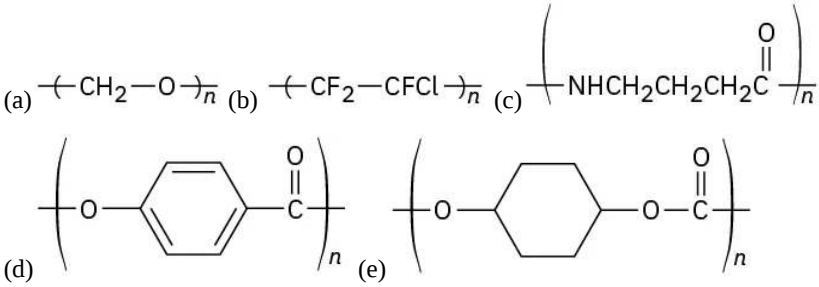
PROBLEM 31.19 Polydicyclopentadiene (PDCPD), marketed as Telene or Metton, is a highly cross-linked thermosetting resin used for molding such impact-resistant parts as cabs for large trucks and earth-moving equipment. PDCPD is prepared by ring-opening metathesis polymerization of dicyclopentadiene, which is itself prepared from 1,3-cyclopentadiene. The polymerization occurs by initial metathesis of the more highly strained double bond in the bicyclo[2.2.1]heptane part of the molecule (Section 4.9) to give a linear polymer, followed by cross-linking of different chains in a second metathesis of the remaining cyclopentene double bond.



- (a) Show the mechanism of the formation of dicyclopentadiene from cyclopentadiene.
- (b) Draw the structure of a representative sample of the initially formed linear polymer containing three monomer units.
- (c) Draw the structure of a representative sample of PDCPD that shows how cross-linking of the linear chains takes place.

General Problems

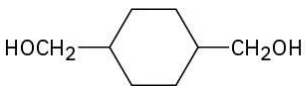
PROBLEM 31.20



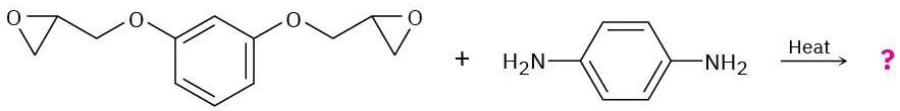
PROBLEM 31.21 Draw a three-dimensional representation of segments of the following polymers:

- (a) Syndiotactic polyacrylonitrile
- (b) Atactic poly(methyl methacrylate)
- (c) Isotactic poly(vinyl chloride)

PROBLEM 31.22 Draw the structure of Kodel, a polyester prepared by heating dimethyl 1,4-benzenedicarboxylate with 1,4-bis(hydroxymethyl)cyclohexane.



PROBLEM 31.23 Show the structure of the polymer that results from heating the following diepoxide and diamine:



PROBLEM 31.24 Nomex, a polyamide used in such applications as fire-retardant clothing, is prepared by reaction of 1,3-benzenediamine with 1,3-benzenedicarbonyl chloride. Show the structure of Nomex.

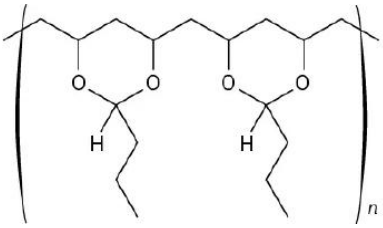
PROBLEM 31.25 Nylon 10,10 is an extremely tough, strong polymer used to make reinforcing rods for concrete. Draw a segment of nylon 10,10, and show its monomer units.

PROBLEM 31.26 1,3-Cyclopentadiene undergoes thermal polymerization to yield a polymer that has no double bonds in the chain. Upon strong heating, the polymer breaks down to regenerate cyclopentadiene. Propose a structure for the polymer.

PROBLEM 31.27 When styrene, C_6H_5CH—Math input error$_2$, is copolymerized in the presence of a few percent *p*-divinylbenzene, a hard, insoluble, cross-linked polymer is obtained. Show how this cross-linking of polystyrene chains occurs.

