CHEMISTRY II



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Chemistry II

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CHAPTER OVERVIEW

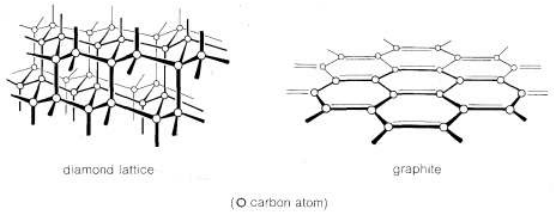
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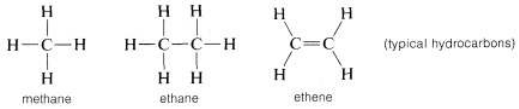
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1.1: Why Is Organic Chemistry Special?

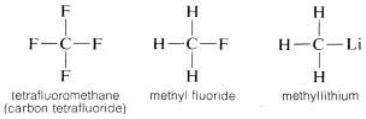
Let us consider some of the factors that make so much of chemistry center on a single element, carbon. One very important feature is that carbon-carbon bonds are strong, so long chains or rings of carbon atoms bonded to one another are possible. Diamond and graphite are two familiar examples, the diamond lattice being a three-dimensional network of carbon atoms, whereas graphite actually more closely resembles a planar network. The lubricating properties of graphite actually are related to its structure, which permits the planes to slide one past the other.



But carbon is not unique in forming bonds to itself because other elements such as boron, silicon, and phosphorus form strong bonds *in the elementary state*. The uniqueness of carbon stems more from the fact that it forms strong carbon-carbon bonds that also are strong when in combination with other elements. For example, the combination of hydrogen with carbon affords a remarkable variety of carbon hydrides, or **hydrocarbons** as they usually are called. In contrast, none of the other second-row elements except boron gives a very extensive system of stable hydrides, and most of the boron hydrides are much more reactive than hydrocarbons, especially to water and air.

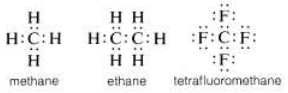


Carbon forms bonds not only with itself and with hydrogen but also with many other elements, including strongly electron-attracting elements such as fluorine and strongly electropositive metals such as lithium:



Why is carbon so versatile in its ability to bond to very different kinds of elements? The special properties of carbon can be attributed to its being a relatively small atom with four valence electrons. To form simple saltlike compounds such as sodium chloride, $Na^{\oplus}Cl^{\ominus}$, carbon would have to either lose the four valence electrons to an element such as fluorine and be converted to a quadripositive ion, $C^{4\oplus}$, or acquire four electrons from an element such as lithium and form a quadrinegative ion, $C^{4\ominus}$. Gain of four electrons would be energetically very unfavorable because of mutual repulsion between the electrons.

Customarily, carbon completes its valence-shell octet by *sharing* electrons with other atoms. In compounds with shared electron bonds (or covalent bonds) such as methane, ethane, or tetrafluoromethane, each of the bonded atoms including carbon has its valence shell filled, as shown in the following electron-pair or Lewis[6] structures:



In this way, repulsions between electrons associated with completion of the valence shell of carbon are compensated by the electron-attracting powers of the positively charged nuclei of the atoms to which the carbon is bonded.

However, the electrons of a covalent bond are not necessarily shared equally by the bonded atoms, especially when the affinities of the atoms for electrons are very different. Thus, carbon-fluorine and carbon-lithium bonds, although they are not ionic, are polarized such that the electrons are associated more with the atom of higher electron affinity. This is usually the atom with the higher effective nuclear charge.

$$\overset{\delta\oplus}{C}\ :\overset{\delta\ominus}{F} \qquad \overset{\delta\ominus}{C}:\ \overset{\delta\oplus}{Li} \qquad (\delta\oplus,\ \delta\ominus \text{ denote partial ionic bonds})$$

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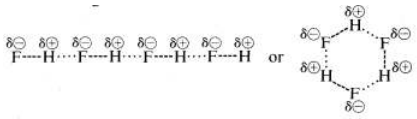
We see then a gradation from purely ionic to purely covalent bonding in different molecules, and this is manifest in their chemical and physical properties. Consider, for instance, the hydrides of the elements in the second horizontal row of the periodic table. Their melting and boiling points,[7] where known, are given below.

	LiH	BeH_2	BH_3	CH_4	NH_3	H_2O	HF
mp, °C	680	(decomposes at 125)	–	−182	−78	0	−83.7
bp, °C	–		–	−161	−33	100	+19.7

Lithium hydride can be regarded as a saltlike *ionic* compound, $\overset{\oplus}{Li}\ :\overset{\ominus}{H}$. Electrostatic attractions between oppositely charged ions in the crystal lattice are strong, thereby causing lithium hydride to be a high-melting, nonvolatile solid like sodium chloride, lithium fluoride, and so on.

Methane, CH_4, is at the other extreme. It boils at -161°, which is about 800° lower even than the melting point of lithium hydride. Because carbon and hydrogen have about the same electron-attracting power, $C-H$ bonds have little ionic character, and methane may be characterized as a *nonpolar* substance. As a result, there is relatively little electrostatic attraction between methane molecules and this allows them to "escape" more easily from each other as gaseous molecules - hence the low boiling point.

Hydrogen fluoride has a boiling point some 200° higher than that of methane. The bonding electron pair of HF is drawn more toward fluorine than to hydrogen so the bond may be formulated as $\overset{\delta\oplus}{H}$ ---- $\overset{\delta\ominus}{F}$. In liquid hydrogen fluoride, the molecules tend to aggregate through what is called **hydrogen bonding** in chains and rings arranged so the positive hydrogen on one molecule attracts a negative fluorine on the next:



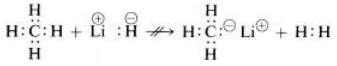
When liquid hydrogen fluoride is vaporized, the temperature must be raised sufficiently to overcome these intermolecular electrostatic attractions; hence the boiling point is high compared to liquid methane. Hydrogen fluoride is best characterized as a *polar*, but not ionic, substance. Although the $O-H$ and $N-H$ bonds of water and ammonia have somewhat less ionic character than the $H-F$ bonds of hydrogen fluoride, these substances also are relatively polar in nature and also associate through hydrogen bonding in the same way as does hydrogen fluoride.

The chemical properties of lithium hydride, methane, and hydrogen fluoride are in accord with the above formulations. Thus, when the bond to the hydrogen is broken, we might expect it to break in the sense $Li^{\oplus}\ \vdots\ H^{\ominus}$ for lithium hydride, and $\overset{\delta\oplus}{H}\ \vdots\ \ddot{F}\ :^{\delta\ominus}$ for hydrogen fluoride so that the electron pair goes with the atom of highest electron affinity. This is indeed the case as the following reaction indicates:

$$Li^{\oplus}\ \vdots\ H^{\ominus}\ +\ H\ \vdots\ \ddot{F}\ :\ \longrightarrow Li^{\oplus}:\ddot{F}:^{\ominus} + H:H$$

Methane, with its relatively nonpolar bonds, is inert to almost all reagents that could remove hydrogen as $H^{\oplus}$ or $H:^{\ominus}$ except under anything but extreme conditions. As would be expected, methyl cations $CH_3^{\oplus}$ and methyl anions $CH_3:^{\ominus}$ are very difficult to generate and are extremely reactive. For this reason, the following reactions are not observed:





From the foregoing you may anticipate that the chemistry of carbon compounds will be largely the chemistry of covalent compounds and will not at all resemble the chemistry of inorganic salts such as sodium chloride. You also may anticipate that the major differences in chemical and physical properties of organic compounds will arise from the nature of the *other* elements bonded to carbon. Thus methane is not expected to, nor does it have, the same chemistry as other one-carbon compounds such as methyllithium, CH_3Li, or methyl fluoride, CH_3F.

[6] G. N. Lewis (1876-1946), the renowned U.S. chemist, was the first to grasp the significance of the electron-pair in molecular structure. He laid the foundation for modern theory of structure and bonding in his treatise on *Valence and the Structure of Atoms and Molecules* (1923).

[7] Throughout this text all temperatures not otherwise designated should be understood to be in ^{o}C; absolute temperatures will be shown as ^{o}K.

Contributors and Attributions

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1.2: sp³ Hybrid Orbitals and the Structure of Methane

Objective

After completing this section, you should be able to describe the structure of methane in terms of the sp^3 hybridization of the central carbon atom.

Key Terms

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

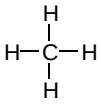
- bond angle
- hybridization
- sp^3 hybrid

Study Notes

The tetrahedral shape is a very important one in organic chemistry, as it is the basic shape of all compounds in which a carbon atom is bonded to four other atoms. Note that the tetrahedral bond angle of $\mathrm{H-C-H}$ is 109.5°.

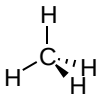
Valence Bond Theory

Valence bond theory's use of overlapping atomic orbitals to explain how chemical bonds form works well in simple diatomic molecules such as H_2. However, when molecules with more than two atoms form stable bonds, we require a more detailed model. A good example is methane (CH_4). According to valence bond theory, the structure of a covalent species can be depicted using a Lewis structure.



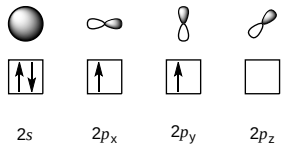
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Experimentally, it has been shown that the four carbon-hydrogen bonds in the methane molecule are identical, meaning they have the same bond energy and the same bond length. Also, VSEPR theory suggests that the geometry at the carbon atom in the methane molecule is tetrahedral **(2)**, and there exists a large body of both theoretical and experimental evidence supporting this prediction.



2

According to valence bond theory, to form a covalent bond forms when an unpaired electron in one atom overlaps with an unpaired electron in a different atom. Now, consider the the electron configuration of the four valence electrons in carbon.



There is a serious mismatch between the electron configuration of carbon ($1s^2 2s^2 2p^2$) and the predicted structure of methane. The modern structure shows that there are only 2 unpaired electrons to share with hydrogens, instead of the 4 needed to create methane. Also, the p_x and p_y orbitals are at 90° to each other. They would form perpendicular bonds instead of the tetrahedral 109.5° bond angle predicted by VSEPR and experimental data. Lastly, there are two different orbitals, 2*s* and 2*p*, which would create different types of C-H bonds. As noted earlier, experimentally, the four carbon-hydrogen bonds in the methane molecule are identical.

Hybrid Orbitals

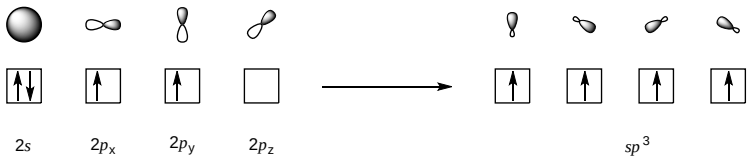
An answer to the problems posed above was offered in 1931 by Linus Pauling. He showed mathematically that an *s* orbital and three *p* orbitals on an atom can combine to form four equivalent hybrid atomic orbitals.

Important Ideals in Understanding Hybridization

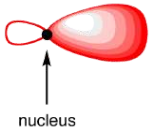
1. Hybrid orbitals do not exist in isolated atoms. They are formed only in covalently bonded atoms.
2. Hybrid orbitals have shapes and orientations that are very different from those of the atomic orbitals in isolated atoms.
3. A set of hybrid orbitals is generated by combining atomic orbitals. The number of hybrid orbitals in a set is equal to the number of atomic orbitals that were combined to produce the set.
4. All orbitals in a set of hybrid orbitals are equivalent in shape and energy.
5. The type of hybrid orbitals formed in a bonded atom create the molecular geometry as predicted by the VSEPR theory.
6. Hybrid orbitals overlap to form σ bonds.
7. Lone pair electrons are often contained in hybrid orbitals

sp^3 Hybridization in Methane

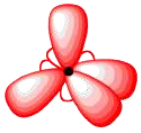
In order to explain this observation, valence bond theory relies on a concept called **orbital hybridization**. In this picture, the four valence orbitals of the carbon (one 2*s* and three 2*p* orbitals) combine mathematically (remember: orbitals are described by equations) to form four equivalent **hybrid orbitals**, which are named ***sp*^{3} orbitals** because they are formed from mixing one *s* and three *p* orbitals. In the new electron configuration, each of the four valence electrons on the carbon occupies a single sp^3 orbital creating four unpaired electrons.



The shape of an sp^3 hybridized orbital is a combination of *s* and *p* atomic orbitals.



Each sp^3-hybridized orbital bears an electron, and electrons repel each other. To minimize the repulsion between electrons, the four sp^3-hybridized orbitals arrange themselves around the carbon nucleus so that they are as far away as possible from each other, resulting in the tetrahedral arrangement predicted by VSPER. The carbon atom in methane is called an "sp^3-hybridized carbon atom." The larger lobes of the sp^3 hybrids are directed towards the four corners of a tetrahedron, meaning that the angle between any two orbitals is 109.5^o.



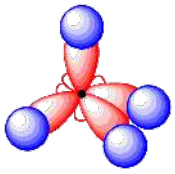
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Bonding in Methane

Each C-H bond in methane, then, can be described as an overlap between a half-filled 1*s* orbital in four hydrogen atoms and the larger lobe of one of the four half-filled sp^3 hybrid orbitals form a four equivalent sigma (σ) bond. This orbital overlap is often described using the notation: sp^3(C)-1*s*(H). The formation of sp^3 hybrid orbitals successfully explains the tetrahedral structure of methane and the equivalency of the the four C-H bonds.

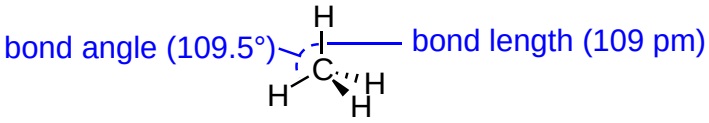
What remains is an explanation of why the sp^3 hybrid orbitals form. When the *s* and 3 *p* orbitals in carbon hybridize the resulting sp^3 hybrid orbital is unsymmetrical with one lobe larger than the other. This means the larger lobe can overlap more effectively

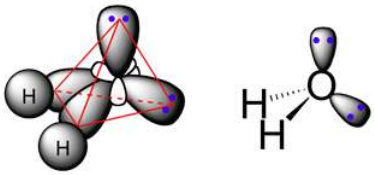
with orbitals from other bonds making them stronger. Hybridizing allows for the carbon to form stronger bonds than it would with unhybridized *s* or *p* orbitals.



6

The four carbon-hydrogen bonds in methane are equivalent and all have a bond length of 109 pm (1.09 x 10-10 m), bond strength of of 429 kJ/mol. All of the H-C-H bond angles are 109.5°.



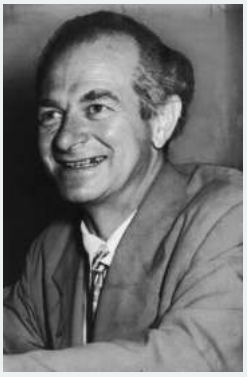


Looking Closer: Linus Pauling

Arguably the most influential chemist of the 20th century, Linus Pauling (1901–1994) is the only person to have won two individual (that is, unshared) Nobel Prizes. In the 1930s, Pauling used new mathematical theories to enunciate some fundamental principles of the chemical bond. His 1939 book *The Nature of the Chemical Bond* is one of the most significant books ever published in chemistry.

Pauling's big contribution to chemistry was valence bond theory, which combined his knowledge of quantum mechanical theory with his knowledge of basic chemical facts, like bond lengths and and bond strengths and shapes of molecules. Valence bond theory, like Lewis's bonding theory, provides a simple model that is useful for predicting and understanding the structures of molecules, especially for organic chemistry. .

By 1935, Pauling's interest turned to biological molecules, and he was awarded the 1954 Nobel Prize in Chemistry for his work on protein structure. (He was very close to discovering the double helix structure of DNA when James Watson and James Crick announced their own discovery of its structure in 1953.) He was later awarded the 1962 Nobel Peace Prize for his efforts to ban the testing of nuclear weapons.



Linus Pauling was one of the most influential chemists of the 20th century.

> In his later years, Pauling became convinced that large doses of vitamin C would prevent disease, including the common cold. Most clinical research failed to show a connection, but Pauling continued to take large doses daily. He died in 1994, having spent a lifetime establishing a scientific legacy that few will ever equal

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1.3: sp² Hybrid Orbitals and the Structure of Ethylene

Objectives

After completing this section, you should be able to

1. account for the formation of carbon-carbon double bonds using the concept of sp^2 hybridization.
2. describe a carbon-carbon double bond as consisting of one σ bond and one π bond.
3. explain the difference between a σ bond and a π bond in terms of the way in which *p* orbitals overlap.

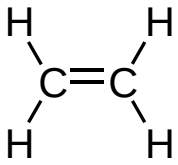
Key Terms

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

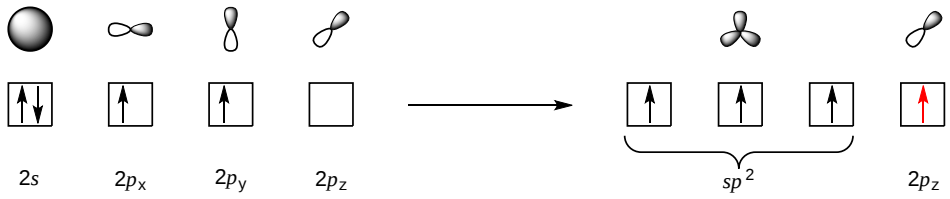
- pi (π) bond
- sp^2 hybridization (hybrid orbital)

Bonding in Ethylene

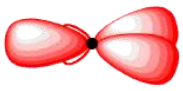
Thus far valence bond theory has been able to describe the bonding in molecules containing only single bonds. However, when molecules contain double or triple bonds the model requires more details. Ethylene (commonly knows as ethene), CH_2CH_2, is the simplest molecule which contains a carbon carbon double bond. The Lewis structure of ethylene indicates that there are one carbon-carbon double bond and four carbon-hydrogen single bonds. Experimentally, the four carbon-hydrogen bonds in the ethylene molecule have been shown to be identical. Because each carbon is surrounded by three electron groups, VSEPR theory says the molecule should have a trigonal planar geometry. Although each carbon has fulfilled its tetravalent requirement, one bond appears different. Clearly, a different type of orbital overlap is involved.



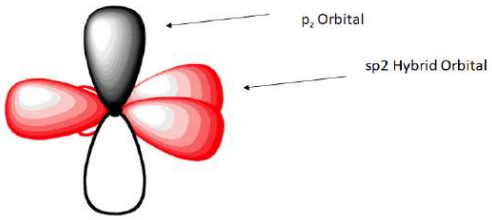
The sigma bonds formed in ethene is by the participation of a different kind of hybrid orbital. Three atomic orbitals on each carbon – the 2*s*, $2p_x$ and $2p_y$ – combine to form three sp^2 hybrids, leaving the $2p_z$ orbital unhybridized. Three of the four valence electrons on each carbon are distributed to the three sp^2 hybrid orbitals, while the remaining electron goes into the unhybridized p_z orbital. Each carbon in ethene is said to be a "sp^2-hybridized carbon." The electron configuration of the sp^2 hybridized carbon shows that there are four unpaired electrons to form bonds. However, the unpaired electrons are contained in two different types of orbitals so it is to be expected that two different types of bonds will form.



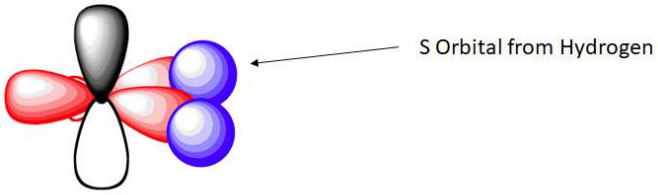
The shape of the sp^2-hybridized orbital has be mathematically shown to to be roughly the same as that of the sp^3-hybridized orbital. To minimize the repulsion between electrons, the three sp^2-hybridized orbitals are arranged with a trigonal planar geometry. Each orbital lobe is pointing to the three corners of an equilateral triangle, with angles of 120° between them. Again, geometry and hybrization can be tied together. Atoms surrounded by three electron groups can be said to have a trigonal planar geometry and sp^2 hybridization.



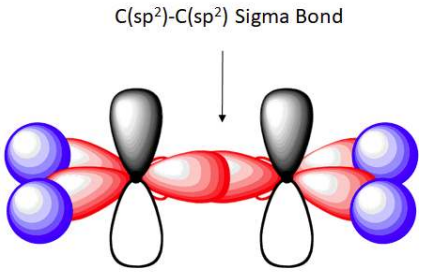
The unhybridized $2p_z$ orbital is *perpendicular* to the plane of the trigonal planar sp^2 hybrid orbtals.



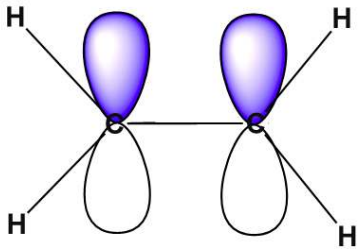
In the ethylene molecule, each carbon atom is bonded to two hydrogen atoms. Thus, overlap two sp^2-hybridized orbitals with the 1s orbitals of two hydrogen atoms for the C-H sigma bonds in ethylene (sp^2(C)-1s(H). Consequently, consistent with the observations, the four carbon-hydrogen bonds in ethylene are identical.