PROBLEM 31.28 Nitroethylene, H_2C=Math input error$_2$, is a sensitive compound that must be prepared with great care. Attempted purification of nitroethylene by distillation often results in low recovery of product and a white coating on the inner walls of the distillation apparatus. Explain.

PROBLEM 31.29 Poly(vinyl butyral) is used as the plastic laminate in the preparation of automobile windshield safety glass. How would you synthesize this polymer?



Poly(vinyl butyral)

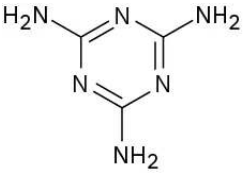
PROBLEM 31.30 What is the structure of the polymer produced by anionic polymerization of *β*-propiolactone using NaOH as catalyst?



***β*-Propiolactone**

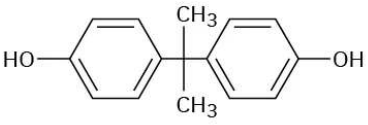
PROBLEM 31.31 Glyptal is a highly cross-linked thermosetting resin produced by heating glycerol and phthalic anhydride (1,2-benzenedicarboxylic acid anhydride). Show the structure of a representative segment of glyptal.

PROBLEM 31.32 Melmac, a thermosetting resin often used to make plastic dishes, is prepared by heating melamine with formaldehyde. Look at the structure of Bakelite shown in Section 31.7, and then propose a structure for Melmac.

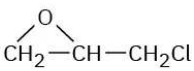


Melamine

PROBLEM 31.33 Epoxy adhesives are cross-linked resins prepared in two steps. The first step involves S_N2 reaction of the disodium salt of bisphenol A with epichlorohydrin to form a low-molecular-weight prepolymer. This prepolymer is then "cured" into a cross-linked resin by treatment with a triamine such as $H_2NCH_2CH_2NHCH_2CH_2NH_2$.



Bisphenol A

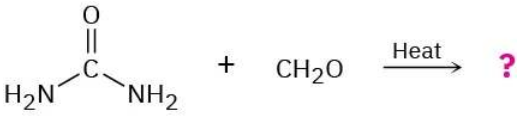


Epichlorohydrin

(a) What is the structure of the prepolymer?

(b) How does addition of the triamine to the prepolymer result in cross-linking?

PROBLEM 31.34 The smoking salons of the Hindenburg and other hydrogen-filled dirigibles of the 1930s were insulated with urea–formaldehyde polymer foams. The structure of this polymer is highly cross-linked, like that of Bakelite (Section 31.7). Propose a structure.



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16.S: Synthetic Polymers (Summary)

Synthetic polymers can be classified as either chain-growth or step-growth. Chain-growth polymers are prepared by chain-reaction polymerization of vinyl monomers in the presence of a radical, an anion, or a cation initiator. Radical polymerization is sometimes used, but alkenes such as 2-methylpropene that have electron-donating substituents on the double bond polymerize easily by a cationic route through carbocation intermediates. Similarly, monomers such as methyl α-cyanoacrylate that have electron-withdrawing substituents on the double bond polymerize by an anionic, conjugate addition pathway.

Copolymerization of two monomers gives a product with properties different from those of either homopolymer. **Graft copolymers** and **block copolymers** are two examples.

Alkene polymerization can be carried out in a controlled manner using a **Ziegler–Natta catalyst**. Ziegler–Natta polymerization minimizes the amount of chain branching in the polymer and leads to stereoregular chains—either **isotactic** (substituents on the same side of the chain) or **syndiotactic** (substituents on alternate sides of the chain), rather than **atactic** (substituents randomly disposed).

Step-growth polymers, the second major class of polymers, are prepared by reactions between difunctional molecules, with individual bonds in the polymer formed independently of one another. **Polycarbonates** are formed from a diester and a diol, and **polyurethanes** are formed from a diisocyanate and a diol.

The chemistry of synthetic polymers is similar to the chemistry of small molecules with the same functional groups, but the physical properties of polymers are greatly affected by size. Polymers can be classified by physical property into four groups: **thermoplastics**, **fibers**, **elastomers**, and **thermosetting resins**. The properties of each group can be accounted for by the structure, the degree of crystallinity, and the amount of cross-linking they contain.

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  - 16.6: Polymer Structure and Physical Properties - *CC BY-NC-SA 4.0*
  - 16.7: Additional Problems - *CC BY-NC-SA 4.0*
  - 16.S: Synthetic Polymers (Summary) - *CC BY-NC-SA 4.0*
- Back Matter - *CC BY-NC-SA 4.0*
  - Index - *CC BY-NC-SA 4.0*
    - 1.0: Index - *CC BY-NC-SA 4.0*
  - Glossary - *CC BY-NC-SA 4.0*
    - 1.0: Appendix C - Glossary - *CC BY-NC-SA 4.0*
  - Detailed Licensing - *CC BY-NC-SA 4.0*
    - 1.0: Detailed Licensing - *CC BY-NC-SA 4.0*
  - Appendix C - Nomenclature of Polyfunctional Organic Compounds - *CC BY-NC-SA 4.0*

- Appendix A - Periodic Table - *CC BY-NC-SA 4.0*
- Appendix B - Acidity Constants for Some Organic Compounds - *CC BY-NC-SA 4.0*

Appendix C - Nomenclature of Polyfunctional Organic Compounds

With more than 40 million organic compounds now known and thousands more being created daily, naming them all is a real problem. Part of the problem is due to the sheer complexity of organic structures, but part is also due to the fact that chemical names have more than one purpose. For the Chemical Abstracts Service (CAS), which catalogs and indexes the worldwide chemical literature, each compound must have only one correct name. It would be chaos if half the entries for CH_3Br were indexed under “M” for methyl bromide and half under “B” for bromomethane. Furthermore, a CAS name must be strictly systematic so that it can be assigned and interpreted by computers; common names are not allowed.

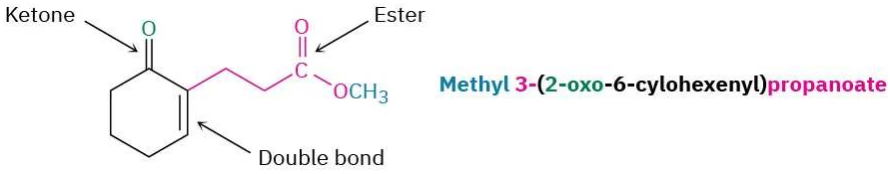
People, however, have different requirements than computers. For people—which is to say students and professional chemists in their spoken and written communications—it’s best that a chemical name be pronounceable and as easy as possible to assign and interpret. Furthermore, it’s convenient if names follow historical precedents, even if that means a particularly well-known compound might have more than one name. People can readily understand that bromomethane and methyl bromide both refer to CH_3Br.

As noted in the text, chemists overwhelmingly use the nomenclature system devised and maintained by the International Union of Pure and Applied Chemistry, or IUPAC. Rules for naming monofunctional compounds were given throughout the text as each new functional group was introduced, and a list of where these rules can be found is given in Table A1.

Table A1: Nomenclature Rules for Functional Groups

Functional group	Text section
Acid anhydrides	21-1
Acid halides	21-1
Acyl phosphates	21-1
Alcohols	17-1
Aldehydes	19-1
Alkanes	3-4
Alkenes	7-3
Alkyl halides	10-1
Alkynes	9-1
Amides	21-1
Amines	24-1
Aromatic compounds	15-1
Carboxylic acids	20-1
Cycloalkanes	4-1
Esters	21-1
Ethers	18-1
Ketones	19-1
Nitriles	20-1
Phenols	17-1
Sulfides	18-7
Thiols	18-7
Thioesters	21-1

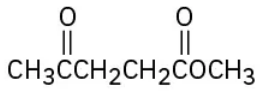
Naming a monofunctional compound is reasonably straightforward, but even experienced chemists often encounter problems when faced with naming a complex polyfunctional compound. Take the following compound, for instance. It has three functional groups, ester, ketone, and C═C, but how should it be named? As an ester with an *-oate* ending, a ketone with an *-one* ending, or an alkene with an *-ene* ending? It's actually named methyl 3-(2-oxo-6-cyclohexenyl)propanoate.