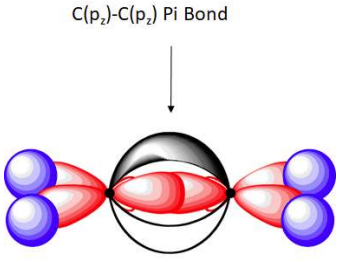
The C-C sigma bond in ethylene is formed by the overlap of an sp^2 hybrid orbital from each carbon.



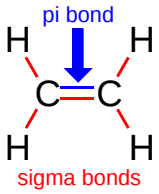
The overlap of hybrid orbitals or a hybrid orbital and a 1s orbtial from hydrogen creates the sigma bond framework of the ethylene molecule. However the unhybridized p_z orbital on each carbon remains.



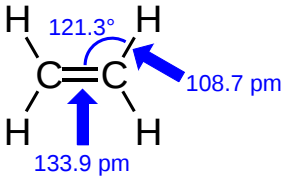
The unhybridized pz orbitals on each carbon overlap to a π bond (pi). The orbital overlap is commonly written as p_z(C)-1p_z(C). In general multiple bonds in molecular compound are formed by the overlap of unhybridized p orbitals. It should be noted that the carbon-carbon double bond in ethlene is made up of two different types of bond, a sigma and a pi.



Overall, ethylene is said to contain five sigma bonds and one pi bond. Pi bonds tend to be weaker than sigma bonds because the side-by-side overlap the p orbitals give a less effective orbital overlap when compared to the end-to-end orbital overlap of a sigma bond. This makes the pi much easier to break which is one of the most important ideas in organic chemistry reactions as we will see in Chapter 7 and subsequent chapters.

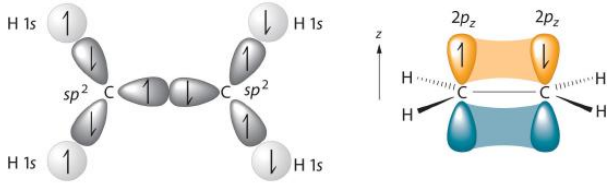


An ethylene molecule is said to be made up of five sigma bonds and one pi bond. The three sp^2 hybrid orbitals on each carbon orient to create the basic trigonal planer geometry. The H-C-C bond angle in ethylene is 121.3° which is very close to the 120° predicted by VSEPR. The four C-H sigma bonds in ethylene . The carbon-carbon double bond in ethylene is both shorter (133.9 pm) and almost twice as strong (728 kJ/mol) than the carbon- carbon single bond in ethylene (154 pm & 377 kJ/mol). Each of the four carbon-hydrogen bond in ethylene are equivalent has have a length of 108.7 pm



Rigidity in Ethene

Because they are the result of side-by-side overlap (rather then end-to-end overlap like a sigma bond), *pi bonds are not free to rotate.* If rotation about this bond were to occur, it would involve disrupting the side-by-side overlap between the two $2p_z$ orbitals that make up the pi bond. If free rotation were to occur the p-orbitals would have to go through a phase where they are 90° from each other, which would break the pi bond because there would be no overlap. Since the pi bond is essential to the structure of ethene it must not break, so there can be not free rotation about the carbon-carbon sigma bond. The presence of the pi bond thus 'locks' the six atoms of ethene into the same plane.



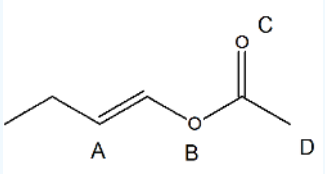
(a) C_2H_4 σ-bonded framework (b) C_2H_4 π bonding

Exercise

Exercise 1.3.1

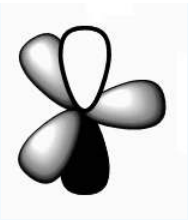
a.

Consider the following molecule:

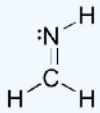


At each atom, what is the hybridization and the bond angle and the bond angle predicted by VSPER?

b. Identify the types of orbitals (white/black and grey) shown in the following diagram:

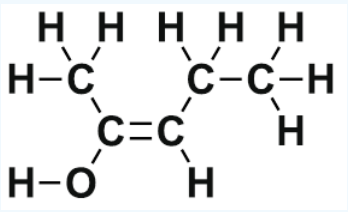


c. 1) Describe the orbitals which overlap to the carbon-nitrogen sigma bond and pie bond in the molecule below:



2) What kind of orbital holds the nitrogen lone pair?

d. For the following molecule please indicate with atoms are being held in the same plane by the carbon-carbon double bond:



Answer

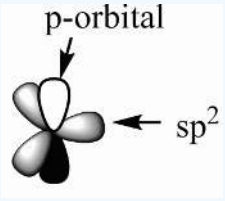
a. A - sp^2, 120°

B - sp^3, 109°

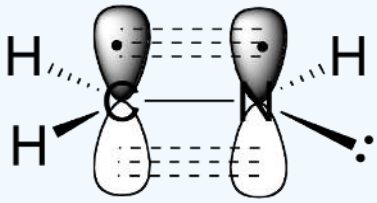
C - sp^2, 120° (with the lone pairs present)

D - sp^3, 109°

b.

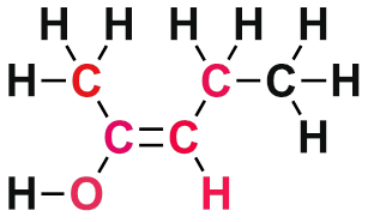


c. 1) The carbon and nitrogen atoms are both sp^2 hybridized. The carbon-nitrogen double bond is composed of a sigma bond formed from two sp^2 orbitals, and a pi bond formed from the side-by-side overlap of two unhybridized $2p$ orbitals.



b) As shown in the figure above, the nitrogen lone pair electrons occupy one of the three sp^2 hybrid orbitals.

d.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Dr. Krista Cunningham

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1.4: sp Hybrid Orbitals and the Structure of Acetylene

Objectives

After completing this section, you should be able to

1. use the concept of *sp* hybridization to account for the formation of carbon-carbon triple bonds, and describe a carbon-carbon triple bond as consisting of one σ bond and two π bonds.
2. list the approximate bond lengths associated with typical carbon-carbon single bonds, double bonds and triple bonds. [You may need to review Sections 1.7 and 1.8.]
3. list the approximate bond angles associated with sp^3-, sp^2- and *sp*-hybridized carbon atoms and predict the bond angles to be expected in given organic compounds. [If necessary, review Sections 1.6, 1.7 and 1.8.]
4. account for the differences in bond length, bond strength and bond angles found in compounds containing sp^3-, sp^2- and sp-hybridized carbon atoms, such as ethane, ethylene and acetylene.

Key Terms

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

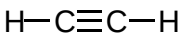
- *sp* hybrid orbital

Study Notes

The bond angles associated with sp^3-, sp^2- and *sp*-hybridized carbon atoms are approximately 109.5°, 120° and 180°, respectively.

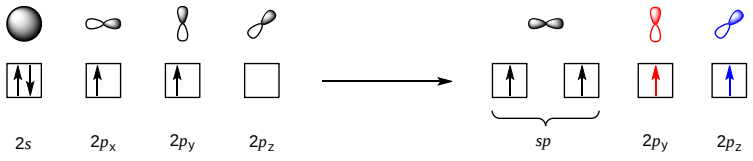
Bonding in acetylene

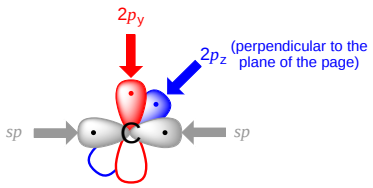
Finally, the hybrid orbital concept applies well to triple-bonded groups, such as alkynes and nitriles. Consider, for example, the structure of ethyne (another common name is acetylene), the simplest alkyne.



ethyne
(acetylene)

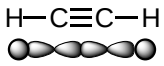
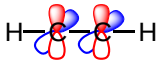
This molecule is linear: all four atoms lie in a straight line. The carbon-carbon triple bond is only 1.20Å long. In the hybrid orbital picture of acetylene, both carbons are ***sp*-hybridized**. In an *sp*-hybridized carbon, the 2*s* orbital combines with the $2p_x$ orbital to form two *sp* hybrid orbitals that are oriented at an angle of 180°with respect to each other (eg. along the x axis). The $2p_y$ and $2p_z$ orbitals remain non-hybridized, and are oriented perpendicularly along the y and z axes, respectively.



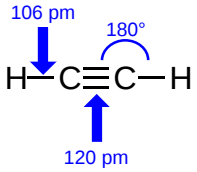


The C-C sigma bond is formed by the overlap of one *sp* orbital from each of the carbons, while the two C-H sigma bonds are formed by the overlap of the second *sp* orbital on each carbon with a 1*s* orbital on a hydrogen. Each carbon atom still has two half-filled $2p_y$ and $2p_z$ orbitals, which are perpendicular both to each other and to the line formed by the sigma bonds. These two

perpendicular pairs of *p* orbitals form two pi bonds between the carbons, resulting in a triple bond overall (one sigma bond plus two pi bonds).

	
sigma bonding in ethylene	pi bonding in ethylene

Acetylene is said to have three sigma bonds and two pi bonds. The carbon-carbon triple bond in acetylene is the shortest (120 pm) and the strongest (965 kJ/mol) of the carbon-carbon bond types. Because each carbon in acetylene has two electron groups, VSEPR predicts a linear geometry and and H-C-C bond angle of 180°.

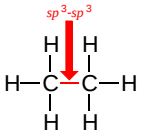
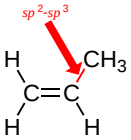
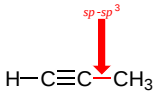


Comparison of C-C bonds Ethane, Ethylene, and Acetylene

Molecule	Bond	Bond Strength (kJ/mol)	Bond Length (pm)
Ethane, CH_3CH_3	**(sp^3) C-C (sp^3)**	**376**	**154**
Ethylene, $H_2C{=}CH_2$	**(sp^2) C=C (sp^2)**	**728**	**134**
Acetylene, HC≡CH	**(*sp*) C≡C (*sp*)**	**965**	**120**

Notice that as the bond order increases the bond length decreases and the bond strength increases.

The hybrid orbital concept nicely explains another experimental observation: single bonds adjacent to double and triple bonds are progressively shorter and stronger than 'normal' single bonds, such as the one in a simple alkane. The carbon-carbon bond in ethane (structure A below) results from the overlap of two sp^3 orbitals.

		
A	B	C

In propene (B), however, the carbon-carbon single bond is the result of overlap between an sp^2 orbital and an sp^3 orbital, while in propyne (C) the carbon-carbon single bond is the result of overlap between an sp orbital and an sp^3 orbital. These are all single bonds, but the single bond in molecule C is shorter and stronger than the one in B, which is in turn shorter and stronger than the one in A.

The explanation here is relatively straightforward. An sp orbital is composed of one *s* orbital and one *p* orbital, and thus it has 50% *s* character and 50% *p* character. sp^2 orbitals, by comparison, have 33% *s* character and 67% *p* character, while sp^3 orbitals have 25% *s* character and 75% *p* character. Because of their spherical shape, 2*s* orbitals are smaller, and hold electrons closer and 'tighter' to the nucleus, compared to 2*p* orbitals. Consequently, bonds involving sp + sp^3 overlap (as in alkyne C) are shorter and stronger than bonds involving sp^2 + sp^3 overlap (as in alkene B). Bonds involving sp^3-sp^3overlap (as in alkane A) are the longest and weakest of the group, because of the 75% '*p*' character of the hybrids.

Hybridization Summary

- A single bond is a sigma bond.
- A double bond is made up of a sigma bond and a pi bond.
- A triple bond is made up of a sigma bond and two pi bonds.

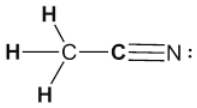
- Sigma bonds are made by the overlap of two hybrid orbitals or the overlap of a hybrid orbital and a s orbital from hydrogen.
- Pi bonds are made by the overlap of two unhybridized p orbitals.
- Lone pair electrons are usually contained in hybrid orbitals.

The hybrid orbitals used (and hence the hybridization) depends on how many electron groups are around the atom in question. An electron group can mean either a bonded atom or a lone pair. Molecular geometry is also decided by the number of electron groups so it is directly linked to hybridization.

# of Electron Groups	Hybrid Orbital Used	Example	Basic Geometry	Basic Bond Angle
2	sp		Linear	180º
3	sp^2		Trigonal Planar	120º
4	sp^3		Tetrahedral	109.5º

Exercises

1) For the molecule acetonitrile:



Acetonitrile

a) How many sigma and pi bonds does it have?

b) What orbitals overlap to form the C-H sigma bonds?

c) What orbitals overlap to form the C-C sigma bond?

d) What orbitals overlap to form the C-N sigma bond?

e) What orbitals overlap to the form the C-N pi bonds?

f) What orbital contains the lone pair electrons on nitrogen?

Solutions

1)

a) 5 sigma and 2 pi

b) An sp^3 hybrid orbital from carbon and an a s orbital from hydrogen.

c) An sp^3 hybrid orbital from one carbon and an a sp^3 orbital from the other carbon.

d) An sp hybrid orbital from carbon and an a sp orbital from nitrogen.

e) An p_y and p_z orbital from carbon and an p_y and p_z orbital from nitrogen.

f) An sp hybrid orbital.

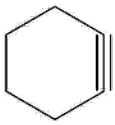
1.9: spsp Hybrid Orbitals and the Structure of Acetylene

1.9 Exercises

Questions

Q1.9.1

1-Cyclohexyne is a very strained molecule. By looking at the molecule explain why there is such a intermolecular strain using the knowledge of hybridization and bond angles.



Solutions

S1.9.1

The alkyne is a sp hybridized orbital. By looking at a sp orbital, we can see that the bond angle is 180°, but in cyclohexane the regular angles would be 109.5°. Therefore the molecule would be strained to force the 180° to be a 109°.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Dr. Krista Cunningham

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1.5: Hybridization of Nitrogen, Oxygen, Phosphorus and Sulfur

Objective

After completing this section, you should be able to apply the concept of hybridization of atoms such as N, O, P and S to explain the structures of simple species containing these atoms.

Key Terms

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

- lone pair electrons

Study Notes

Nitrogen is frequently found in organic compounds. As with carbon atoms, nitrogen atoms can be sp^3-, sp^2- or sp-hybridized.

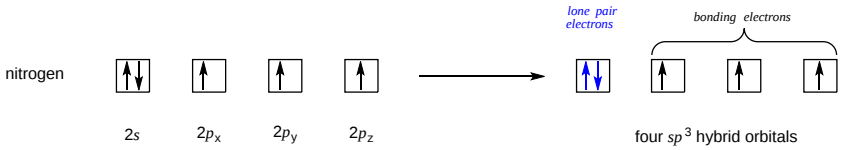
Note that, in this course, the term “lone pair” is used to describe an unshared pair of electrons.

The valence-bond concept of orbital hybridization can be extrapolated to other atoms including nitrogen, oxygen, phosphorus, and sulfur. In other compounds, covalent bonds that are formed can be described using hybrid orbitals.

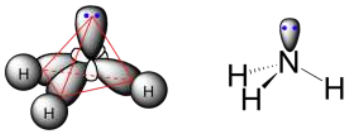
Nitrogen

Bonding in NH_3

The nitrogen in NH_3 has five valence electrons. After hybridization these five electrons are placed in the four equivalent sp^3 hybrid orbitals. The electron configuration of nitrogen now has one sp^3 hybrid orbital completely filled with two electrons and three sp^3 hybrid orbitals with one unpaired electron each. The two electrons in the filled sp^3 hybrid orbital are considered non-bonding because they are already paired. These electrons will be represented as a lone pair on the structure of NH_3. The three unpaired electrons in the hybrid orbitals are considered bonding and will overlap with the s orbitals in hydrogen to form N-H sigma bonds. Note! This bonding configuration was predicted by the Lewis structure of NH_3.

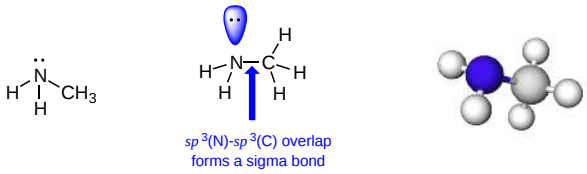


The four sp^3 hybrid orbitals of nitrogen orientate themselves to form a tetrahedral geometry. The three N-H sigma bonds of NH_3 are formed by sp^3(N)-1s(H) orbital overlap. The fourth sp^3 hybrid orbital contains the two electrons of the lone pair and is not directly involved in bonding.



Methyl amine

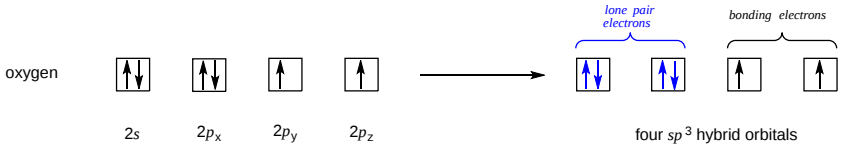
The nitrogen is sp^3 hybridized which means that it has four sp^3 hybrid orbitals. Two of the sp^3 hybridized orbitals overlap with s orbitals from hydrogens to form the two N-H sigma bonds. One of the sp^3 hybridized orbitals overlap with an sp^3 hybridized orbital from carbon to form the C-N sigma bond. The lone pair electrons on the nitrogen are contained in the last sp^3 hybridized orbital. Due to the sp^3 hybridization the nitrogen has a tetrahedral geometry. However, the H-N-H and H-N-C bonds angles are less than the typical 109.5º due to compression by the lone pair electrons.



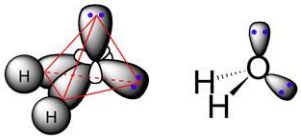
Oxygen

Bonding in H_2O

The oxygen in H_2O has six valence electrons. After hybridization these six electrons are placed in the four equivalent sp^3 hybrid orbitals. The electron configuration of oxygen now has two sp^3 hybrid orbitals completely filled with two electrons and two sp^3 hybrid orbitals with one unpaired electron each. The filled sp^3 hybrid orbitals are considered non-bonding because they are already paired. These electrons will be represented as a two sets of lone pair on the structure of H_2O . The two unpaired electrons in the hybrid orbitals are considered bonding and will overlap with the s orbitals in hydrogen to form O-H sigma bonds. Note! This bonding configuration was predicted by the Lewis structure of H_2O.

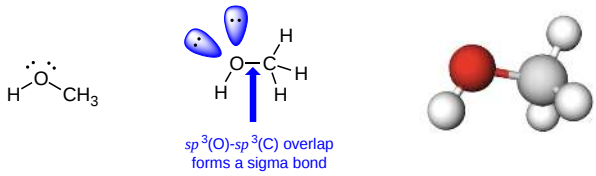


The four sp^3 hybrid orbitals of oxygen orientate themselves to form a tetrahedral geometry. The two O-H sigma bonds of H_2O are formed by sp^3(O)-1s(H) orbital overlap. The two remaining sp^3 hybrid orbitals each contain two electrons in the form of a lone pair.



Methanol

The oxygen is sp^3 hybridized which means that it has four sp^3 hybrid orbitals. One of the sp^3 hybridized orbitals overlap with s orbitals from a hydrogen to form the O-H sigma bonds. One of the sp^3 hybridized orbitals overlap with an sp^3 hybridized orbital from carbon to form the C-O sigma bond. Both the sets of lone pair electrons on the oxygen are contained in the remaining sp^3 hybridized orbital. Due to the sp^3 hybridization the oxygen has a tetrahedral geometry. However, the H-O-C bond angles are less than the typical 109.5° due to compression by the lone pair electrons.

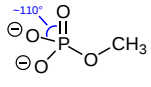


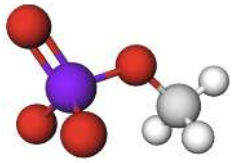
Phosphorus

Methyl phosphate

The bond pattern of phosphorus is analogous to nitrogen because they are both in period 15. However, phosphorus can have have expanded octets because it is in the n = 3 row. Typically, phosphorus forms five covalent bonds. In biological molecules, phosphorus is usually found in organophosphates. Organophosphates are made up of a phosphorus atom bonded to four oxygens, with one of the oxygens also bonded to a carbon. In methyl phosphate, the phosphorus is sp^3 hybridized and the O-P-O bond angle varies from 110° to 112°.

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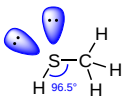


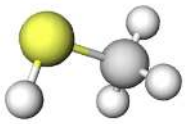
Sulfur

Methanethiol & Dimethyl Sulfide

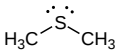
Sulfur has a bonding pattern similar to oxygen because they are both in period 16 of the periodic table. Because sulfur is positioned in the third row of the periodic table it has the ability to form an expanded octet and the ability to form more than the typical number of covalent bonds. In biological system, sulfur is typically found in molecules called thiols or sulfides. In a thiol, the sulfur atom is bonded to one hydrogen and one carbon and is analogous to an alcohol O-H bond. In a sulfide, the sulfur is bonded to two carbons. The simplest example of a thiol is methane thiol (CH_3SH) and the simplest example of a sulfide is dimethyl sulfide [$(CH_3)_3S$]. In both cases the sulfur is sp^3 hybridized, however the sulfur bond angles are much less than the typical tetrahedral 109.5^o being 96.6^o and 99.1^o respectively.