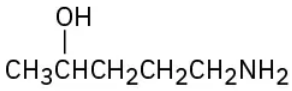


The name of a polyfunctional organic molecule has four parts—suffix, parent, prefixes, and locants—which must be identified and expressed in the proper order and format. Let's look at each of the four.

Name Part 1. The Suffix: Functional-Group Precedence

Although a polyfunctional organic molecule might contain several different functional groups, we must choose just one suffix for nomenclature purposes. It's not correct to use two suffixes. Thus, keto ester **1** must be named either as a ketone with an *-one* suffix or as an ester with an *-oate* suffix, but it can't be named as an *-onoate*. Similarly, amino alcohol **2** must be named either as an alcohol (*-ol*) or as an amine (*-amine*), but it can't be named as an *-olamine* or *-aminol*.

1. 

2. 

The only exception to the rule requiring a single suffix is when naming compounds that have double or triple bonds. Thus, the unsaturated acid $H_2C{=}$ is 3-butenoic acid, and the acetylenic alcohol $HC{\equiv}$ is 5-pentyn-1-ol.

How do we choose which suffix to use? Functional groups are divided into two classes, principal groups and subordinate groups, as shown in Table A2. Principal groups can be cited either as prefixes or as suffixes, while subordinate groups are cited only as prefixes. Within the principal groups, an order of priority has been established: the proper suffix for a given compound is determined by choosing the principal group of highest priority. For example, Table A2 indicates that keto ester **1** should be named as an ester rather than as a ketone because an ester functional group is higher in priority than a ketone. Similarly, amino alcohol **2** should be named as an alcohol rather than as an amine. Thus, the name for **1** is methyl 4-oxopentanoate and the name for **2** is 5-amino-2-pentanol. Further examples are shown:

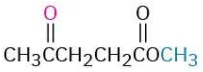
Table A2: Classification of Functional Groups [a]

Functional group	Name as suffix	Name as prefix
Principal groups		
Carboxylic acids	-oic acid	carboxy
	-carboxylic acid	
Acid anhydrides	-oic anhydride	—
	-carboxylic anhydride	
Esters	-oate	alkoxycarbonyl
	-carboxylate	
Thioesters	-thioate	alkylthiocarbonyl
	-carbothioate	
Acid halides	-oyl halide	halocarbonyl
	-carbonyl halide	
Amides	-amide	carbamoyl
	-carboxamide	
Nitriles	-nitrile	cyano
	-carbonitrile	
Aldehydes	-al	oxo
	-carbaldehyde	
Ketones	-one	oxo
Alcohols	-ol	hydroxy
Phenols	-ol	hydroxy
Thiols	-thiol	mercapto
Amines	-amine	amino
Imines	-imine	imino
Ethers	ether	alkoxy
Sulfides	sulfide	alkylthio
Disulfides	disulfide	—
Alkenes	-ene	—
Alkynes	-yne	—
Alkanes	-ane	—
Subordinate groups		
Azides	—	azido
Halides	—	halo

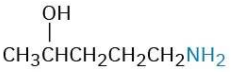
[a]Principal groups are listed in order of decreasing priority; subordinate groups have no priority order.

Functional group	Name as suffix	Name as prefix
Nitro compounds	—	nitro

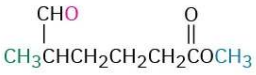
[a]Principal groups are listed in order of decreasing priority; subordinate groups have no priority order.



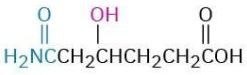
1. Methyl 4-oxopentanoate
(an ester with a ketone group)



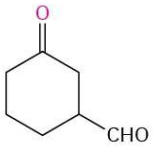
2. 5-Amino-2-pentanol
(an alcohol with an amine group)



3. Methyl 5-methyl-6-oxohexanoate
(an ester with an aldehyde group)



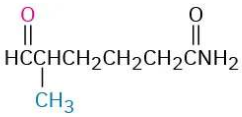
4. 5-Carbamoyl-4-hydroxypentanoic acid
(a carboxylic acid with amide and alcohol groups)



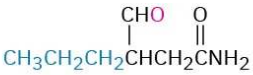
5. 3-Oxocyclohexanecarbaldehyde
(an aldehyde with a ketone group)