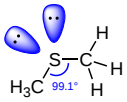


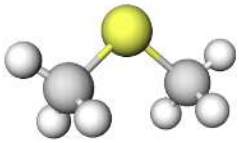




methanethiol





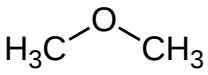


dimethyl sulfide

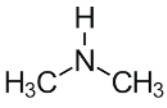
Exercises

1) Insert the missing lone pairs of electrons in the following molecules, and tell what hybridization you expect for each of the indicated atoms.

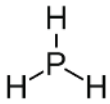
a) The oxygen is dimethyl ether:



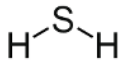
b) The nitrogen in dimethyl amine:



c) The phosphorus in phosphine:



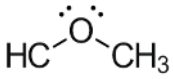
d) The sulfur in hydrogen sulfide:



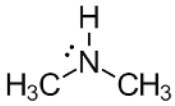
Solutions

1)

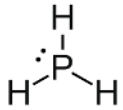
a) sp^3 hybridization



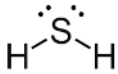
b) sp^3 hybridization



c) sp^3 hybridization



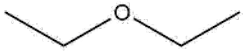
d) sp^3 hybridization



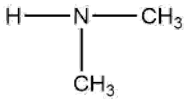
Questions

Q1.10.1

Identify geometry and lone pairs on each heteroatom of the molecules given.



Diethyl Ether



Dimethylamine

Solutions

S1.10.1

Diethyl ether would have two lone pairs of electrons and would have a bent geometry around the oxygen.

Dimethyl amine would have one lone pair and would show a pyramidal geometry around the nitrogen.

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1.6: Lone Pair Electrons and Bonding Theories

Learning Objective

- contrast valence bond theory and molecular orbital theory
- identify the orbitals occupied by lone pair electrons

Valence Bond and Molecular Orbital Theories

The table below summarizes the main points of the two complementary bonding theories. Both theories provide different, useful ways of describing molecular structure. We will use both theories and often blend them to analyze and predict chemical structure and reactivity. The bonding theories are reviewed in greater detail in the next two sections.

Comparison of Bonding Theories

Valence Bond Theory	Molecular Orbital Theory
considers bonds as localized between one pair of atoms	considers electrons delocalized throughout the entire molecule
creates bonds from overlap of atomic orbitals (*s*, *p*, *d*…) and hybrid orbitals (*sp*, sp^2, sp^3…)	combines atomic orbitals to form molecular orbitals (σ, σ*, π, π*)
forms σ or π bonds	creates bonding and antibonding interactions based on which orbitals are filled
predicts molecular shape based on the number of regions of electron density	predicts the arrangement of electrons in molecules
needs multiple structures to describe resonance	

Orbitals of Lone Pair Electrons

There are situations in which we will want to integrate molecular orbital and valence bond theories. Identifying the orbitals of lone pair electrons is one situation. Hybridized orbitals create sigma bonds and hold lone pairs. The sigma bonds create the "framework" that holds all the atoms together as a molecule or ion. Un-hybridized p orbitals create pi bonds perpendicular to this sigma framework. In the future, we will learn that some lone pair electrons on heteroatoms of rings can occupy p orbitals to create aromaticity. Stay tuned for upcoming attractions. For the first ten chapters of this text, we will only focus on non-aromatic compounds.

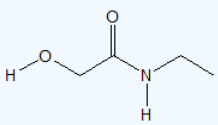
To identify the orbitals of the lone pair electrons in non-aromatic compounds, we can follow a two-step approach.

Step 1: Add any missing lone pair electrons to the heteroatoms (atoms other than carbon and hydrogen).

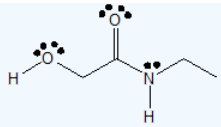
Step 2: Determine the hybridization of any atoms with lone pairs (heteroatoms). Lone pairs occupy the hybridized orbitals.

Example

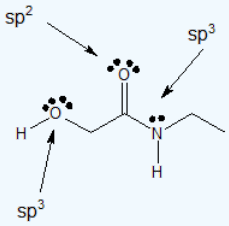
To identify the orbitals of the lone pair electrons in the compound below, we will follow the approach above.



Step 1: Add lone pairs.



Step 2: Determine the hybridization of any atom with lone pairs.



The lone pairs on each heteroatom occupy the indicated hybridized orbital.

NOTE: These guidelines only apply for non-aromatic compounds. There can be exceptions to these guidelines for some heterocyclic aromatic compounds. These exceptions are fully explained in a later chapter of this text.

Exercise

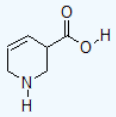
1. For the compound below:

a) add the lone pair electrons

b) label the hybridization and electron geometry for all non-hydrogen atoms

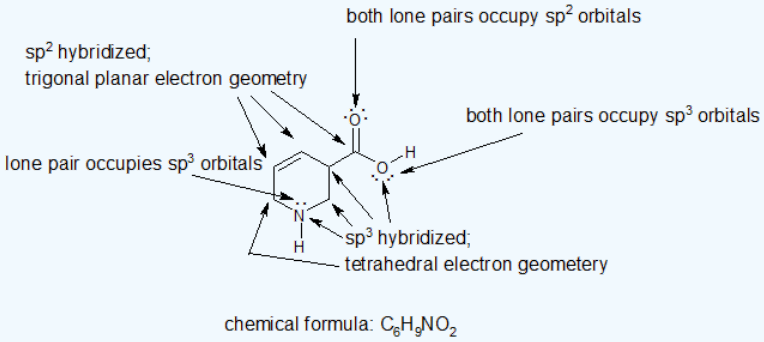
c) specify the hybridization of the orbital for each lone pair

d) What is the chemical formula of this compound?



Answer

1.



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1.7: A Review of Isomerism

Objective

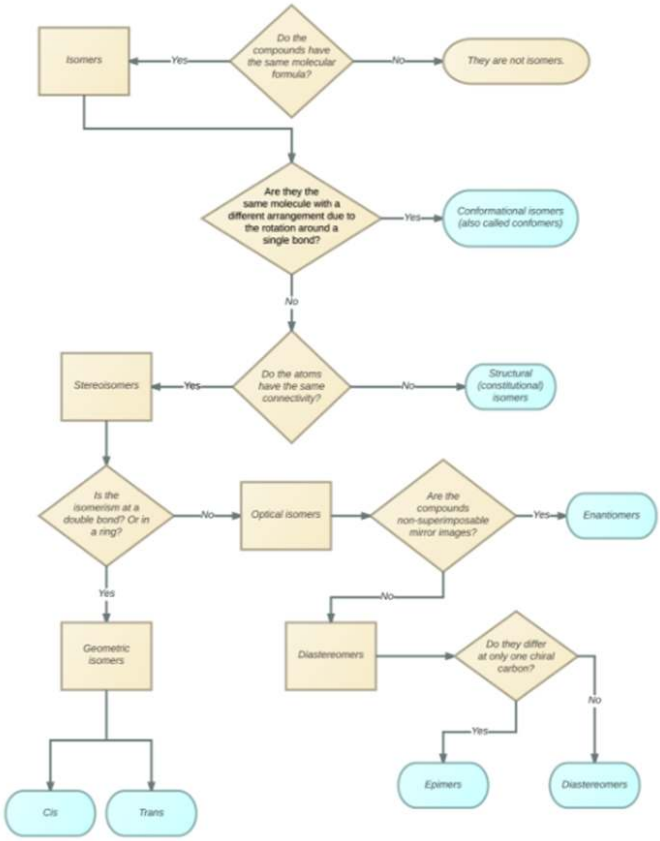
After completing this section, you should be able to

- explain the differences among constitutional (structural) isomers and stereoisomers (geometric isomers)
- identify isomers of a chemical formula

Key Terms

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

- constitutional
- (structural) isomers
- stereoisomers
- enantiomers
- diastereoisomers



Different types of isomers (Vladsinger)

Conformational Isomers

The C–C single bonds in ethane, propane, and other alkanes are formed by the overlap of an sp^3 hybrid orbital on one carbon atom with an sp^3 hybrid orbital on another carbon atom, forming a σ bond. Each sp^3 hybrid orbital is cylindrically symmetrical (all cross-sections are circles), resulting in a carbon–carbon single bond that is also cylindrically symmetrical about the C–C axis. Because rotation about the carbon–carbon single bond can occur without changing the overlap of the sp^3 hybrid orbitals, there is no significant electronic energy barrier to rotation. Consequently, many different arrangements of the atoms are possible, each

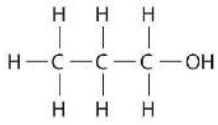
corresponding to different degrees of rotation. Differences in three-dimensional structure resulting from rotation about a σ bond are called differences in conformation, and each different arrangement is called a conformational isomer (or conformer).



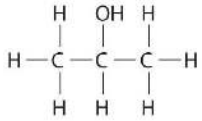
Conformational Isomers of Pentane

Structural Isomers

Unlike conformational isomers, which do not differ in connectivity, structural isomers differ in connectivity, as illustrated here for 1-propanol and 2-propanol. Although these two alcohols have the same molecular formula (C_3H_8O), the position of the –OH group differs, which leads to differences in their physical and chemical properties.

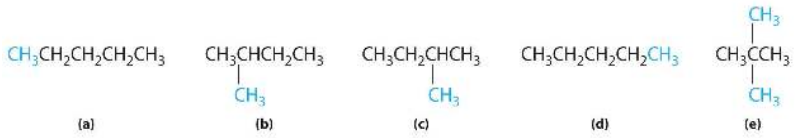


1-Propanol (*n*-propanol)



2-Propanol (isopropanol)

In the conversion of one structural isomer to another, at least one bond must be broken and reformed at a different position in the molecule. Consider, for example, the following five structures represented by the formula C_5H_{12}:



(a) (b) (c) (d) (e)

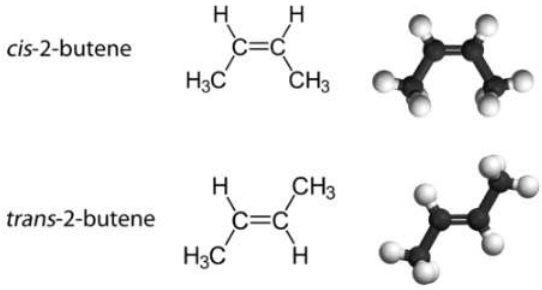
Of these structures, (a) and (d) represent the same compound, as do (b) and (c). No bonds have been broken and reformed; the molecules are simply rotated about a 180° vertical axis. Only three—n-pentane (a) and (d), 2-methylbutane (b) and (c), and 2,2-dimethylpropane (e)—are structural isomers. Because no bonds are broken in going from (a) to (d) or from (b) to (c), these alternative representations are not structural isomers. The three structural isomers—either (a) or (d), either (b) or (c), and (e)—have distinct physical and chemical properties.

Stereoisomers

Stereoisomers have the same connectivity in their atoms but a different arrangement in three-dimensional space. There are different classifications of stereoisomers depending on how the arrangements differ from one another. Notice that in the structural isomers, there was some difference in the connection of atoms. For example, 1-butene has a double bond followed by two single bonds while 2-butene has a single bond, then a double bond, then a single bond. A stereoisomer will have the same connectivity among all atoms in the molecule.

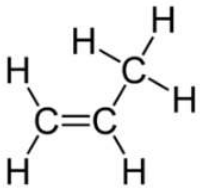
Geometric Isomers

With a molecule such as 2-butene, a different type of isomerism called geometric isomerism can be observed. **Geometric isomers** are isomers in which the order of atom bonding is the same but the arrangement of atoms in space is different. The double bond in an alkene is not free to rotate because of the nature of the bond. Therefore, there are two different ways to construct the 2-butene molecule (see figure below). The image below shows the two geometric isomers, called *cis*-2-butene and *trans*-2-butene.



Geometric Isomers of 2-Butene

The *cis* isomer has the two single hydrogen atoms on the same side of the molecule, while the *trans* isomer has them on opposite sides of the molecule. In both molecules, the bonding order of the atoms is the same. In order for geometric isomers to exist, there must be a rigid structure in the molecule to prevent free rotation around a bond. This occurs with a double bond or a ring. In addition, the two carbon atoms must each have two different groups attached in order for there to be geometric isomers. Propene (see figure below) has no geometric isomers because one of the carbon atoms (the one on the far left) involved in the double bond has two single hydrogens bonded to it.

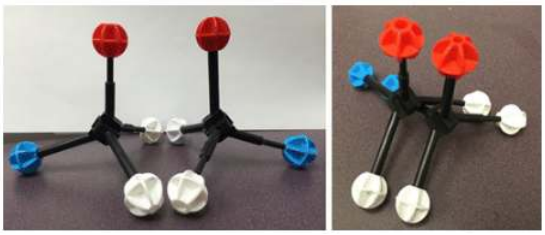


Physical and chemical properties of geometric isomers are generally different. As with alkenes, alkynes display structural isomerism beginning with 1-butyne and 2-butyne. However, there are no geometric isomers with alkynes because there is only one other group bonded to the carbon atoms that are involved in the triple bond.

Optical Isomers

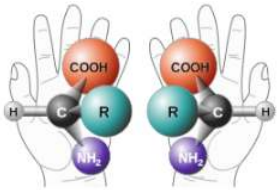
Stereoisomers that are not geometric isomers are known as optical isomers. Optical isomers differ in the placement of substituted groups around one or more atoms of the molecule. They were given their name because of their interactions with plane-polarized light. Optical isomers are labeled enantiomers or diastereomers.

Enantiomers are non-superimposable mirror images. A common example of a pair of enantiomers is your hands. Your hands are mirror images of one another but no matter how you turn, twist, or rotate your hands, they are not superimposable.



Two models that are mirror images and superimposable.

Since they are superimposable, they are the same molecule and are not isomers.

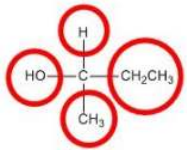


Your hands and some molecules are mirror images but are not superimposable.

These pairs of molecules are called enantiomers.

:

Objects that have non-superimposable mirror images are called **chiral**. When examining a molecule, carbon atoms with four unique groups attached are considered chiral. Look at the figure below to see an example of a chiral molecule. Note that we have to look beyond the first atom attached to the central carbon atom. The four circles indicate the four unique groups attached to the central carbon atom, which is chiral.



A chiral carbon has four unique groups attached to it

:

Another type of optical isomer are **diastereomers**, which are non-mirror image optical isomers. Diastereomers have a different arrangement around one or more atoms while some of the atoms have the same arrangement. As shown in the figure below, note that the orientation of groups on the first and third carbons are different but the second one remains the same so they are not the same molecule. The solid wedge indicates a group coming out of the page/screen towards you and the dashed line indicates that a group is going away from you "behind" the page/screen.

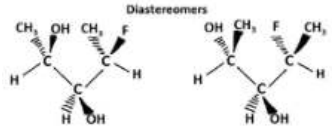


Figure 1.7.1: Diastereomers differ at one or more atom. These molecules are not mirror images and they are not superimposable. They are optical isomers because they have the same connectivity between atoms but a different arrangement of substituent groups.

Epimers are a sub-group of diastereomers that differ at only one location. All epimers are diastereomers but not all diastereomers are epimers.

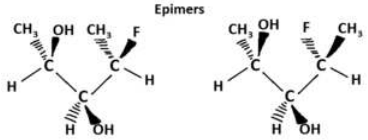


Figure 1.7.2: Epimers have a different arrangement around one atom, while arrangements around the other atoms are the same.

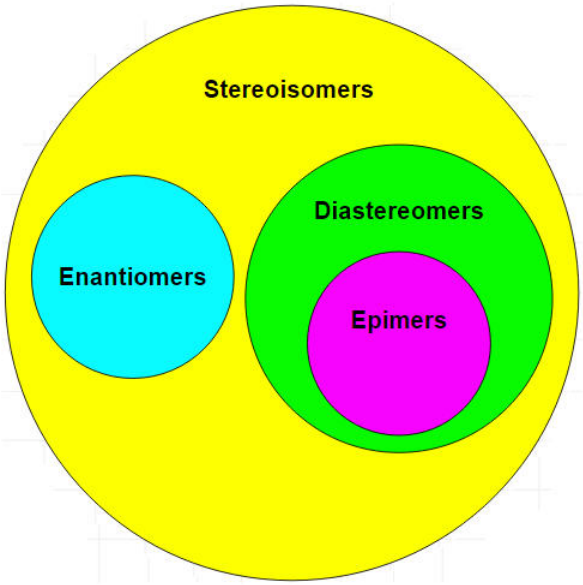
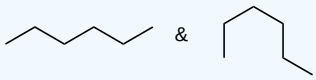


Diagram showing the division of stereoisomers (also known as optical isomers)

Exercise 1.7.1

What kind of isomers are the following pairs?

a) 

b) 

c) 

Answer

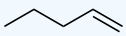
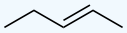
a) Since both structures have the same formula (C_6H_{12}) and they have the same connectivity, but are in a different arrangement of the atoms in space, they are conformational isomers.

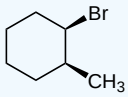
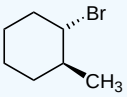
b) Since both structures have the same formula (C_2H_6O) but different connectivity, they are structural isomers.

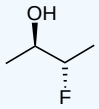
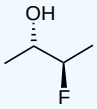
c) Since both structures have the same formula (C_3H_9Br) and the same connectivity but the structure on the left has *R* stereochemistry and the structure on the right has *S* stereochemistry, they are stereoisomers called enantiomers.

Exercise 1.7.2

What kind of isomers are the following pairs?

a)  & 

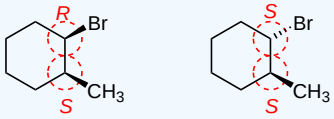
b)  & 

c)  & 

Answer

a) Since both structures have the same formula (C_2H_6O) but different connectivity of where the double bond is, they are structural isomers.

b) Both structures have the same formula and the same connectivity but the structure on the left has (*R*,*S*) stereochemistry and the structure on the right has (S,S) stereochemistry, they are stereoisomers that are diastereomers.

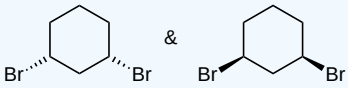


c) Both structures and have the same connectivity but their stereochemistry differs so they are stereoisomers. Since the one on the left is (R,S) and the one on the right is (S,R), they are non-super imposable mirror images of each other and enantiomers.



Exercise 1.7.3

What is the relationship between the following pairs?

a) 

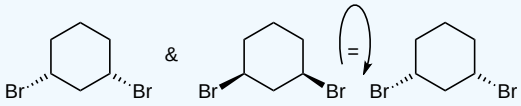
b) 

c) (*R*) – 2 chlorohexane & 1-chlorohexane

d) (2*R*, 3*R*) dichlorohexane & (2*S*, 3*R*) dichlorohexane

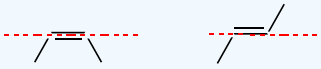
Answer

a) Both structures have the same connectivity and same chemical formula and when you rotate the structure on the right you can see that these are the same compound both with (R,S) stereochemistry.

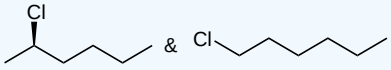


b)) Since both structures have the same formula (C_4H_8) and the same connectivity they are stereoisomers since they differ in what is known as cis/trans isomerism (covered more in Ch 7).Due to the pi bond between carbons 2 & 3, there is not free

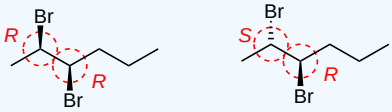
rotation between the C2-C3 bond so the structure on the left has the carbon chains on the same side of the double bond (cis) and the structure on the right has the carbon chains on opposite sides of the double bond (trans).



c) Looking at the structures below, you can see that they have the same formula ($C_6H_{13}Cl$) and different connectivity, so they are structural isomers.



d) Looking at the structures below, you can see that they have the same formula ($C_6H_{12}Br_2$) and the same connectivity, but the structure on the left is (*R*,*R*) and the structure on the right is (*S*,*R*) so since they differ by only one stereocenter, they are stereoisomers that are diastereomers (& epimers in this case).



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- Dr. Zachary Sharrett (Sonoma State University)

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1.8: Enantiomers and the Tetrahedral Carbon

Objectives

After completing this section, you should be able to

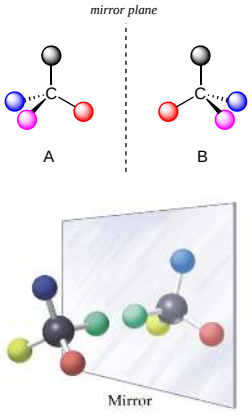
1. use molecular models to show that only a tetrahedral carbon atom satisfactorily accounts for the lack of isomerism in molecules of the type CH_2XY, and for the existence of optical isomerism in molecules of the type CHXYZ.
2. determine whether two differently oriented wedge-and-broken-line structures are identical or represent a pair of enantiomers.