Name Part 2. The Parent: Selecting the Main Chain or Ring

The parent, or base, name of a polyfunctional organic compound is usually easy to identify. If the principal group of highest priority is part of an open chain, the parent name is that of the longest chain containing the largest number of principal groups. For example, compounds **6** and **7** are isomeric aldehydo amides, which must be named as amides rather than as aldehydes according to Table A2. The longest chain in compound **6** has six carbons, and the substance is named 5-methyl-6-oxohexanamide. Compound **7** also has a chain of six carbons, but the longest chain that contains both principal functional groups has only four carbons. Thus, compound **7** is named 4-oxo-3-propylbutanamide.

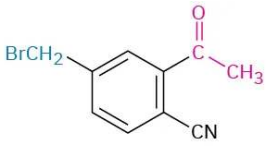


6. 5-Methyl-6-oxohexanamide



7. 4-Oxo-3-propylbutanamide

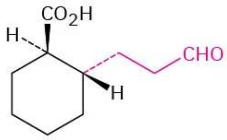
If the highest-priority principal group is attached to a ring, the parent name is that of the ring system. Compounds **8** and **9**, for instance, are isomeric keto nitriles and must both be named as nitriles according to Table A2. Substance **8** is named as a benzonitrile because the −CN functional group is a substituent on the aromatic ring, but substance **9** is named as an acetonitrile because the −CN functional group is on an open chain. Thus, their names are 2-acetyl-(4-bromomethyl)benzonitrile **(8)** and (2-acetyl-4-bromophenyl)acetonitrile **(9)**. As further examples, compounds **10** and **11** are both keto acids and must be named as acids, but the parent name in **10** is that of a ring system (cyclohexanecarboxylic acid) and the parent name in **11** is that of an open chain (propanoic acid). Thus, their names are *trans*-2-(3-oxopropyl)cyclohexanecarboxylic acid **(10)** and 3-(2-oxocyclohexyl)propanoic acid **(11)**.



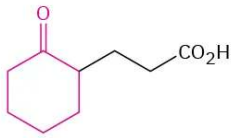
8. 2-Acetyl-(4-bromomethyl)benzonitrile



9. (2-Acetyl-4-bromophenyl)acetonitrile



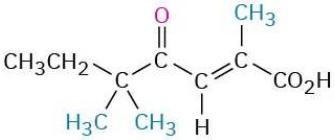
10. *trans*-2-(3-oxopropyl)cyclo-hexanecarboxylic acid



11. 3-(2-Oxocyclohexyl)propanoic acid

Name Parts 3 and 4. The Prefixes and Locants

With the parent name and the suffix established, the next step is to identify and give numbers, or *locants*, to all substituents on the parent chain or ring. The substituents include all alkyl groups and all functional groups other than the one cited in the suffix. For example, compound **12** contains three different functional groups (carboxyl, keto, and double bond). Because the carboxyl group is highest in priority and the longest chain containing the functional groups has seven carbons, compound **12** is a heptenoic acid. In addition, the parent chain has a keto (oxo) substituent and three methyl groups. Numbering from the end nearer the highest-priority functional group gives the name (*E*)-2,5,5-trimethyl-4-oxo-2-heptenoic acid. Look back at some of the other compounds we've named to see other examples of how prefixes and locants are assigned.

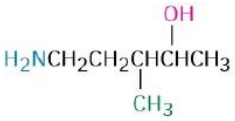


12. (*E*)-2,5,5-Trimethyl-4-oxo-2-heptenoic acid

Writing the Name

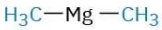
With the name parts established, the entire name can be written out. Several additional rules apply:

1. **Order of prefixes.** When the substituents have been identified, the parent chain has been numbered, and the proper multipliers such as *di-* and *tri-* have been assigned, the name is written with the substituents listed in alphabetical, rather than numerical, order. Multipliers such as *di-* and *tri-* are not used for alphabetization, but the italicized prefixes *iso-* and *sec- are* used.

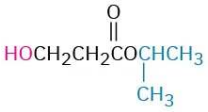


13. 5-Amino-3-methyl-2-pentanol

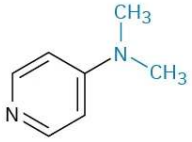
2. **Use of hyphens; single- and multiple-word names.** The general rule is to determine whether the parent is itself an element or compound. If it is, then the name is written as a single word; if it isn't, then the name is written as multiple words. Methylbenzene is written as one word, for instance, because the parent—benzene—is a compound. Diethyl ether, however, is written as two words because the parent—ether—is a class name rather than a compound name. Some further examples follow:



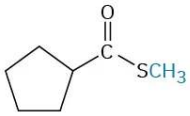
14. Dimethylmagnesium
(one word, because magnesium is an element)



15. Isopropyl 3-hydroxypropanoate
(two words, because "propanoate" is not a compound)

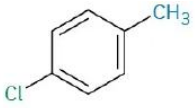


16. 4-(Dimethylamino)pyridine
(one word, because pyridine is a compound)

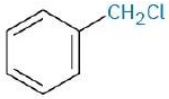


17. Methyl cyclopentanecarbothioate
(two words, because "cyclopentane-carbothioate" is not a compound)

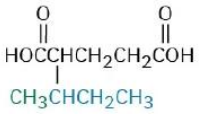
3. **Parentheses.** Parentheses are used to denote complex substituents when ambiguity would otherwise arise. For example, chloromethylbenzene has two substituents on a benzene ring, but (chloromethyl)benzene has only one complex substituent. Note that the expression in parentheses is not set off by hyphens from the rest of the name.