Study Notes

Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. One of the most interesting types of isomer is the mirror-image stereoisomer, a non-superimposable set of two molecules that are mirror images of one another. The existence of these molecules are determined by a a concept known as **chirality**. The word “chiral” was derived from the Greek word for hand, because our hands are a good example of chirality since they are non-superimposable mirror images of each other.

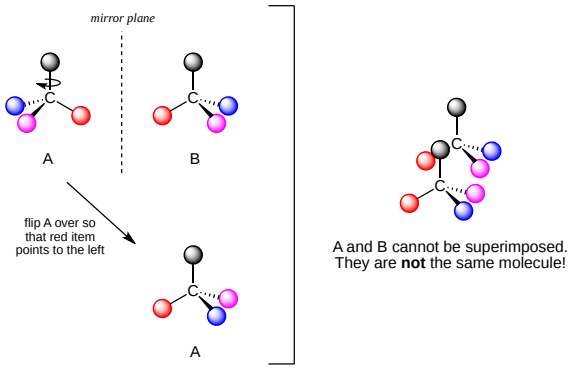
Chiral Molecules

The term **chiral**, from the Greek work for 'hand', refers to anything which cannot be superimposed on its own mirror image. Certain organic molecules are chiral meaning that they are not superimposable on their mirror image. Chiral molecules contain one or more **chiral centers**, which are almost always tetrahedral (sp^3-hybridized) carbons with four different substituents. Consider the molecule A below: a tetrahedral carbon, with four different substituents denoted by balls of four different colors.



The mirror image of A, which we will call B, is drawn on the right side of the figure, and an imaginary mirror is in the middle. Notice that every point on A lines up through the mirror with the same point on B: in other words, if A looked in the mirror, it would see B looking back.

Now, if we flip compound A over and try to superimpose it point for point on compound B, we find that we cannot do it: if we superimpose any two colored balls, then the other two are misaligned.



A is not superimposable on its mirror image (B), thus by definition A is a chiral molecule. It follows that B also is not superimposable on *its* mirror image (A), and thus it is also a chiral molecule.

A and B are called **stereoisomers or optical isomers**: molecules with the same molecular formula and the same bonding arrangement, but *a different arrangement of atoms in space*. **Enantiomers** are pairs of stereoisomers which are mirror images of each other: thus, A and B are enantiomers. It should be self-evident that a chiral molecule will always have one (and *only* one) enantiomer: enantiomers come in pairs. Enantiomers have identical physical properties (melting point, boiling point, density, and so on). However, enantiomers do differ in how they interact with polarized light (we will learn more about this soon) and they may also interact in very different ways with other chiral molecules - proteins, for example. We will begin to explore this last idea in later in this chapter, and see many examples throughout the remainder of our study of biological organic chemistry.

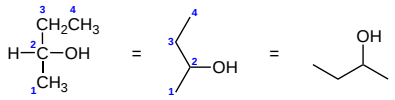
The Many Synonyms of the Chiral Carbon

Be aware - all of the following terms can be used to describe a chiral carbon.

chiral carbon = asymmetric carbon = optically active carbon = stereo carbon = stereo center = chiral center

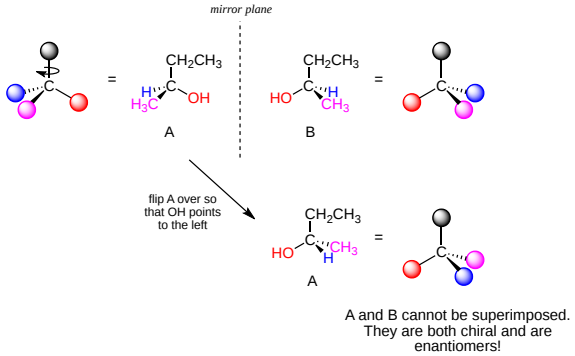
Let's apply our chirality discussion to real molecules.

Consider 2-butanol, drawn in two dimensions below.



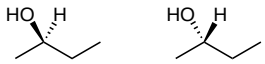
2-butanol
(drawn in 2D)

Carbon #2 is a chiral center: it is sp^3-hybridized and tetrahedral (even though it is not drawn that way above), and the four substituents attached to is are different: a hydrogen (H) , a methyl ($-CH_3$) group, an ethyl ($-CH_2CH_3$) group, and a hydroxyl (OH) group. If the bonding at C_2 of 2-butanol is drawn in three dimensions and this structure called A. Then the mirror image of A can be drawn to form structure B.



When we try to superimpose A onto B, we find that we cannot do it. Because structure A and B are not superimposable on their mirror image they are both chiral molecules. Because A and B are different due only to the arrangement of atoms in space they are

stereoisomers. Because A and B are mirror images of each other they are also enantiomers. When looking at simplified line structures is clear that there are two distinct ways of drawing 2-butanol which only differ in their spatial arrangement around a chiral carbon.

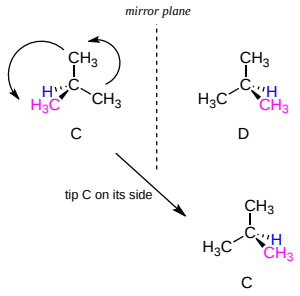


two enantiomers of 2-butanol

The 3D Structures of the Two Enantiomers of 2-Butanol

For comparison, 2-propanol, is an achiral molecule because is lacks a chiral carbon. Carbon #2 is bonded to two identical substituents (methyl groups), and so it is not a chiral carbon. Being achiral means that 2-propanol should be superimposable on its mirror image which is shown in the figure below. A more detailed explaination on why 2-propanol is achiral will be given in the next section.

2-propanol is achiral:



C and D can be superimposed.
They are the same molecule!

Stereoisomers

Stereoisomers have been defined as molecules with the same connectivity but different arrangements of the atoms in space. It is important to note that there are two types of stereoisomers: geometric and optical.

Optical isomers are molecules whose structures are mirror images but cannot be superimposed on one another in any orientation. Optical isomers have identical physical properties, although their chemical properties may differ in asymmetric environments. Molecules that are nonsuperimposable mirror images of each other are said to be chiral. 25.7.1a" id="MathJax-Element-1-Frame" role="presentation" style="position:relative;" tabindex="0">

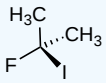
Geometric isomers differ in the relative position(s) of substituents in a rigid molecule. Simple rotation about a C–C σ bond in an alkene, for example, cannot occur because of the presence of the π bond. The substituents are therefore rigidly locked into a particular spatial arrangement. Thus a carbon–carbon multiple bond, or in some cases a ring, prevents one geometric isomer from being readily converted to the other. The members of an isomeric pair are identified as either cis or trans, and interconversion between the two forms requires breaking and reforming one or more bonds. Because their structural difference causes them to have different physical and chemical properties, cis and trans isomers are actually two distinct chemical compounds.mers have the same connectivity, but different arrangements of atoms in space. Geometric isomers will be discussed in more detain in **Sections 7.4 and 7.5**.

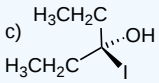
? Exercise 1.8.1

Identify the following molecules as chiral or achiral.

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a) 

b) 

c) 

d) 

e) 

f) 

Answer

a) chiral (4 different groups off C)

b) achiral (2 identical -CH_3 substituents off central C)

c) achiral (2 identical -CH_2CH_3 substituents off central C)

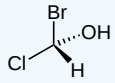
d) achiral (2 identical CH_3 substituents off carbon 2)

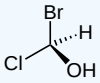
e) chiral (4 different groups off carbon 2)

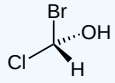
f) achiral (2 identical CH_3 substituents off central C)

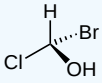
? Exercise 1.8.2

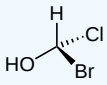
Determine if the following sets of compounds in each group are enantiomers or the same compound.

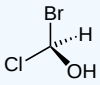
a) 

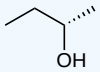
&


b) 

&


c) 

&


d) 

&


Answer

a) enantiomers – non superimposable mirror images

b) same compound – when you rotate the molecule on the right it is identical to the one on the left

c) enantiomers – non superimposable mirror images

d) enantiomers – non superimposable mirror images

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
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1.9: Polar Covalent Bonds - Dipole Moments

Learning Objectives

After completing this section, you should be able to

1. explain how dipole moments depend on both molecular shape and bond polarity
2. predict whether a molecule will possess a dipole moment from the molecular formula or structure
3. use the presence or absence of a dipole moment as an aid to deducing the structure of a given compound

Key Terms

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

- dipole moment

Study Notes

You must be able to combine your knowledge of molecular shapes and bond polarities to determine whether or not a given compound will have a dipole moment. Conversely, the presence or absence of a dipole moment may also give an important clue to a compound's structure. BCl_3, for example, has no dipole moment, while NH_3 does. This suggests that in BCl_3 the chlorines around boron are in a trigonal planar arrangement, while the hydrogens around nitrogen in NH_3 have a less symmetrical arrangement - trigonal pyramidal.

Remember that the C-H bond is assumed to be non-polar.

Molecular Dipole Moments

In molecules containing more than one polar bond, the molecular dipole moment is just the vector combination of what can be regarded as individual "**bond dipole moments**". Mathematically, dipole moments are *vectors*; they possess both a *magnitude* and a *direction*. The dipole moment of a molecule is therefore the *vector sum* of the dipole moments of the individual bonds in the molecule. If the individual bond dipole moments cancel one another, there is no net dipole moment. Such is the case for CO_2, a linear molecule (Figure 1.9.1*a*). Each C–O bond in CO_2 is polar, yet experiments show that the CO_2 molecule has no dipole moment. Because the two C–O bond dipoles in CO_2 are equal in magnitude and oriented at 180° to each other, they cancel. As a result, the CO_2 molecule has no *net* dipole moment even though it has a substantial separation of charge. In contrast, the H_2O molecule is not linear (Figure 1.9.1*b*); it is bent in three-dimensional space, so the dipole moments do not cancel each other. Thus a molecule such as H_2O has a net dipole moment. We expect the concentration of negative charge to be on the oxygen, the more electronegative atom, and positive charge on the two hydrogens. This charge polarization allows H_2O to hydrogen-bond to other polarized or charged species, including other water molecules.

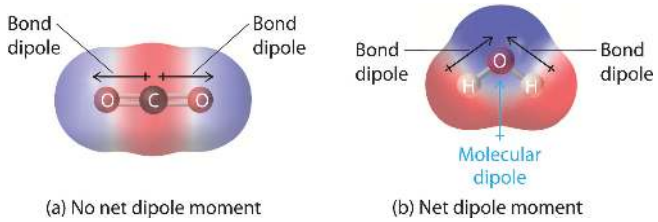


Figure 1.9.1: How Individual Bond Dipole Moments Are Added Together to Give an Overall Molecular Dipole Moment for Two Triatomic Molecules with Different Structures. (a) In CO_2, the C–O bond dipoles are equal in magnitude but oriented in opposite directions (at 180°). Their vector sum is zero, so CO_2 therefore has no net dipole. (b) In H_2O, the O–H bond dipoles are also equal in magnitude, but they are oriented at 104.5° to each other. Hence the vector sum is not zero, and H_2O has a net dipole moment.

The following is a simplified equation for a simple separated two-charge system that is present in diatomic molecules or when considering a bond dipole within a molecule.

$$\mu_{diatomic} = Q \times r \tag{1.9.1}$$

This bond dipole, μ (Greek mu) is interpreted as the dipole from a charge separation over a distance r between the partial charges Q^+ and Q^- (or the more commonly used terms δ^+ - δ^-); the orientation of the dipole is along the axis of the bond. The units on dipole moments are typically debyes (D) where one debye is equal to 3.336 x 10^{30} coulomb meters (C · m) in SI units. Consider a simple system of a single electron and proton separated by a fix distance. The unit charge on an electron is 1.60 X 1019 C and the proton & electron are 100 pm apart (about the length of a typical covalent bond), the dipole moment is calculated as:

$$\begin{aligned} \mu &= Qr \\ &= (1.60 \times 10^{-19}\ C)(1.00 \times 10^{-10}\ m) \\ &= 1.60 \times 10^{-29}\ C \cdot m \end{aligned} \tag{1.9.2}$$

$$\mu = (1.60 \times 10^{-29}\ C \cdot m)\left(\frac{1\ D}{3.336 \times 10^{-30}\ C \cdot m}\right)$$

$$= 4.80\ D \tag{1.9.3}$$

$4.80\ D$ is a key reference value and represents a pure charge of +1 and -1 separated by 100 pm. However, if the charge separation were increased then the dipole moment increases (linearly):

- If the proton and electron were separated by 120 pm:

$$\mu = \frac{120}{100}(4.80\ D) = 5.76\ D \tag{1.9.4}$$

- If the proton and electron were separated by 150 pm:

$$\mu = \frac{150}{100}(4.80\ D) = 7.20\ D \tag{1.9.5}$$

- If the proton and electron were separated by 200 pm:

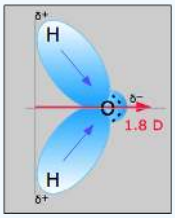
$$\mu = \frac{200}{100}(4.80\ D) = 9.60\ D \tag{1.9.6}$$

Example 1.9.1: Water

The water molecule in Figure 1.9.1 can be used to determine the direction and magnitude of the dipole moment. From the electronegativities of oxygen and hydrogen, the difference is 1.2e for each of the hydrogen-oxygen bonds. Next, because the oxygen is the more electronegative atom, it exerts a greater pull on the shared electrons; it also has two lone pairs of electrons. From this, it can be concluded that the dipole moment points from between the two hydrogen atoms toward the oxygen atom. Using the equation above, the dipole moment is calculated to be 1.85 D by multiplying the distance between the oxygen and hydrogen atoms by the charge difference between them and then finding the components of each that point in the direction of the net dipole moment (the angle of the molecule is 104.5˚).

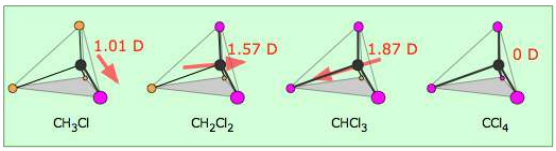
The bond moment of O-H bond =1.5 D, so the net dipole moment is

$$\mu = 2(1.5)\cos\left(\frac{104.5^\circ}{2}\right) = 1.84\ D$$



Dipoles with Differing Atoms

In more complex molecules with more than one polar covalent bonds, the three-dimensional geometry and the compound's symmetry determine whether the molecule has a net dipole moment. The manner in which the individual bonds contribute to the dipole moment of the molecule is nicely illustrated by the series of chloromethanes shown below. The electronegative chlorine draws electrons towards itself.



Consider CCl_4, (left panel in figure below), which as a molecule is not polar - in the sense that it doesn't have an end (or a side) which is slightly negative and one which is slightly positive. The whole of the outside of the molecule is somewhat negative, but there is no overall separation of charge from top to bottom, or from left to right. In contrast, $CHCl_3$ is a polar molecule (right panel in figure above). However, although a molecule like $CHCl_3$ has a tetrahedral geometry, the atoms bonded to carbon are not identical. Consequently, the bond dipole moments do not cancel one another, and the result is a molecule which has a dipole moment. The hydrogen at the top of the molecule is less electronegative than carbon and so is slightly positive. This means that the molecule now has a slightly positive "top" and a slightly negative "bottom", and so is overall a polar molecule.

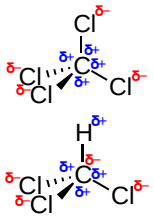


Figure 1.9.3: Bond polarities for CCl_4 (left) and $CHCl_3$(right)

Electron densities in a molecule (and the dipole moments that unbalanced electron distributions can produce) are easily visualized with electrostatic potential maps. In this example, $CHCl_3$, the blue area centered on carbon represents a electron-deficient positive area, of the molecule, the red area centered on the chlorine, represents a electron-abundant negative area. This charge separation creates a net dipole moment of 1.87 D which points in the direction of the chlorine. In, CCl_4 the evenly spaced red areas represent that there is no separation of charge in the molecule. CCl_4 has a net dipole moment of zero which makes it a nonpolar molecule.

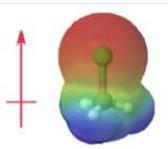
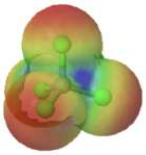
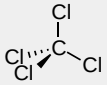
	
	
chloromethane	tetrachloromethane
(μ = 1.87 D)	(μ = 0 D)

***Figure* 1.9.4:** Electrostatic potential maps and dipole moments for chloromethane and tetrachloromethane (carbon tetrachloride).

Molecules with asymmetrical charge distributions have a net dipole moment

Other examples of molecules with polar bonds are shown in Figure 1.9.2. In molecules like BCl_3 and CCl_4, that have only one type of bond and a molecular geometries that are highly symmetrical (trigonal planar and tetrahedral), the individual bond dipole moments completely cancel, and there is no net dipole moment. However, although a molecule like $CHCl_3$ has a tetrahedral geometry, the atoms bonded to carbon are not identical. Consequently, the bond dipole moments do not cancel one another, and the result is a molecule which has a dipole moment.

							
net dipole	no net dipole	net dipole	net dipole	no net dipole	net dipole	no net dipole	no net dipole
HCl	BCl_3	CH_2O	NH_3	CCl_4	$CHCl_3$	PF_5	SF_6

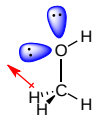
Figure* 1.9.5: Molecules with Polar Bonds. Individual bond dipole moments are indicated in black. Due to their different three-dimensional structures, some molecules with polar bonds have a net dipole moment (HCl, CH_2O, NH_3, and $CHCl_3$), indicated in red, whereas others do not because the bond dipole moments cancel (BCl_3, CCl_4, PF_5, and SF_6).*

Table 1.9.1: Dipole Moments of Some Compounds

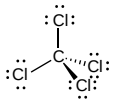
Compound	Dipole Moment (Debyes)
NaCl	9.0 (measured in the gas phase)
CH_2O	2.33
CH_3Cl	1.87
H_2O	1.85
CH_3OH	1.70
NH_3	1.47
CH_3NH_2	1.31

CO_2	0
CCl_4	0
CH_4	0
CH_3CH_3	0

The table above give the dipole moment of some common substances. Sodium chloride has the largest dipole listed (9.00 D) because it is an ionic compounds. Even small organic compounds such as formaldehyde (CH_2O, 2.33 D) and methanol (CH_3OH, 1.70 D) have significant dipole moments. Both of these molecules contain the strongly electronegative oxygen atom lone pair electrons which gives rise to considerable dipole moments.

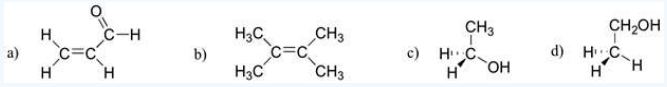
	
methanol	formaldehyde
(μ = 1.70 D)	(μ = 2.33 D)

In contrast many organic molecule have a zero dipole moment despite the fact that they are made up of polar covalent bonds. In, structures with highly symmetrical molecular geometries, the polar bonds and the lone pair electrons can can exactly cancel leaving no overall charge separation.

		
carbon dioxide	carbon tetrachloride	ethane
(μ = 0 D)	(μ = 0 D)	(μ = 0 D)

Exercise 1.9.1

Which of the molecules below have molecular dipole moments?



Answer

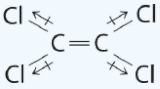
Only molecule (b) does *not* have a molecular dipole, due to its symmetry (bond dipoles are equal and in opposite directions). Add texts here.

Exercise 1.9.2

Draw out the line structure of the molecule with a molecular formula of C_2Cl_4. Indicate all of the individual bond polarities and predict if the molecule is polar or nonpolar.

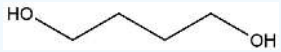
Answer

Although the C–Cl bonds are rather polar, the individual bond dipoles cancel one another in this symmetrical structure, and Cl2C=CCl2" id="MathJax-Element-47-Frame" role="presentation" style="position:relative;" tabindex="0">does not have a net dipole moment.



Exercise 1.9.3

The following molecule has no net dipole moment, explain.

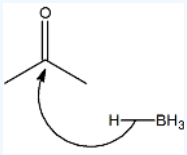


Answer

The hydroxyl groups are oriented opposite of one another and therefore the dipole moments would “cancel” one another out. Therefore having a zero net-dipole.

Exercise 1.9.4

Within reactions with carbonyls, such as a hydride reduction reaction, the carbonyl is attacked from the carbon side and not the oxygen side. Using knowledge of electronegativity explain why this happens.



Answer

The oxygen is more electronegative than the carbon and therefore creates a dipole along the bond. This leads to having a partial positive charge on the carbon and the reduction can take place.



Exercise 1.9.1

Which molecule(s) has a net dipole moment?

a. H_2S
b. NHF_2
c. BF_3

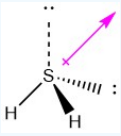
Answer

Strategy:

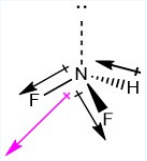
For each three-dimensional molecular geometry, predict whether the bond dipoles cancel. If they do not, then the molecule has a net dipole moment.