18. *p*-Chloromethylbenzene



19. (Chloromethyl)benzene



20. 2-(1-Methylpropyl)pentanedioic acid

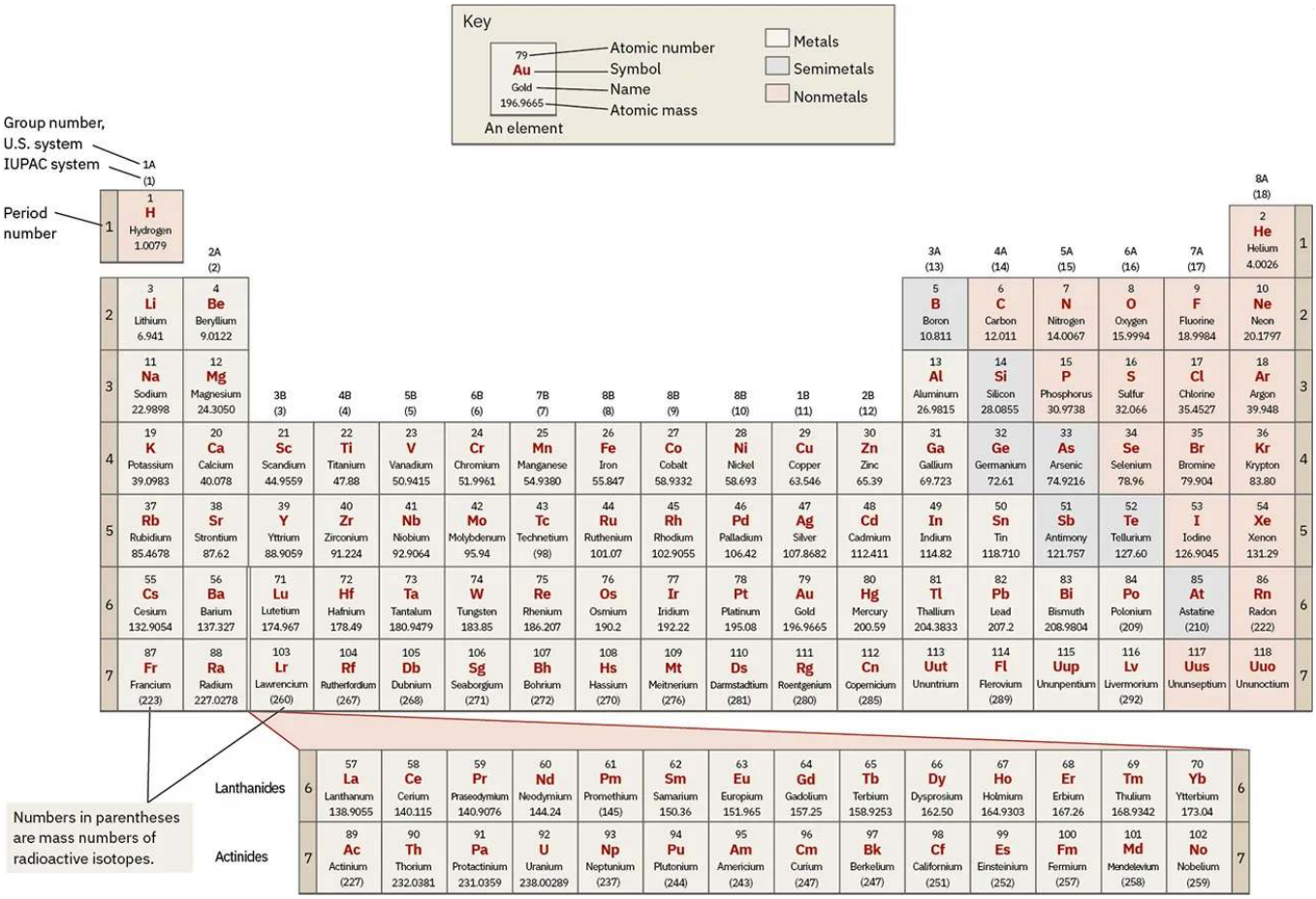
Additional Reading

Further explanations of the rules of organic nomenclature can be found online at ACD Labs (accessed May 2023) and in the following references:

1. "A Guide to IUPAC Nomenclature of Organic Compounds," CRC Press, Boca Raton, FL, 1993.
2. "Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H," International Union of Pure and Applied Chemistry, Pergamon Press, Oxford, 1979.

- **32.0: Appendix A - Nomenclature of Polyfunctional Organic Compounds** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

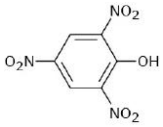
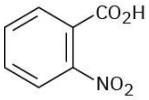
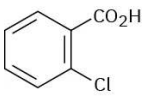
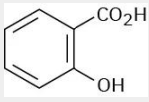
Appendix A - Periodic Table

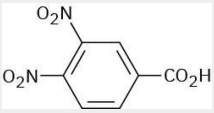
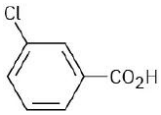
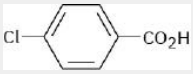
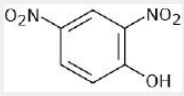
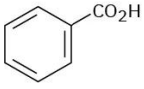
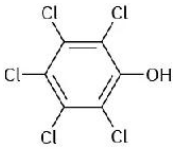


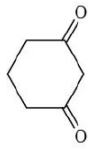
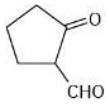
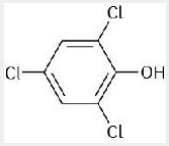
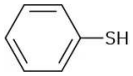
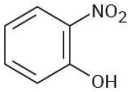
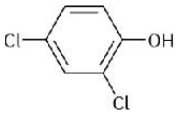
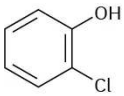
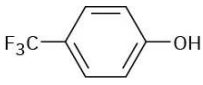
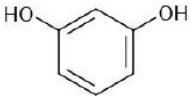
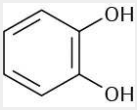
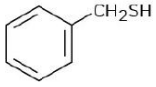
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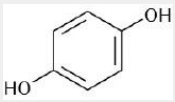
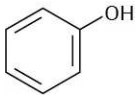
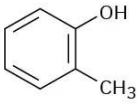
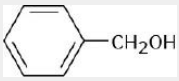
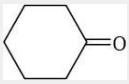
Appendix B - Acidity Constants for Some Organic Compounds

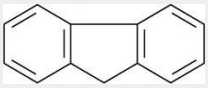
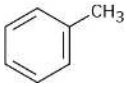
Table B1: Acidity Constants for Some Organic Compounds