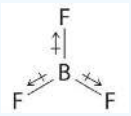
Solution:

The total number of electrons around the central atom, S, is eight, which gives four electron pairs. Two of these electron pairs are bonding pairs and two are lone pairs, so the molecular geometry of H_2S is bent. The bond dipoles cannot cancel one another, so the molecule has a net dipole moment.



Difluoroamine has a trigonal pyramidal molecular geometry. Because there is one hydrogen and two fluorines, and because of the lone pair of electrons on nitrogen, the molecule is not symmetrical, and the bond dipoles of NHF_2 cannot cancel one another. This means that NHF_2 has a net dipole moment. We expect polarization from the two fluorine atoms, the most electronegative atoms in the periodic table, to have a greater affect on the net dipole moment than polarization from the lone pair of electrons on nitrogen.



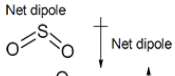


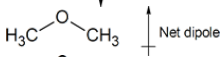
- The molecular geometry of BF_3 is trigonal planar. Because all the B–F bonds are equal and the molecule is highly symmetrical, the dipoles cancel one another in three-dimensional space. Thus BF_3 has a net dipole moment of zero:

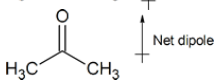
Additional Exercises

1. Determine whether each of the compounds listed below possesses a dipole moment. For the polar compounds, indicate the direction of the dipole moment.
   a. O=C=O
   b. ICl
   c. SO_2
   d. CH_3-O-CH_3
   e. $CH_3C(=O)CH_3$

Answers:

1. a. CO_2 nonpolar
   b. I—Cl
   
   Net dipole
   c. 

   d. 

   e. 

2.2 Polar Covalent Bonds: Dipole Moments

2.2 Exercises

Questions

Q2.2.1

The following molecule has no dipole moment in the molecule itself, explain.



Q2.2.2

Which of the following molecules has a net dipole?



Q2.2.3

Within reactions with carbonyls, such as a reduction reaction, the carbonyl is attacked from the carbon side and not the oxygen side. Using knowledge of electronegativity explain why this happens.



Solutions

S2.2.1

The hydroxyl groups are oriented opposite of one another and therefore the dipole moments would “cancel” one another out. Therefore having a zero net-dipole.

S2.2.2

1, 3, and 4 have a net dipoles.

S2.2.3

The oxygen is more electronegative than the carbon and therefore creates a dipole along the bond. This leads to having a partial positive charge on the carbon and the reduction can take place.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Dr. Krista Cunningham

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1.10: Organic Acids and Organic Bases

Objective

After completing this section, you should be able to

- predict the relative acidity of two organic molecules from their structures.
- predict the relative basicity of two organic molecules from their structures.

This page explains the acidity of simple organic acids and looks at the factors which affect their relative strengths.

Organic acids as weak acids

For the purposes of this topic, we are going to take the definition of an acid as "a substance which donates hydrogen ions (protons) to other things". We are going to get a measure of this by looking at how easily the acids release hydrogen ions to water molecules when they are in solution in water.

An acid in solution sets up this equilibrium:

$$AH_{(aq)} + H_2O_{(l)} \rightleftharpoons A^-_{(aq)} + H_3O^+_{(aq)} \tag{1.10.1}$$

A hydronium ion is formed together with the anion (negative ion) from the acid. This equilibrium is sometimes simplified by leaving out the water to emphasize the ionization of the acid.

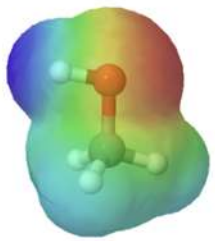
$$AH_{(aq)} \rightleftharpoons A^-_{(aq)} + H^+_{(aq)} \tag{1.10.2}$$

If you write it like this, you must include the state symbols - "(aq)". Writing $H^+_{(aq)}$ implies that the hydrogen ion is attached to a water molecule as H_3O^+. Hydrogen ions are always attached to something during chemical reactions.

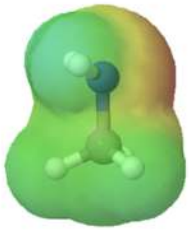
The organic acids are weak in the sense that this ionization is very incomplete. At any one time, most of the acid will be present in the solution as un-ionized molecules. For example, in the case of dilute ethanoic acid, the solution contains about 99% of ethanoic acid molecules - at any instant, only about 1% have actually ionized. The position of equilibrium therefore lies well to the left.

Weak acid polarization

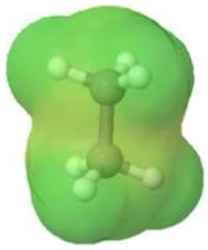
Organic acids can usually can be characterized in electrostatic potential maps by the presence of of a positively polarized hydrogen atom shown in blue. When looking at the maps below, methanol has a slightly polarized O-H bond and is considered very weakly acidic. The O-H bond in methyl amine is less polarized, as shown by the lighter blue color around the hydrogen, making it less acidic than methanol. However, the C-H bond in ethane lack virtually any polarity, as shown by the lack of a blue color, making it non-acidic. The following discussion will explain the difference in acidity of these and other organic molecules molecules.



methanol



methylamine



ethane

Comparing the strengths of weak acids

Acid strength is strongly correlated to stability of the conjugate base that will form by removing a proton. In order to analyze how acidic a molecule is likely to be, then you need to estimate the stability of its conjugate base.

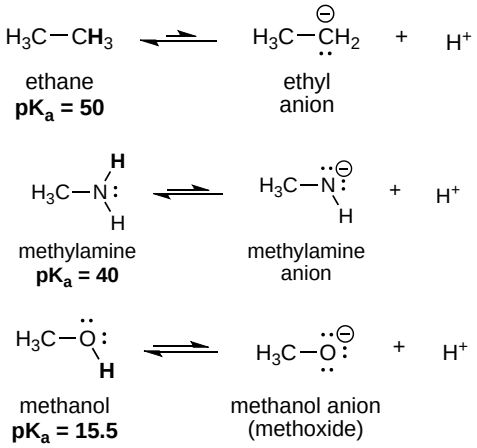
Stabilization of the Conjugate Base - Four Main Considerations:

1. Size and electronegativity of the atom holding the charge
2. Can the charge be delocalized by resonance?
3. Are there any inductive effects?
4. Hybridization of orbital holding the charge

These considerations are listed in order of importance and are explained individually, but must be looked at collectively.

1. Size and Electronegativity Effects in Acidity

When comparing elements, it depends on the positional relationship of the elements on the periodic table. When moving a period (aka across a row) of the main group elements, the valence electrons all occupy orbitals in the same shell. These electrons have comparable energy, so this factor does not help us discern differences relative stability. Differences in electronegativity are now the dominant factor. This trend is shown when comparing the pKa values of ethane, methyl amine, and methanol which reflects the relative electronegativities of the C < N < O. The key to understanding this trend is to consider the hypothetical conjugate base in each case*: the more stable the conjugate base, the stronger the acid*. In general, the more electronegative an atom, the better it is able to bear a negative charge. In the ethyl anion, the negative charge is borne by carbon, in the methylamine anion by nitrogen, and in the methoxide anion by an oxygen. Remember the periodic trend in electronegativity: it also increases as we move from left to right along a row, meaning that oxygen is the most electronegative of three elements being considered. This makes the negative charge on the methoxide anion the most stable of the three conjugate bases and methanol the strongest of the three acids. Likewise, carbon is the least electronegative making ethane the weakest of the three acids.



Within a Group (aka down a column) As we move down the periodic table, the electrons are occupying higher energy subshells creating a larger atomic size and volume. As the volume of an element increases, any negative charge present tends to become more spread out which decreases electron density and increases stability. The figure below shows spheres representing the atoms of the *s* and *p* blocks from the periodic table to scale, showing the two trends for the atomic radius.

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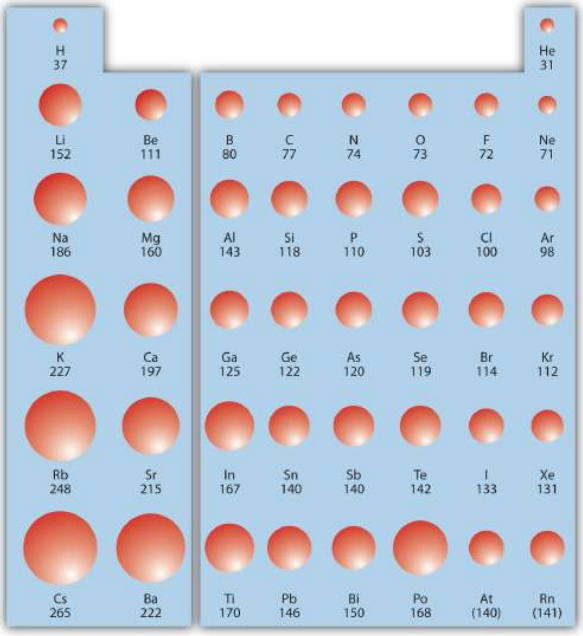
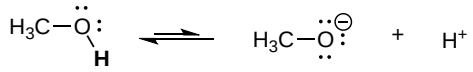
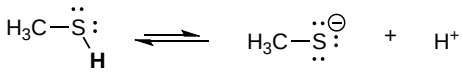


Figure 1.10.1: Atomic Radii Trends on the Periodic Table. Although there are some reversals in the trend (e.g., see Po in the bottom row), atoms generally get smaller as you go across the periodic table and larger as you go down any one column. Numbers are the radii in pm.

This relationship of atomic size and electron density is illustrated when we compare the relative acidities of methanol, CH_3OH, with methanethiol, CH_3SH. The lower pKa value of 10.4 for methanethiol indicates that it is a stronger acid than methanol with a pKa value of 15.5. It is important to remember that neither compound is considered an acid. These relationships become useful when trying to deprotonate compounds to increase their chemical reactivity in non-aqueous reaction conditions.

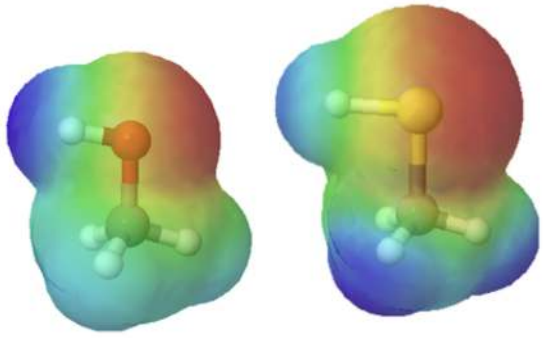


methanol
pK_a = 15.5



methanethiol
pK_a = 10.4

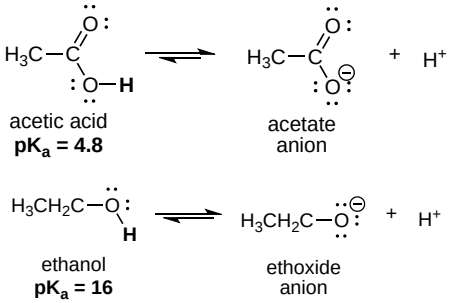
The difference in size can easily be seen when looking at the electrostatic potential maps for methanol (Left) and methanethiol (Right). The sulfur atom methanethiol is larger than the oxygen atom in methanol. The larger size of sulfur will be better able to delocalize and stabilize the negative charge in its conjugate base metanethiolate.



2.

Resonance Effects in Acidity

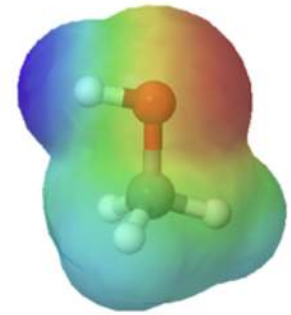
This section will focus on how the resonance structures of different organic groups contributes to their relative acidity even though the same element acts as the proton donor. When evaluating conjugate bases for the presence of resonance contributors, remember to look for movable electrons (lone pairs and pi bonding electrons). Delocalizing electrons over two or more atoms spreads out the electron density, increasing the stability of the conjugate base, and increasing the acidity of the corresponding acid. 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.

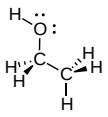


In both species, the negative charge on the conjugate base is held by an oxygen, so periodic trends cannot be invoked. For acetic acid, however, there is a key difference: a resonance contributor can be drawn in which the negative charge is drawn on the second oxygen of the group. The two resonance forms for the conjugate base are equal in energy, according to our 'rules of resonance' (Section 2.5). What this means is that the negative charge on the acetate ion is not located on one oxygen or the other: rather it is shared between the two. Chemists use the term 'delocalization of charge' to describe this situation. In the ethoxide ion, by contrast, the negative charge is 'locked' on the single oxygen. This stabilization leads to a markedly increased acidity.

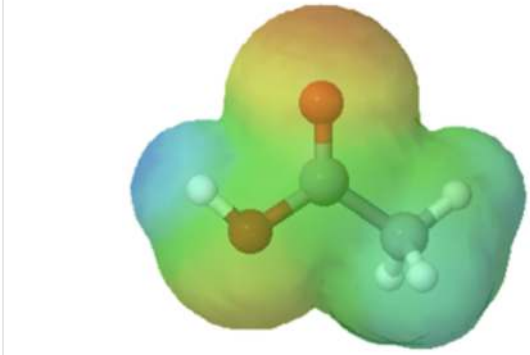
The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of nearly 12 pK_a units between ethanol and acetic acid (and remember, pK_a is a log expression, so we are talking about a difference of over 10^{12} between the acidity constants for the two molecules). The acetate ion is much more stable than the ethoxide ion, due to the effects of resonance delocalization.

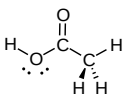
The effects of conjugation can be seen when comparing the electrostatic potential maps of ethanol and acetic acid. Conjugation creates a greater polarization in the O-H bond in acetic acid as shown by its darker blue color.





ethanol



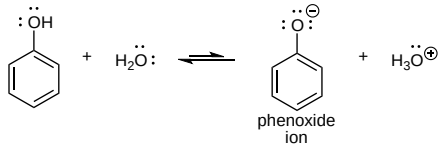


acetic acid

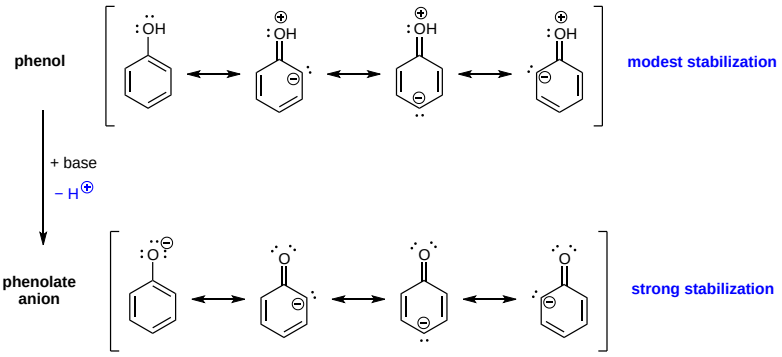
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Why is Phenol Acidic?

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 aqueous solution:

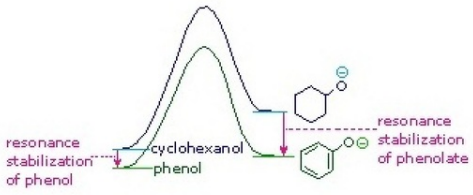


Since phenol is a very weak acid, the position of equilibrium lies well to the left. However, phenol can lose a hydrogen ion because the phenoxide ion (or phenolate ion - the two terms can be used interchangeably) formed is stabilized due to resonance. The negative charge on the oxygen atom is delocalized around the ring since one of the lone pairs on the oxygen atom can be in a p orbital and overlap with the pi electrons on the benzene ring.



This overlap leads to a delocalization which extends from the ring out over the oxygen atom. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread out around the whole ion. Spreading the charge around makes the ion more stable than it would be if all the charge remained on the oxygen. However, oxygen is the most electronegative element in the ion and the delocalized electrons will be drawn towards it. That means that there will still be a lot of charge around the oxygen which will tend to attract the hydrogen ion back again. That is why phenol is only a very weak acid.

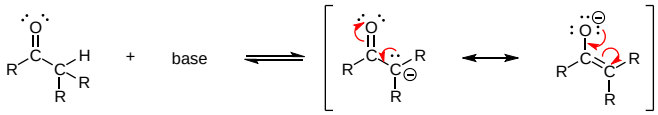
This explains why phenol is a much stronger acid than cyclohexanol. As can be seen in the following energy diagram, resonance stabilization is increased for the conjugate base of phenol vs. cyclohexanol after removal of a proton.



The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of contributors to the resonance hybrid. 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 hydrogen α (alpha) to carbonyl

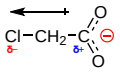
Alkyl hydrogen atoms bonded to a carbon atom in a α (alpha) position (directly adjacent) relative to a C=O group display unusual acidity. While the pKa values for alkyl C-H bonds in is typically on the order of 40-50, pKa values for these alpha hydrogens is more on the order of 19-20. This is almost exclusively due to the resonance stabilization of the product carbanion, called an enolate, as illustrated in the diagram below. The effect of the the stabilizing C=O is seen when comparing the pKa for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25).



enolate ion

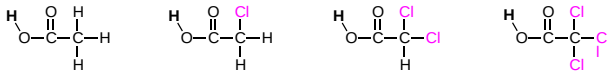
3. Inductive Effects

The inductive effect is an experimentally observed effect of the transmission of charge through a chain of atoms in a molecule, resulting in a permanent dipole in a bond. For example, in a carboxylic acid group the presence of chlorine on adjacent carbons increases the acidity of the carboxylic acid group. A chlorine atom is more electronegative than hydrogen, and thus is able to 'induce', or 'pull' electron density towards itself, away from the carboxylate group. This further spreads out the electron density of the conjugate base, which has a stabilizing effect. In this context, the chlorine substituent is called an **electron-withdrawing group**. Notice that the pK_a-lowering effect of each chlorine atom, while significant, is not as dramatic as the delocalizing resonance effect illustrated by the difference in pK_a values between an alcohol and a carboxylic acid. In general, *resonance effects are more powerful than inductive effects*.



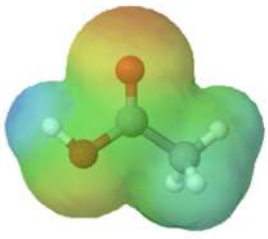
negative charge is delocalized by being pulled out onto chlorine atom

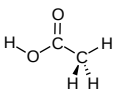
Compare the pK_a values of acetic acid and its mono-, di-, and tri-chlorinated derivatives:



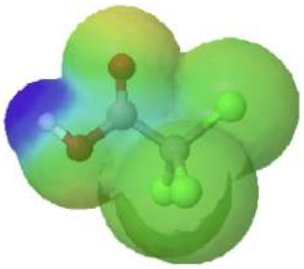
pK_a = 4.8 **pK_a = 2.8** **pK_a = 1.3** **pK_a = 0.64**

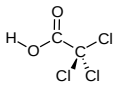
The inductive effects of chlorine can be clearly seen when looking at the electrostatic potential maps of acetic acid (Left) and trichloroacetic acid (Right). The O-H bond in trichloroacetic acid is highly polarized as shown by the dark blue color. This illustrates that tricholoracetic acid is a much stronger acid than acetic acid.





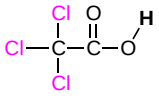
acetic acid



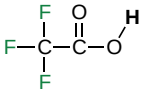


trichloroacetic acid

Because the inductive effect depends on electronegativity, fluorine substituents have a more pronounced pK_a-lowering effect than chlorine substituents.

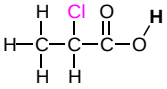


trichloroacetic acid
pK_a = 0.64

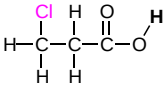


trifluoroacetic acid
pK_a = −0.25

In addition, the inductive takes place through covalent bonds, and its influence decreases markedly with distance – thus a chlorine two carbons away from a carboxylic acid group has a decreased effect compared to a chlorine just one carbon away. 2-chloropropanoic acid has a pK_a of 2.8 while for 3-chloropropanoic acid, the pK_a is 4.0.

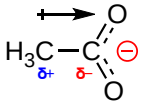


2-chloropropanoic acid
pK_a = 2.8
stronger acid



3-chloropropanoic acid
pK_a = 4.0

Alkyl groups (hydrocarbons) are weak inductive electron donators. In this case the inductive effect pushes electron density onto the conjugate base, causing the electron density to become more concentrated and producing a destabilizing effect.



more negative charge pushed towards already negative end

The inductive effects of alkyl groups causes a significant variation in the acidities of different carboxylic acids. Notice that the inductive effect drops off after the alkyl chain is about three carbons long.

	pK_a
HCOOH (Methanoic Acid or Formic Acid)	3.75
CH_3COOH (Ethanoic Acid or Acetic Acid)	4.76
CH_3CH_2COOH (Propanoic Acid)	4.87
$CH_3CH_2CH_2COOH$ (Butanoic Acid)	4.82

4. Orbital Hybridization

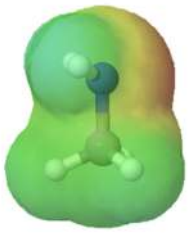
The hybridization of an orbital affects its electronegativity. Within a shell, the s orbitals occupy the region closer to the nucleus than the p orbitals. Therefore, the spherical s orbitals are more electronegative than the lobed p orbitals. The relative electronegativity of hybridized orbitals is sp > sp^2 > sp^3 since the percentage of s-character is decreasing as more p-orbitals are added to the hybrids. This trend indicates the sp hybridized orbitals are more stable with a negative charge than sp^3 hybridized orbitals. The table below shows how orbital hybridization influences relative acidity.

compound	**conjugate base**	**hybridization**	***s* character**	**pK_a**	
		sp^3	25%	50	weakest acid
		sp^2	33%	44	↓
				36	↓
		sp	50%	25	↓
				16	strongest acid

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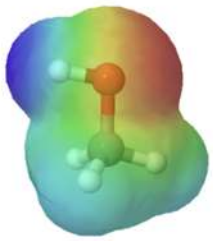
Comparing the Strengths of Weak Bases

Technically, organic bases are characterized by the presence of an atom with lone pair electrons. These lone pairs contain a high electron density, which is shown red in the electrostatic potential maps, and can bond to H^+. Below are the maps of methanol, methyl amine, and acetone. All three compounds can be protonated with a sufficiently strong acid. Note, that all three of these compounds also have the ability to donate a proton when reacted with a strong enough base. Whether these compounds act as a acid or base depends on the conditions.



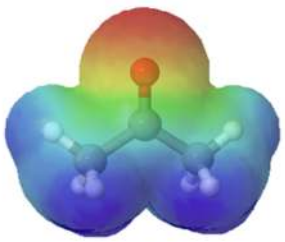


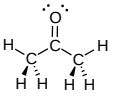
methylamine





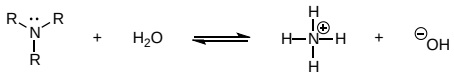
methanol



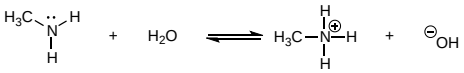


acetone

It is common to compare basicity's quantitatively by using the pK$_a$'s of their conjugate acids rather than their pK$_b$'s. Since pK$_a$ + pK$_b$ = 14, **the higher the pK$_a$ the stronger the base**, in contrast to the usual inverse relationship of pK$_a$ with acidity. Recall that ammonia (NH_3) acts as a base because the nitrogen atom has a lone pair of electrons that can accept a proton. The conjugate acid of most simple alkyl amines have pK$_a$'s in the range 9.5 to 11.0, and their water solutions are basic (have a pH of 11 to 12, depending on concentration). This can be illustrated by the reaction below where an amine removes a proton from water to form substituted ammonium (e.g. NH_4^+) ions and hydroxide (OH^-) ions:



Amines are one of the only neutral functional groups which are considered basic. This is a direct consequence of the presence of the unshared electron pair on the nitrogen. The unshared electron pair is less tightly held by the nitrogen of an amine than the corresponding oxygen of an alcohol, which makes it more available to act as a base. As a specific example, methylamine reacts with water to form the methylammonium ion and the OH^- ion.



Example: Ammonia

All of the have similarities to ammonia and so we'll start by looking at the reason for its basic properties. For the purposes of this topic, we are going to take the definition of a base as "a substance which combines with hydrogen ions (protons)". We are going to get a measure of this by looking at how easily the bases take hydrogen ions from water molecules when they are in solution in water.

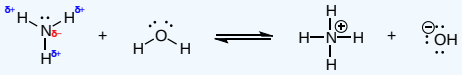
Ammonia in solution sets up this equilibrium:

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^- \tag{2.10.1}$$

An ammonium ion is formed together with hydroxide ions. Because the ammonia is only a weak base, it doesn't hang on to the extra hydrogen ion very effectively and so the reaction is reversible. At any one time, about 99% of the ammonia is present as unreacted molecules. The position of equilibrium lies well to the left.

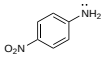
The ammonia reacts as a base because of the active lone pair on the nitrogen. Nitrogen is more electronegative than hydrogen and so attracts the bonding electrons in the ammonia molecule towards itself. That means that in addition to the lone pair, there

is a build-up of negative charge around the nitrogen atom. That combination of extra negativity and active lone pair attracts the new hydrogen from the water.



When looking at the table below, it is clear that the basicity of nitrogen containing compounds is greatly influenced by their structures. The variance in the basicity of these compounds can mostly be explained by the effects of electron delocalization discussed above.

Table 1.10.1: pKa of conjugate acids of a series of amines.

Compound										
pK_a	11.0	10.7	10.7	9.3	5.2	4.6	1.0	0.0	-1.0	-10.0

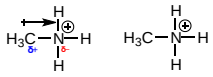
Inductive Effects in Nitrogen Basicity

Alkylamines are more basic than ammonia since alkyl groups donate electrons to the more electronegative nitrogen. This inductive effect makes the electron density on the alkylamine nitrogen greater than the nitrogen of ammonium. That means that there will be a small amount of extra negative charge built up on the nitrogen atom. That extra negativity around the nitrogen makes the lone pair even more attractive towards hydrogen ions. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia.



methyl group pushes electron density toward the nitrogen, making it more basic

Making the nitrogen more negative helps the lone pair to pick up a hydrogen ion. What about the effect on the positive methylammonium ion formed? Is this more stable than a simple ammonium ion? Compare the methylammonium ion with an ammonium ion:



CH_3 group pushes electron density toward nitrogen

In the methylammonium ion, the positive charge is spread around the ion by the "electron-pushing" effect of the methyl group. The more you can spread charge around, the more stable an ion becomes. In the ammonium ion there is not any way of spreading the charge.

To summarize:

- The nitrogen is more negative in methylamine than in ammonia, and so it picks up a hydrogen ion more readily.
- The ion formed from methylamine is more stable than the one formed from ammonia, and so is less likely to shed the hydrogen ion again.

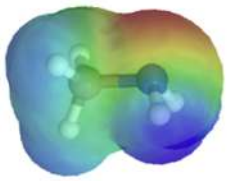
Taken together, these mean that methylamine is a stronger base than ammonia.

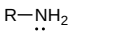
Compound	pK_a
NH_3	9.3
CH_3NH_2	10.66

$(CH_3)_2NH$	10.74
$(CH_3)_3N$	9.81

Resonance Effects in Nitrogen Basicity

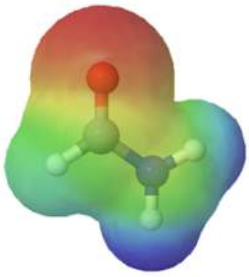
The resonance effect also explains why a nitrogen atom is basic when it is in an amine, but *not* significantly basic when it is part of an amide group. While the lone pair of electrons in an amine nitrogen is localized in one place, the lone pair on an amide nitrogen is delocalized by resonance. The lone pair is stabilized by resonance delocalization. Here's another way to think about it: the lone pair on an amide nitrogen is not available for bonding with a proton – these two electrons are too stable being part of the delocalized pi-bonding system. The electrostatic potential map show 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 decreases the basicity of the lone pair electrons on the nitrogen in an amide.





amine

pK_a of conjugate acid ~ 11





amide

pK_a of conjugate acid ~ −1

Aniline, the amine analog of phenol, is substantially less basic than an amine (as evidenced by the pK_a of the conjugate acids).



cyclohexylamine

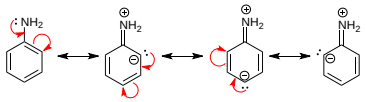
pK_a of conjugate acid ~ 10



aniline

pK_a of conjugate acid ~ 5

We can use the same reasoning that we used when comparing the acidity of a phenol to that of an alcohol. In aniline, the lone pair on the nitrogen atom is stabilized by resonance with the aromatic pi system, making it less available for bonding and thus less basic.



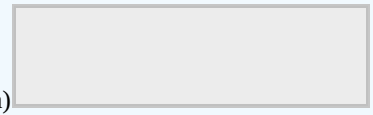
lone pair is stabilized through resonance

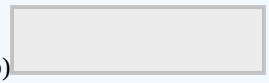
In these cases, you seem to be breaking the same oxygen-hydrogen bond each time, and so you might expect the strengths to be similar. The most important factor in determining the relative acid strengths of these molecules is the nature of the ions formed. You always get a hydronium ion - so that's constant - but the nature of the anion (the negative ion) varies markedly from case to case.

Exercises

Exercise 1.10.1

Select the more basic from each of the following pairs of compounds.

(a) 

(b) 

Answer

a)  The lone pair of electrons on the amide nitrogen are less available to react with a proton.

(b) NaOH -- The hydroxide has a negative charge with three lone pairs of electrons that can react with a proton.

Exercise 1.10.2

The 4-methylbenzylammonium ion has a pK_a of 9.51, and the butylammonium ion has a pK_a of 10.59. Which is more basic? What's the pK_b for each compound?

Answer

The butylammonium is more basic. Remember that $pK_a+pK_b = 14$. The pK_b for butylammonium is 3.41, the pK_b for 4-methylbenzylammonium is 4.49.

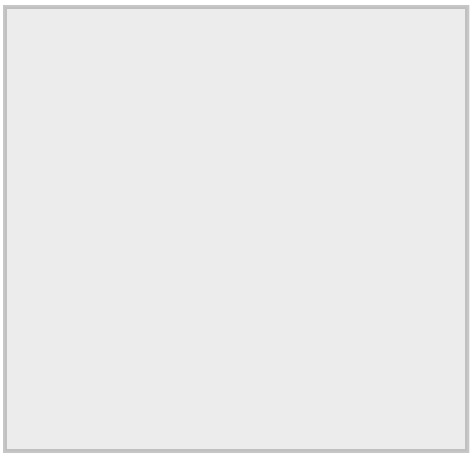
2.10 Organic Acids and Organic Bases

2.10 Exercises

Questions

Q2.10.1

Determine which of the one of the molecules is an acid or a base.



Solutions

S2.10.1

1 = Base

2 = Acid

3 = Acid

4 = Acid

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1.11: Noncovalent Interactions Between Molecules

Objectives

After completing this section, you should be able to

1. identify the various intermolecular forces that may be at play in a given organic compound.
2. describe how intermolecular forces influence the physical properties, 3-dimensional shape and structure of compounds.

Key Terms

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

- dipole-dipole forces
- London dispersion forces
- hydrogen bond
- intermolecular forces
- noncovalent interaction
- van der Waals forces

Study Notes

Much of the material in this section should be familiar to you from your pre-requisite general chemistry course. Nonetheless, this section is important, as it covers some of the fundamental factors that influence many physical and chemical properties.

Introduction

The properties of liquids are intermediate between those of gases and solids, but are more similar to solids. In contrast to *intra*molecular forces, such as the covalent bonds that hold atoms together in molecules and polyatomic ions, *inter*molecular forces hold molecules together in a liquid or solid. Intermolecular forces are generally much weaker than covalent bonds. For example, it requires 927 kJ to overcome the intramolecular forces and break both O–H bonds in 1 mol of water, but it takes only about 41 kJ to overcome the intermolecular attractions and convert 1 mol of liquid water to water vapor at 100°C. (Despite this seemingly low value, the intermolecular forces in liquid water are among the strongest such forces known!) Given the large difference in the strengths of intra- and intermolecular forces, changes between the solid, liquid, and gaseous states almost invariably occur for molecular substances *without breaking covalent bonds*.

Note

The properties of liquids are intermediate between those of gases and solids but are more similar to solids.

Intermolecular forces determine bulk properties such as the melting points of solids and the boiling points of liquids. Liquids boil when the molecules have enough thermal energy to overcome the intermolecular attractive forces that hold them together, thereby forming bubbles of vapor within the liquid. Similarly, solids melt when the molecules acquire enough thermal energy to overcome the intermolecular forces that lock them into place in the solid.

Intermolecular forces are electrostatic in nature; that is, they arise from the interaction between positively and negatively charged species. Like covalent and ionic bonds, intermolecular interactions are the sum of both attractive and repulsive components. Because electrostatic interactions fall off rapidly with increasing distance between molecules, intermolecular interactions are most important for solids and liquids, where the molecules are close together. These interactions become important for gases only at very high pressures, where they are responsible for the observed deviations from the ideal gas law.

In this section, we explicitly consider three kinds of intermolecular interactions: dipole-dipole forces, dispersion forces, and hydrogen bonds. These intermolecular interactions are also called van der Waals forces or noncovalent interactions. There are two additional types of electrostatic interaction that you are already familiar with: the ion–ion interactions that are responsible for ionic bonding and the ion–dipole interactions that occur when ionic substances dissolve in a polar substance such as water. These are less common with organic molecules, so will not be described further in this section.

Dipole–Dipole Interactions

Polar covalent bonds behave as if the bonded atoms have localized fractional charges that are equal but opposite (i.e., the two bonded atoms generate a *dipole*). If the structure of a molecule is such that the individual bond dipoles do not cancel one another, then the molecule has a net dipole moment. Molecules with net dipole moments tend to align themselves so that the positive end of one dipole is near the negative end of another and vice versa, as shown in Figure 2.12.1 parts (a and b). Arrangements in which two positive or two negative ends are adjacent (parts (c and d) in Figure 2.12.1) are higher energy as the similar charges would repel one another. Hence dipole–dipole interactions, such as those in parts (a and b) in Figure 2.12.1, are *attractive intermolecular interactions*, whereas those in part (c and d) are *repulsive intermolecular interactions*.

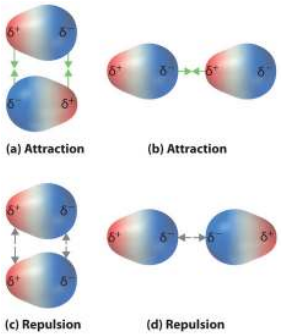


Figure 2.12.1 Attractive and Repulsive Dipole–Dipole Interactions. (a and b) Molecular orientations in which the positive end of one dipole (δ^+) is near the negative end of another (δ^-) (and vice versa) produce attractive interactions. (c and d) Molecular orientations that juxtapose the positive or negative ends of the dipoles on adjacent molecules produce repulsive interactions.

Because molecules in a liquid move freely and continuously, molecules always experience both attractive and repulsive dipole–dipole interactions simultaneously, as shown in Figure 2.12.2. On average, however, the attractive interactions dominate.

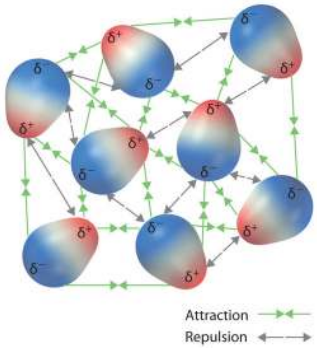
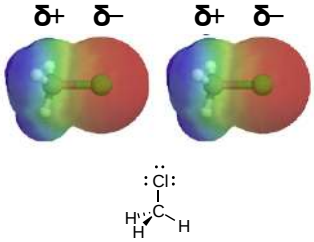


Figure 2.12.2 Both Attractive and Repulsive Dipole–Dipole Interactions Occur in a Liquid Sample with Many Molecules

Chloromethane is an example of a polar molecule. An electrostatic potential map shows a high electron density (seen in red) around the electronegative chlorine giving it a partial negative charge. The other end of the molecule has electron density pulled away from it giving it a partial positive charge seen in blue. The positive and negative ends of different chloromethane molecules are attracted to one another through this electrostatic interaction.



chloromethane
(μ = 1.87 D)

Because each end of a dipole possesses only a fraction of the charge of an electron, dipole–dipole interactions are substantially weaker than the interactions between two ions, each of which has a charge of at least ±1, or between a dipole and an ion, in which one of the species has at least a full positive or negative charge. In addition, the attractive interaction between dipoles falls off

much more rapidly with increasing distance than do ion–ion interactions. Recall that the attractive energy between two ions is proportional to $1/r$, where r is the distance between the ions. Doubling the distance ($r \rightarrow 2r$) decreases the attractive energy by one-half. In contrast, the energy of the interaction of two dipoles is proportional to $1/r^6$, so doubling the distance between the dipoles decreases the strength of the interaction by 2^6, or 64-fold. Thus a substance such as HCl, which is partially held together by dipole–dipole interactions, is a gas at room temperature and 1 atm pressure, whereas NaCl, which is held together by ionic interactions, is a high-melting-point solid. Within a series of compounds of similar molar mass, the strength of the intermolecular interactions increases as the dipole moment of the molecules increases, as shown in Table 2.12.1. Using what we learned about predicting relative bond polarities from the electronegativities of the bonded atoms, we can make educated guesses about the relative boiling points of similar molecules.

Table 2.12.1: Relationships between the Dipole Moment and the Boiling Point for Organic Compounds of Similar Molar Mass

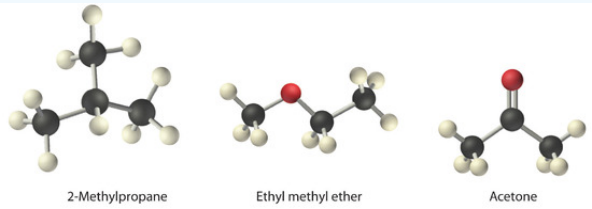
Compound	Molar Mass (g/mol)	Dipole Moment (D)	Boiling Point (K)
C_3H_6 (cyclopropane)	42	0	240
CH_3OCH_3 (dimethyl ether)	46	1.30	248
CH_3CN (acetonitrile)	41	3.9	355

Note

The attractive energy between two ions is proportional to $1/r$, whereas the attractive energy between two dipoles is proportional to $1/r^6$.

Example 2.12.1

Arrange ethyl methyl ether ($CH_3OCH_2CH_3$), 2-methylpropane [isobutane, $(CH_3)_2CHCH_3$], and acetone (CH_3COCH_3) in order of increasing boiling points. Their structures are as follows:



Strategy:

Compare the molar masses and the polarities of the compounds. Compounds with higher molar masses and that are polar will have the highest boiling points.

Solution:

The three compounds have essentially the same molar mass (58–60 g/mol), so we must look at differences in polarity to predict the strength of the intermolecular dipole–dipole interactions and thus the boiling points of the compounds. The first compound, 2-methylpropane, contains only C–H bonds, which are not very polar because C and H have similar electronegativity values. It should therefore have a very small (but nonzero) dipole moment and a very low boiling point. Ethyl methyl ether has a structure similar to H_2O; it contains two polar C–O single bonds oriented at about a 109° angle to each other, in addition to relatively nonpolar C–H bonds. As a result, the C–O bond dipoles partially reinforce one another and generate a significant dipole moment that should give a moderately high boiling point. Acetone contains a polar C=O double bond oriented at about 120° to two methyl groups with nonpolar C–H bonds. The C–O bond dipole therefore corresponds to the molecular dipole, which should result in both a rather large dipole moment and a high boiling point. Thus we predict the following order of boiling points: 2-methylpropane < ethyl methyl ether < acetone. This result is in good agreement with the actual data: 2-methylpropane, boiling point = −11.7°C, and the dipole moment (μ) = 0.13 D; methyl ethyl ether, boiling point = 7.4°C and μ = 1.17 D; acetone, boiling point = 56.1°C and μ = 2.88 D.

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Exercise 1.11.1

Arrange carbon tetrafluoride (CF_4), ethyl methyl sulfide ($CH_3SC_2H_5$), dimethyl sulfoxide [$(CH_3)_2S{=}O$], and 2-methylbutane [isopentane, $(CH_3)_2CHCH_2CH_3$] in order of decreasing boiling points.

Answer

dimethyl sulfoxide (boiling point = 189.9°C) > ethyl methyl sulfide (boiling point = 67°C) > 2-methylbutane (boiling point = 27.8°C) > carbon tetrafluoride (boiling point = −128°C)

London Dispersion Forces

Thus far we have considered only interactions between polar molecules, but other factors must be considered to explain why many nonpolar molecules, such as bromine, benzene, and hexane, are liquids at room temperature, and others, such as iodine and naphthalene, are solids. Even the noble gases can be liquefied or solidified at low temperatures, high pressures, or both.

What kind of attractive forces can exist between nonpolar molecules or atoms? This question was answered by Fritz London (1900–1954), a German physicist who later worked in the United States. In 1930, London proposed that temporary fluctuations in the electron distributions within atoms and nonpolar molecules could result in the formation of short-lived instantaneous dipole moments, which produce attractive forces called London dispersion forces between otherwise nonpolar substances.

Table 2.12.2: Normal Melting and Boiling Points of Some Elements and Nonpolar Compounds

Substance	Molar Mass (g/mol)	Melting Point (°C)	Boiling Point (°C)
Ar	40	−189.4	−185.9
Xe	131	−111.8	−108.1
N_2	28	−210	−195.8
O_2	32	−218.8	−183.0
F_2	38	−219.7	−188.1
I_2	254	113.7	184.4
CH_4	16	−182.5	−161.5

Consider a pair of adjacent He atoms, for example. On average, the two electrons in each He atom are uniformly distributed around the nucleus. Because the electrons are in constant motion, however, their distribution in one atom is likely to be asymmetrical at any given instant, resulting in an instantaneous dipole moment. As shown in part (a) in Figure 2.12.3, the instantaneous dipole moment on one atom can interact with the electrons in an adjacent atom, pulling them toward the positive end of the instantaneous dipole or repelling them from the negative end. The net effect is that the first atom causes the temporary formation of a dipole, called an induced dipole, in the second. Interactions between these temporary dipoles cause atoms to be attracted to one another. These attractive interactions are weak and fall off rapidly with increasing distance. London was able to show with quantum mechanics that the attractive energy between molecules due to temporary dipole–induced dipole interactions falls off as $1/r^6$. Doubling the distance therefore decreases the attractive energy by 2^6, or 64-fold.