Compound	pK_a
CH_3SO_3H	−1.8
$CH(NO_2)_3$	0.1
	0.3
CCl_3CO_2H	0.5
CF_3CO_2H	0.5
CBr_3CO_2H	0.7
HO2CC≡CCO2H	1.2; 2.5
HO_2CCO_2H	1.2; 3.7
$CHCl_2CO_2H$	1.3
$CH_2(NO_2)CO_2H$	1.3
$HC{\equiv}CCO_2H$ semantics	1.9
(Z) $HO_2CCH{=}CHCO_2H$	1.9; 6.3
	2.4
CH_3COCO_2H	2.4
$NCCH_2CO_2H$	2.5
CH3C≡CCO2H	2.6
CH_2FCO_2H	2.7
CH_2ClCO_2H	2.8
$HO_2CCH_2CO_2H$	2.8; 5.6
CH_2BrCO_2H	2.9
	3.0
	3.0
CH_2ICO_2H	3.2
$CHOCO_2H$	3.2

Compound	pK_a
	3.4
	3.5
$HSCH_2CO_2H$	3.5; 10.2
$CH_2(NO_2)_2$	3.6
$CH_3OCH_2CO_2H$	3.6
$CH_3COCH_2CO_2H$	3.6
$HOCH_2CO_2H$	3.7
HCO_2H	3.7
	3.8
	4.0
$CH_2BrCH_2CO_2H$	4.0
	4.1
	4.2
$H_2C{=}CHCO_2H$	4.2
$HO_2CCH_2CH_2CO_2H$	4.2; 5.7
$HO_2CCH_2CH_2CH_2CO_2H$	4.3; 5.4
	4.5
$H_2C{=}C(CH_3)CO_2H$	4.7
CH_3CO_2H	4.8
$CH_3CH_2CO_2H$	4.8
$(CH_3)_3CCO_2H$	5.0
$CH_3COCH_2NO_2$	5.1

Compound	pK_a
	5.3
$O_2NCH_2CO_2CH_3$	5.8
	5.8
	6.2
	6.6
HCO_3H	7.1
	7.2
$(CH_3)_2CHNO_2$	7.7
	7.8
CH_3CO_3H	8.2
	8.5
$CH_3CH_2NO_2$	8.5
	8.7
$CH_3COCH_2COCH_3$	9.0
	9.3; 11.1
	9.3; 12.6
	9.4

Compound	pK_a
	9.9; 11.5
	9.9
$CH_3COCH_2SOCH_3$	10.0
	10.3
CH_3NO_2	10.3
CH_3SH	10.3
$CH_3COCH_2CO_2CH_3$	10.6
CH_3COCHO	11.0
$CH_2(CN)_2$	11.2
CCl_3CH_2OH	12.2
Glucose	12.3
msub$CH_3)_2C{=}NOH$	12.4
$CH_2(CO_2CH_3)_2$	12.9
$CHCl_2CH_2OH$	12.9
$CH_2(OH)_2$	13.3
$HOCH_2CH(OH)CH_2OH$	14.1
CH_2ClCH_2OH	14.3
	15.0
	15.4
CH_3OH	15.5
$H_2C{=}CHCH_2OH$	15.5
CH_3CH_2OH	16.0
$CH_3CH_2CH_2OH$	16.1
CH_3COCH_2Br	16.1
	16.7
CH_3CHO	17

Compound	pK_a
$(CH_3)_2CHCHO$	17
$(CH_3)_2CHOH$	17.1
$(CH_3)_3COH$	18.0
CH_3COCH_3	19.3
	23
$CH_3CO_2CH_2CH_3$	25
$HC{\equiv}CH$ semantics	25
CH_3CN	25
$CH_3SO_2CH_3$	28
$(C_6H_5)_3CH$	32
$(C_6H_5)_2CH_2$	34
CH_3SOCH_3	35
NH_3	36
$CH_3CH_2NH_2$	36
$(CH_3CH_2)_2NH$	40
	41
	43
$H_2C{=}CH_2$	44
CH_4	~60

An acidity list covering more than 5000 organic compounds has been published: E.P. Serjeant and B. Dempsey (eds.), "Ionization Constants of Organic Acids in Aqueous Solution," IUPAC Chemical Data Series No. 23, Pergamon Press, Oxford, 1979.

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