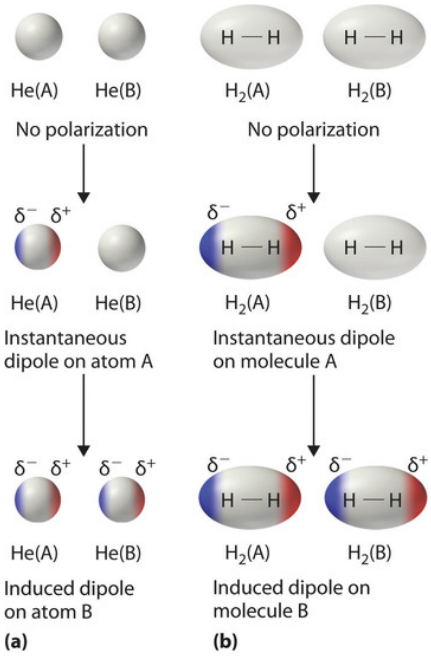


Figure 2.12.3 Instantaneous Dipole Moments. The formation of an instantaneous dipole moment on one He atom (a) or an H_2 molecule (b) results in the formation of an induced dipole on an adjacent atom or molecule.

Instantaneous dipole–induced dipole interactions between nonpolar molecules can produce intermolecular attractions just as they produce interatomic attractions in monatomic substances like Xe. This effect, illustrated for two H_2 molecules in part (b) in Figure 2.12.3, tends to become more pronounced as atomic and molecular masses increase (Table 2.12.3). For example, Xe boils at −108.1°C, whereas He boils at −269°C. The reason for this trend is that the strength of London dispersion forces is related to the ease with which the electron distribution in a given atom can be perturbed. In small atoms such as He, the two 1*s* electrons are held close to the nucleus in a very small volume, and electron–electron repulsions are strong enough to prevent significant asymmetry in their distribution. In larger atoms such as Xe, however, the outer electrons are much less strongly attracted to the nucleus because of filled intervening shells. As a result, it is relatively easy to temporarily deform the electron distribution to generate an instantaneous or induced dipole. The ease of deformation of the electron distribution in an atom or molecule is called its polarizability. Because the electron distribution is more easily perturbed in large, heavy species than in small, light species, we say that heavier substances tend to be much more *polarizable* than lighter ones.

Note

For similar substances, London dispersion forces get stronger with increasing molecular size.

The polarizability of a substance also determines how it interacts with ions and species that possess permanent dipoles. Thus London dispersion forces are responsible for the general trend toward higher boiling points with increased molecular mass and greater surface area in a homologous series of compounds, such as the alkanes (part (a) in Figure 2.12.4). The strengths of London dispersion forces also depend significantly on molecular shape because shape determines how much of one molecule can interact with its neighboring molecules at any given time. For example, part (b) in Figure 2.12.4 shows 2,2-dimethylpropane (neopentane) and *n*-pentane, both of which have the empirical formula C_5H_{12}. Neopentane is almost spherical, with a small surface area for intermolecular interactions, whereas *n*-pentane has an extended conformation that enables it to come into close contact with other *n*-pentane molecules. As a result, the boiling point of neopentane (9.5°C) is more than 25°C lower than the boiling point of *n*-pentane (36.1°C).

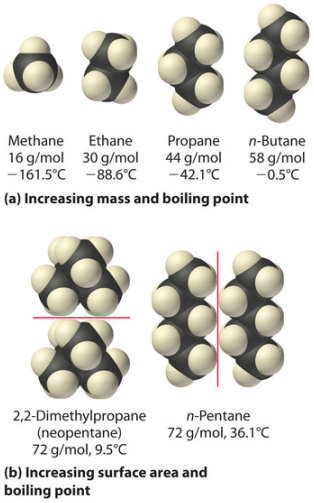


Figure 2.12.4 Mass and Surface Area Affect the Strength of London Dispersion Forces. (a) In this series of four simple alkanes, larger molecules have stronger London forces between them than smaller molecules and consequently higher boiling points. (b) Linear *n*-pentane molecules have a larger surface area and stronger intermolecular forces than spherical neopentane molecules. As a result, neopentane is a gas at room temperature, whereas *n*-pentane is a volatile liquid.

All molecules, whether polar or nonpolar, are attracted to one another by London dispersion forces in addition to any other attractive forces that may be present. In general, however, dipole–dipole interactions in small polar molecules are significantly stronger than London dispersion forces, so the former predominate.

✔ Example 2.12.2

Arrange *n*-butane, propane, 2-methylpropane [isobutane], and *n*-pentane in order of increasing boiling points.

Strategy:

Determine the intermolecular forces in the compounds and then arrange the compounds according to the strength of those forces. The substance with the weakest forces will have the lowest boiling point.

Solution:

The four compounds are alkanes and nonpolar, so London dispersion forces are the only important intermolecular forces. These forces are generally stronger with increasing molecular mass, so propane should have the lowest boiling point and *n*-pentane should have the highest, with the two butane isomers falling in between. Of the two butane isomers, 2-methylpropane is more compact, and *n*-butane has the more extended shape. Consequently, we expect intermolecular interactions for *n*-butane to be stronger due to its larger surface area, resulting in a higher boiling point. The overall order is thus as follows, with actual boiling points in parentheses: propane (−42.1°C) < 2-methylpropane (−11.7°C) < *n*-butane (−0.5°C) < *n*-pentane (36.1°C).

Exercise 1.11.2

Arrange GeH_4, $SiCl_4$, SiH_4, CH_4, and $GeCl_4$ in order of decreasing boiling points.

Answer

$GeCl_4$ (87°C) > $SiCl_4$ (57.6°C) > GeH_4 (−88.5°C) > SiH_4 (−111.8°C) > CH_4 (−161°C)

Hydrogen Bonds

Molecules with hydrogen atoms bonded to electronegative atoms such as O, N, and F (and to a much lesser extent Cl and S) tend to exhibit unusually strong intermolecular interactions. These result in much higher boiling points than are observed for substances in which London dispersion forces dominate, as illustrated for the covalent hydrides of elements of groups 14–17 in Figure 2.12.5. Methane and its heavier congeners in group 14 form a series whose boiling points increase smoothly with increasing molar mass. This is the expected trend in nonpolar molecules, for which London dispersion forces are the exclusive intermolecular forces. In contrast, the hydrides of the lightest members of groups 15–17 have boiling points that are more than 100°C greater than predicted

on the basis of their molar masses. The effect is most dramatic for water: if we extend the straight line connecting the points for H_2Te and H_2Se to the line for period 2, we obtain an estimated boiling point of −130°C for water! Imagine the implications for life on Earth if water boiled at −130°C rather than 100°C.

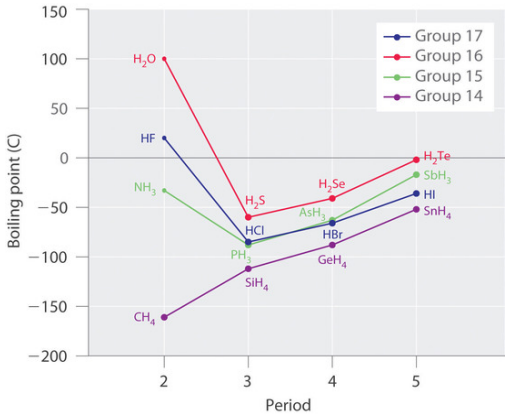


Figure 2.12.5: The Effects of Hydrogen Bonding on Boiling Points. These plots of the boiling points of the covalent hydrides of the elements of groups 14–17 show that the boiling points of the lightest members of each series for which hydrogen bonding is possible (HF, NH_3, and H_2O) are anomalously high for compounds with such low molecular masses.

Why do strong intermolecular forces produce such anomalously high boiling points and other unusual properties, such as high enthalpies of vaporization and high melting points? The answer lies in the highly polar nature of the bonds between hydrogen and very electronegative elements such as O, N, and F. The large difference in electronegativity results in a large partial positive charge on hydrogen and a correspondingly large partial negative charge on the O, N, or F atom. Consequently, H–O, H–N, and H–F bonds have very large bond dipoles that can interact strongly with one another. Because a hydrogen atom is so small, these dipoles can also approach one another more closely than most other dipoles. The combination of large bond dipoles and short dipole–dipole distances results in very strong dipole–dipole interactions called hydrogen bonds, as shown for ice in Figure 2.12.6.

A hydrogen bond is usually indicated by a dotted line between the hydrogen atom attached to O, N, or F (the *hydrogen bond donor*) and the atom that has the lone pair of electrons (the *hydrogen bond acceptor*). Because each water molecule contains two hydrogen atoms and two lone pairs, a tetrahedral arrangement maximizes the number of hydrogen bonds that can be formed. In the structure of ice, each oxygen atom is surrounded by a distorted tetrahedron of hydrogen atoms that form bridges to the oxygen atoms of adjacent water molecules. The bridging hydrogen atoms are *not* equidistant from the two oxygen atoms they connect, however. Instead, each hydrogen atom is 101 pm from one oxygen and 174 pm from the other. In contrast, each oxygen atom is bonded to two H atoms at the shorter distance and two at the longer distance, corresponding to two O–H covalent bonds and two O···H hydrogen bonds from adjacent water molecules, respectively. The resulting open, cagelike structure of ice means that the solid is actually slightly less dense than the liquid, which explains why ice floats on water rather than sinks.

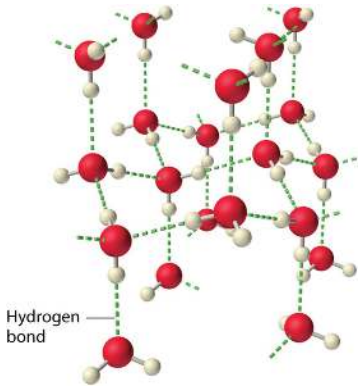


Figure 2.12.6: The Hydrogen-Bonded Structure of Ice

Each water molecule accepts two hydrogen bonds from two other water molecules and donates two hydrogen atoms to form hydrogen bonds with two more water molecules, producing an open, cage-like structure. The structure of liquid water is very similar, but in the liquid, the hydrogen bonds are continually broken and formed because of rapid molecular motion.

Note

Hydrogen bond formation requires *both* a hydrogen bond donor *and* a hydrogen bond acceptor.

Because ice is less dense than liquid water, rivers, lakes, and oceans freeze from the top down. In fact, the ice forms a protective surface layer that insulates the rest of the water, allowing fish and other organisms to survive in the lower levels of a frozen lake or sea. If ice were denser than the liquid, the ice formed at the surface in cold weather would sink as fast as it formed. Bodies of water would freeze from the bottom up, which would be lethal for most aquatic creatures. The expansion of water when freezing also explains why automobile or boat engines must be protected by “antifreeze” and why unprotected pipes in houses break if they are allowed to freeze.

Although hydrogen bonds are significantly weaker than covalent bonds, with typical dissociation energies of only 15–25 kJ/mol, they have a significant influence on the physical properties of a compound. Compounds such as HF can form only two hydrogen bonds at a time as can, on average, pure liquid NH_3. Consequently, even though their molecular masses are similar to that of water, their boiling points are significantly lower than the boiling point of water, which forms *four* hydrogen bonds at a time.

Example 2.12.3

Considering CH_3OH, C_2H_6, Xe, and $(CH_3)_3N$, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

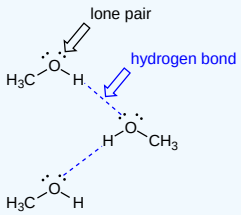
Strategy:

A. Identify the compounds with a hydrogen atom attached to O, N, or F. These are likely to be able to act as hydrogen bond donors.
B. Of the compounds that can act as hydrogen bond donors, identify those that also contain lone pairs of electrons, which allow them to be hydrogen bond acceptors. If a substance is both a hydrogen donor and a hydrogen bond acceptor, draw a structure showing the hydrogen bonding.

Solution:

A Of the species listed, xenon (Xe), ethane (C_2H_6), and trimethylamine [$(CH_3)_3N$] do not contain a hydrogen atom attached to O, N, or F; hence they cannot act as hydrogen bond donors.

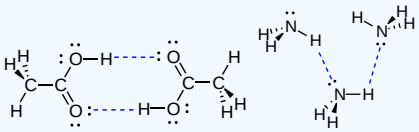
B The one compound that can act as a hydrogen bond donor, methanol (CH_3OH), contains both a hydrogen atom attached to O (making it a hydrogen bond donor) and two lone pairs of electrons on O (making it a hydrogen bond acceptor); methanol can thus form hydrogen bonds by acting as either a hydrogen bond donor or a hydrogen bond acceptor. The hydrogen-bonded structure of methanol is as follows:



Exercise 2.12.3

Considering CH_3CO_2H, $(CH_3)_3N$, NH_3, and CH_3F, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

Answer: CH_3CO_2H and NH_3;



Example 2.12.4

Arrange C_{60} (buckminsterfullerene, which has a cage structure), NaCl, He, Ar, and N_2O in order of increasing boiling points.

Given: compounds

Asked for: order of increasing boiling points

Strategy:

Identify the intermolecular forces in each compound and then arrange the compounds according to the strength of those forces. The substance with the weakest forces will have the lowest boiling point.

Solution:

Electrostatic interactions are strongest for an ionic compound, so we expect NaCl to have the highest boiling point. To predict the relative boiling points of the other compounds, we must consider their polarity (for dipole–dipole interactions), their ability to form hydrogen bonds, and their molar mass (for London dispersion forces). Helium is nonpolar and by far the lightest, so it should have the lowest boiling point. Argon and N_2O have very similar molar masses (40 and 44 g/mol, respectively), but N_2O is polar while Ar is not. Consequently, N_2O should have a higher boiling point. A C_{60} molecule is nonpolar, but its molar mass is 720 g/mol, much greater than that of Ar or N_2O. Because the boiling points of nonpolar substances increase rapidly with molecular mass, C_{60} should boil at a higher temperature than the other nonionic substances. The predicted order is thus as follows, with actual boiling points in parentheses: He (−269°C) < Ar (−185.7°C) < N_2O (−88.5°C) < C_{60} (>280°C) < NaCl (1465°C).

Exercise 2.12.4

Arrange 2,4-dimethylheptane, Ne, CS_2, Cl_2, and KBr in order of decreasing boiling points.

Answer: KBr (1435°C) > 2,4-dimethylheptane (132.9°C) > CS_2 (46.6°C) > Cl_2 (−34.6°C) > Ne (−246°C)

Summary

Molecules in liquids are held to other molecules by intermolecular interactions, which are weaker than the intramolecular interactions that hold the atoms together within molecules and polyatomic ions. Transitions between the solid and liquid or the liquid and gas phases are due to changes in intermolecular interactions but do not affect intramolecular interactions. The three major types of intermolecular interactions are dipole–dipole interactions, London dispersion forces (these two are often referred to collectively as **van der Waals forces**), and hydrogen bonds. **Dipole–dipole interactions** arise from the electrostatic interactions of the positive and negative ends of molecules with permanent dipole moments; their strength is proportional to the magnitude of the dipole moment and to $1/r^6$, where r is the distance between dipoles. **London dispersion forces** are due to the formation of **instantaneous dipole moments** in polar or nonpolar molecules as a result of short-lived fluctuations of electron charge distribution, which in turn cause the temporary formation of an **induced dipole** in adjacent molecules. Like dipole–dipole interactions, their energy falls off as $1/r^6$. Larger atoms tend to be more **polarizable** than smaller ones because their outer electrons are less tightly bound and are therefore more easily perturbed. **Hydrogen bonds** are especially strong dipole–dipole interactions between molecules that have hydrogen bonded to a highly electronegative atom, such as O, N, or F. The resulting partially positively charged H atom on one molecule (the *hydrogen bond donor*) can interact strongly with a lone pair of electrons of a partially negatively charged O, N, or F atom on adjacent molecules (the *hydrogen bond acceptor*). Because of strong O···Hhydrogen bonding between water molecules, water has an unusually high boiling point, and ice has an open, cagelike structure that is less dense than liquid water.

Key Takeaway

- Intermolecular forces are electrostatic in nature and include van der Waals forces and hydrogen bonds.

Problems

1. Which are stronger—dipole–dipole interactions or London dispersion forces? Which are likely to be more important in a molecule with heavy atoms? Explain your answers.

2. Liquid water is essential for life as we know it, but based on its molecular mass, water should be a gas under standard conditions. Why is water a liquid rather than a gas under standard conditions?
3. Why are intermolecular interactions more important for liquids and solids than for gases? Under what conditions must these interactions be considered for gases?
4. In group 17, elemental fluorine and chlorine are gases, whereas bromine is a liquid and iodine is a solid. Why?
5. Identify the most important intermolecular interaction in each of the following.
   a) SO_2
   b) HF
   c) CO_2
   d) CCl_4
   e) CH_2Cl_2
6. Both water and methanol have anomalously high boiling points due to hydrogen bonding, but the boiling point of water is greater than that of methanol despite its lower molecular mass. Why? Draw the structures of these two compounds, including any lone pairs, and indicate potential hydrogen bonds.
7. Do you expect the boiling point of H_2S to be higher or lower than that of H_2O? Justify your answer.
8. Some recipes call for vigorous boiling, while others call for gentle simmering. What is the difference in the temperature of the cooking liquid between boiling and simmering? What is the difference in energy input?

Solutions

1. Dipole-Diple interactions are stronger because molecules polarity is permanent. Molecules involved in London dispersion forces are only temporarily polar

2. Water is a liquid under standard conditions because of its unique ability to form four strong hydrogen bonds per molecule.

3. In solids and liquids the molecules are in direct contact. In gases the molecules only contact during collisions. Intermolecules forces become inmportant when gases are cooled to the point where they form a liquid. 4. As the atomic mass of the halogens increases, so does the number of electrons and the average distance of those electrons from the nucleus. Larger atoms with more electrons are more easily polarized than smaller atoms, and the increase in polarizability with atomic number increases the strength of London dispersion forces. These intermolecular interactions are strong enough to favor the condensed states for bromine and iodine under normal conditions of temperature and pressure. 5. a) The V-shaped SO2 molecule has a large dipole moment due to the polar S=O bonds, so dipole–dipole interactions will be most important.

b) The H–F bond is highly polar, and the fluorine atom has three lone pairs of electrons to act as hydrogen bond acceptors; hydrogen bonding will be most important.

c) Although the C=O bonds are polar, this linear molecule has no net dipole moment; hence, London dispersion forces are most important.

d) This is a symmetrical molecule that has no net dipole moment, and the Cl atoms are relatively polarizable; thus, London dispersion forces will dominate.

e) This molecule has a small dipole moment, as well as polarizable Cl atoms. In such a case, dipole–dipole interactions and London dispersion forces are often comparable in magnitude.

6) Water has two polar O–H bonds with H atoms that can act as hydrogen bond donors, plus two lone pairs of electrons that can act as hydrogen bond acceptors, giving a net of four hydrogen bonds per H2O molecule. Although methanol also has two lone pairs of electrons on oxygen that can act as hydrogen bond acceptors, it only has one O–H bond with an H atom that can act as a hydrogen bond donor. Consequently, methanol can only form two hydrogen bonds per molecule on average, versus four for water. Hydrogen bonding therefore has a much greater effect on the boiling point of water.

7) H2O would have the higher boiling point because it can form the stronger hydrogen bonding intermolecular force. 8) Vigorous boiling causes more water molecule to escape into the vapor phase, but does not affect the temperature of the liquid. Vigorous boiling requires a higher energy input than does gentle simmering.

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CHAPTER OVERVIEW

2: Organic Compounds- Alkanes and Their Stereochemistry

This chapter begins with an introduction to the concept of the functional group, a concept that facilitates the systematic study of organic chemistry. Next, we introduce the fundamentals of organic nomenclature (i.e., the naming of organic chemicals) through examination of the alkane family of compounds. We then discuss, briefly, the occurrence and properties of alkanes, and end with a description of *cis-trans* isomerism in cycloalkanes.

2.1: Functional Groups
2.2: Alkanes and Alkane Isomers
2.3: Alkyl Groups
2.4: Naming Alkanes
2.5: Properties of Alkanes
2.6: Conformations of Ethane
2.7: Conformations of Other Alkanes
2.8: Gasoline - A Deeper Look
2.S: Organic Compounds- Alkanes and Their Stereochemistry (Summary)

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2.1: Functional Groups

Objectives

After completing this section, you should be able to

1. explain why the properties of a given organic compound are largely dependent on the functional group or groups present in the compound.
2. identify the functional groups present in each of the following compound types: alkenes, alkynes, arenes, (alkyl and aryl) halides, alcohols, ethers, aldehydes, ketones, esters, carboxylic acids, (carboxylic) acid chlorides, amides, amines, nitriles, nitro compounds, sulfides and sulfoxides.
3. identify the functional groups present in an organic compound, given its structure.
4. given the structure of an organic compound containing a single functional group, identify which of the compound types listed under Objective 2, above, it belongs to.
5. draw the structure of a simple example of each of the compound types listed in Objective 2.

Key Terms

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

- functional group

Study Notes

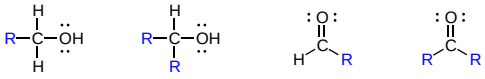
The concept of functional groups is a very important one. We expect that you will need to refer back to tables at the end of Section 3.1 quite frequently at first, as it is not really feasible to learn the names and structures of all the functional groups and compound types at one sitting. Gradually they will become familiar, and eventually you will recognize them automatically.

Functional groups are small groups of atoms that exhibit a characteristic reactivity. A particular functional group will almost always display its distinctive chemical behavior when it is present in a compound. Because of their importance in understanding organic chemistry, functional groups have specific names that often carry over in the naming of individual compounds incorporating the groups.

As we progress in our study of organic chemistry, it will become extremely important to be able to quickly recognize the most common functional groups, because they are the key structural elements that define how organic molecules react. For now, we will only worry about drawing and recognizing each functional group, as depicted by Lewis and line structures. Much of the remainder of your study of organic chemistry will be taken up with learning about how the different functional groups tend to behave in organic reactions.

Drawing abbreviated organic structures

Often when drawing organic structures, chemists find it convenient to use the letter 'R' to designate part of a molecule outside of the region of interest. If we just want to refer in general to a functional group without drawing a specific molecule, for example, we can use 'R groups' to focus attention on the group of interest:



The 'R' group is a convenient way to abbreviate the structures of large biological molecules, especially when we are interested in something that is occurring specifically at one location on the molecule.

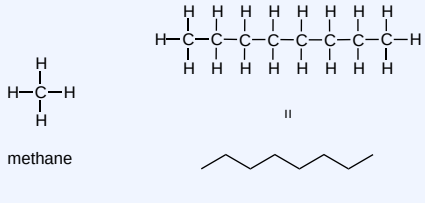
Common Functional Groups

In the following sections, many of the common functional groups found in organic chemistry will be described. Tables of these functional groups can be found at the bottom of the page.

Hydrocarbons

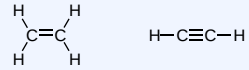
The simplest functional group in organic chemistry (which is often ignored when listing functional groups) is called an **alkane**, characterized by single bonds between two carbons and between carbon and hydrogen. Some examples of alkanes include methane, CH_4, is the natural gas you may burn in your furnace or on a stove. Octane, C_8H_{18}, is a component of gasoline.

Alkanes

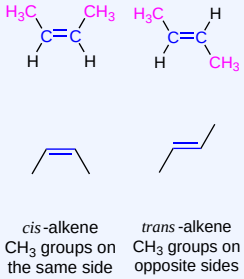


Alkenes (sometimes called **olefins**) have carbon-carbon double bonds, and **alkynes** have carbon-carbon triple bonds. Ethene, the simplest alkene example, is a gas that serves as a cellular signal in fruits to stimulate ripening. (If you want bananas to ripen quickly, put them in a paper bag along with an apple - the apple emits ethene gas, setting off the ripening process in the bananas). Ethyne, commonly called acetylene, is used as a fuel in welding blow torches.

Alkenes and alkynes



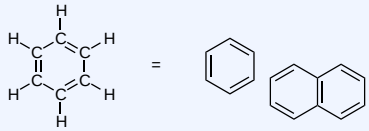
Alkenes have trigonal planar electron geometry (due to sp^2 hybrid orbitals at the alkene carbons) while alkynes have linear geometry (due to sp hybrid orbitals at the alkyne carbons). Furthermore, many alkenes can take two geometric forms: ***cis*** or ***trans*** *(or Z and E which will be explained in detail in Chapter 7)*. The *cis* and *trans* forms of a given alkene are different molecules with different physical properties there is a very high energy barrier to rotation about a double bond. In the example below, the difference between *cis* and *trans* alkenes is readily apparent.



Alkanes, alkenes, and alkynes are all classified as **hydrocarbons**, because they are composed solely of carbon and hydrogen atoms. Alkanes are said to be **saturated hydrocarbons**, because the carbons are bonded to the maximum possible number of hydrogens - in other words, they are *saturated* with hydrogen atoms. The double and triple-bonded carbons in alkenes and alkynes have fewer hydrogen atoms bonded to them - they are thus referred to as **unsaturated hydrocarbons**. As we will see in Chapter 7, hydrogen can be added to double and triple bonds, in a type of reaction called 'hydrogenation'.

The **aromatic** group is exemplified by benzene (which used to be a commonly used solvent on the organic lab, but which was shown to be carcinogenic), and naphthalene, a compound with a distinctive 'mothball' smell. Aromatic groups are planar (flat) ring structures, and are widespread in nature. We will learn more about the structure and reactions of aromatic groups in Chapter 15.

Aromatics

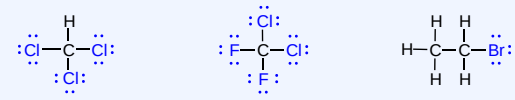


benzene naphthalene

Functional Groups with Carbon Single Bonds to other Atoms

Halides

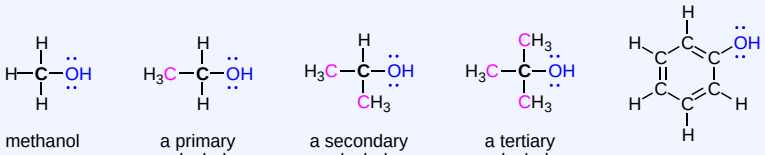
When the carbon of an alkane is bonded to one or more halogens, the group is referred to as a **alkyl halide** or **haloalkane**. The presence of a halogen atom (F, Cl, Br, or I), is often represented by X due to the similar chemistry of halogens. Chloroform is a useful solvent in the laboratory, and was one of the earlier anesthetic drugs used in surgery. Chlorodifluoromethane was used as a refrigerant and in aerosol sprays until the late twentieth century, but its use was discontinued after it was found to have harmful effects on the ozone layer. Bromoethane is a simple alkyl halide often used in organic synthesis. Alkyl halides groups are quite rare in biomolecules.



trichloromethane (chloroform) dichlorodifluoromethane (Freon-12) bromoethane

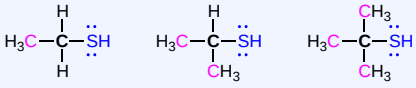
Alcohols and Thiols

In the **alcohol** functional group, a carbon is single-bonded to an OH group (the OH group, by itself, is referred to as a **hydroxyl**). Except for methanol, all alcohols can be classified as primary, secondary, or tertiary. In a **primary alcohol**, the carbon bonded to the OH group is also bonded to only one other carbon. In a **secondary alcohol** and **tertiary alcohol,** the carbon is bonded to two or three other carbons, respectively. When the hydroxyl group is *directly* attached to an aromatic ring, the resulting group is called a **phenol**.



methanol a primary alcohol a secondary alcohol a tertiary alcohol a phenol

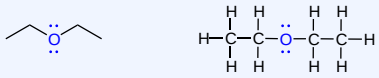
The sulfur analog of an alcohol is called a **thiol** (the prefix *thio*, derived from the Greek, refers to sulfur).



a primary thiol a secondary thiol a tertiary thiol

Ethers and sulfides

In an **ether** functional group, a central oxygen is bonded to two carbons. Below are the line and Lewis structures of diethyl ether, a common laboratory solvent and also one of the first medical anaesthesia agents.

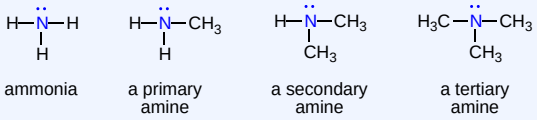


In **sulfides**, the oxygen atom of an ether has been replaced by a sulfur atom.

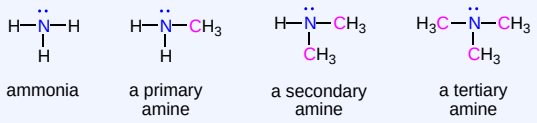


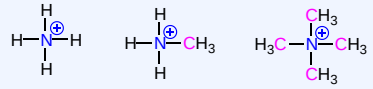
Amines

Amines are characterized by nitrogen atoms with single bonds to hydrogen and carbon. Just as there are primary, secondary, and tertiary alcohols, there are primary, secondary, and tertiary amines. Ammonia is a special case with no carbon atoms.

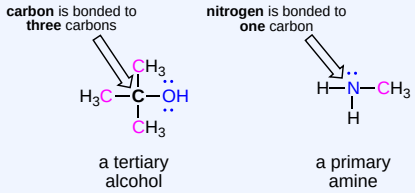


One of the most important properties of amines is that they are basic, and are readily protonated to form **ammonium** cations. In the case where a nitrogen has four bonds to carbon (which is somewhat unusual in biomolecules), it is called a quaternary ammonium ion.





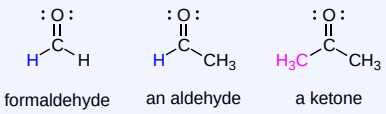
Note: Do not be confused by how the terms 'primary', 'secondary', and 'tertiary' are applied to alcohols and amines - the definitions are different. In alcohols, what matters is how many other carbons the alcohol *carbon* is bonded to, while in amines, what matters is how many carbons the *nitrogen* is bonded to.



Carbonyl Containing Functional Groups

Aldehydes and Ketones

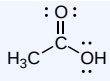
There are a number of functional groups that contain a carbon-oxygen double bond, which is commonly referred to as a **carbonyl**. **Ketones** and **aldehydes** are two closely related carbonyl-based functional groups that react in very similar ways. In a ketone, the carbon atom of a carbonyl is bonded to two other carbons. In an aldehyde, the carbonyl carbon is bonded on one side to a hydrogen, and on the other side to a carbon. The exception to this definition is formaldehyde, in which the carbonyl carbon has bonds to two hydrogens.



Carboxylic acids and acid derivatives

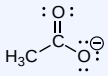
If a carbonyl carbon is bonded on one side to a carbon (or hydrogen) and on the other side to a **heteroatom** (in organic chemistry, this term generally refers to oxygen, nitrogen, sulfur, or one of the halogens), the functional group is considered to be one of the **'carboxylic acid derivatives'**, a designation that describes a grouping of several functional groups. The eponymous member of this grouping is the **carboxylic acid** functional group, in which the carbonyl is bonded to a hydroxyl (OH) group.


formic acid

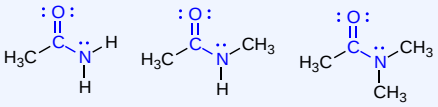

acetic acid
(vinegar)

As the name implies, carboxylic acids are acidic, meaning that they are readily deprotonated to form the conjugate base form, called a **carboxylate** (much more about carboxylic acids in Chapter 20).

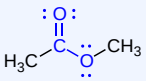

formate

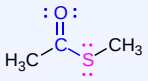

acetate

In **amides**, the carbonyl carbon is bonded to a nitrogen. The nitrogen in an amide can be bonded either to hydrogens, to carbons, or to both. Another way of thinking of an amide is that it is a carbonyl bonded to an amine.

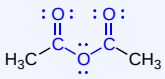


In **esters**, the carbonyl carbon is bonded to an oxygen which is itself bonded to another carbon. Another way of thinking of an ester is that it is a carbonyl bonded to an alcohol. **Thioesters** are similar to esters, except a sulfur is in place of the oxygen.

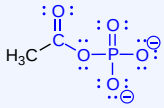

an ester

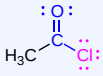

a thioester

In an **acid anhydride**, there are two carbonyl carbons with an oxygen in between. An acid anhydride is formed from combination of two carboxylic acids with the loss of water (anhydride).


an anhydride

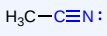
In an **acyl phosphate**, the carbonyl carbon is bonded to the oxygen of a phosphate, and in an **acid chloride**, the carbonyl carbon is bonded to a chlorine.


an acyl
phosphate


an acid
chloride

Nitriles and Imines

In a **nitrile** group, a carbon is triple-bonded to a nitrogen. Nitriles are also often referred to as **cyano** groups.

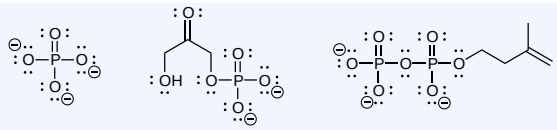

a nitrile

Molecules with carbon-nitrogen double bonds are called **imines**, or **Schiff bases**.


imines

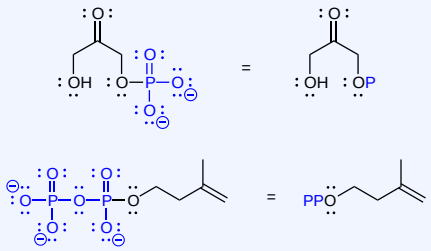
Phosphates

Phosphorus is a very important element in biological organic chemistry, and is found as the central atom in the **phosphate** group. Many biological organic molecules contain phosphate, diphosphate, and triphosphate groups, which are linked to a carbon atom by the **phosphate ester** functionality.



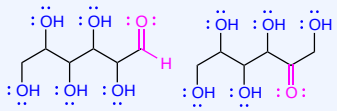
inorganic phosphate | an organic phosphate ester | an organic diphosphate ester

Because phosphates are so abundant in biological organic chemistry, it is convenient to depict them with the abbreviation 'P'. Notice that this 'P' abbreviation includes the oxygen atoms and negative charges associated with the phosphate groups.



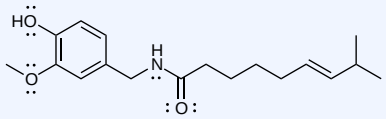
Molecules with Multiple Functional Groups

A single compound may contain several different functional groups. The six-carbon sugar molecules glucose and fructose, for example, contain aldehyde and ketone groups, respectively, and both contain five alcohol groups (a compound with several alcohol groups is often referred to as a '**polyol**').



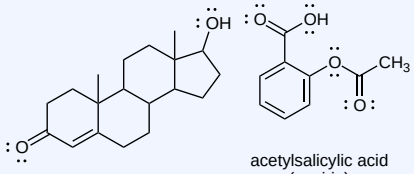
glucose | fructose

Capsaicin, the compound responsible for the heat in hot peppers, contains phenol, ether, amide, and alkene functional groups.



capsaicin

The male sex hormone testosterone contains ketone, alkene, and secondary alcohol groups, while acetylsalicylic acid (aspirin) contains aromatic, carboxylic acid, and ester groups.

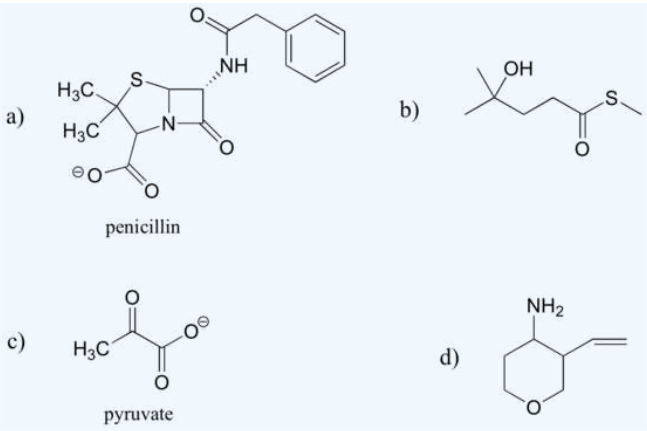


testosterone | acetylsalicylic acid (aspirin)

While not in any way a complete list, this section has covered most of the important functional groups that we will encounter in biological and laboratory organic chemistry. The table found below provides a summary of all of the groups listed in this section, plus a few more that will be introduced later in the text.

Exercise 2.1.1

Identify the functional groups in the following organic compounds. State whether alcohols and amines are primary, secondary, or tertiary.



Answer

a) carboxylate, sulfide, aromatic, two amide groups (one of which is cyclic)

b) tertiary alcohol, thioester

c) carboxylate, ketone

d) ether, primary amine, alkene

2: Draw one example each (there are many possible correct answers) of compounds fitting the descriptions below, using line structures. Be sure to designate the location of all non-zero formal charges. All atoms should have complete octets (phosphorus may exceed the octet rule).

a) a compound with molecular formula $C_6H_{11}NO$ that includes alkene, secondary amine, and primary alcohol functional groups

b) an ion with molecular formula $C_3H_5O_6P^{2-}$ that includes aldehyde, secondary alcohol, and phosphate functional groups.

c) A compound with molecular formula C_6H_9NO that has an amide functional group, and does *not* have an alkene group.

Functional Group Tables

Exclusively Carbon Functional Groups

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	alkene	$H_2C{=}CH_2$	ethene	ethylene
	alkyne	$HC{\equiv}CH$	ethyne	acetylene
	arene	C_6H_6	benzene	benzene

Functional Groups with Single Bonds to Heteroatoms

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	halide	H_3C-I	iodomethane	methyl iodide
	alcohol	CH_3CH_2OH	ethanol	ethyl alcohol
	ether	$CH_3CH_2OCH_2CH_3$	diethyl ether	ether

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	amine	$H_3C\text{-}NH_2$	aminomethane	methylamine
	nitro compound	$H_3C\text{-}NO_2$	nitromethane	
	thiol	$H_3C\text{-}SH$	methanethiol	methyl mercaptan
	sulfide	$H_3C\text{-}S\text{-}CH_3$	dimethyl sulfide	

Functional Groups with Multiple Bonds to Heteroatoms

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	nitrile	$H_3C\text{-}CN$	ethanenitrile	acetonitrile
	aldehyde	H_3CCHO	ethanal	acetaldehyde
	ketone	H_3CCOCH_3	propanone	acetone
	carboxylic acid	H_3CCO_2H	ethanoic Acid	acetic acid
	ester	$H_3CCO_2CH_2CH_3$	ethyl ethanoate	ethyl acetate
	acid halide	H_3CCOCl	ethanoyl chloride	acetyl chloride
	amide	$H_3CCON(CH_3)_2$	N,N-dimethylethanamide	N,N-dimethylacetamide
	acid Anhydride	$(H_3CCO)_2O$	ethanoic anhydride	acetic anhydride

Exercises

3.1 Functional Groups

3.1 Exercises

Questions

Q3.1.1

The following is the molecule for ATP, or the molecule responsible for energy in human cells. Identify the functional groups for ATP.



Solutions

S3.1.1



Contributors and Attributions

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2.2: Alkanes and Alkane Isomers

Objectives

After completing this section, you should be able to

1. draw the Kekulé structure, condensed structure and shorthand structure of each of the first ten straight-chain alkanes.
2. name each of the first ten straight-chain alkanes, given its molecular formula, Kekulé structure, condensed structure or shorthand structure.
3. explain the difference in structure between a straight- and a branched-chain alkane, and illustrate the difference using a suitable example.
4. explain why the number of possible isomers for a given molecular formula increases as the number of carbon atoms increases.
5. draw all the possible isomers that correspond to a given molecular formula of the type $C_n H_{2n+2}$, where *n* is ≤ 7.

Key Terms

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

- branched-chain alkane
- constitutional or structural isomer
- homologous series
- isomer
- saturated hydrocarbon
- straight-chain alkane (or normal alkane)

Study Notes

A series of compounds in which successive members differ from one another by a CH_2 unit is called a homologous series. Thus, the series CH_4, C_2H_6, C_3H_8 . . . C_nH_{2n+2}, is an example of a homologous series.

It is important that you commit to memory the names of the first 10 straight-chain alkanes (i.e., from CH_4 to $C_{10}H_{22}$). You will use these names repeatedly when you begin to learn how to derive the systematic names of a large variety of organic compounds. You need not remember the number of isomers possible for alkanes containing more than seven carbon atoms. Such information is available in reference books when it is needed. When drawing isomers, be careful not to deceive yourself into thinking that you can draw more isomers than you are supposed to be able to. Remember that it is possible to draw each isomer in several different ways and you may inadvertently count the same isomer more than once.

Alkanes are organic compounds that consist entirely of single-bonded carbon and hydrogen atoms and lack any other functional groups. Alkanes are often called saturated hydrocarbons because they have the maximum possible number of hydrogens per carbon. In Section 1.7, thealkane molecule, ethane, was shown to contain a C-C sigma bond. By adding more C-C sigma bond larger and more complexed alkanes can be formed. Methane (CH_4), ethane (C_2H_6), and propane (C_3H_8) are the beginning of a series of compounds in which any two members in a sequence differ by one carbon atom and two hydrogen atoms—namely, a CH_2 unit. Any family of compounds in which adjacent members differ from each other by a definite factor (here a CH_2 group) is called a homologous series. The members of such a series, called *homologs*, have properties that vary in a regular and predictable manner.

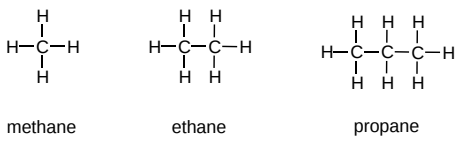


Figure 25.3.1 : The Three Simplest Alkanes

Methane (CH_4), ethane (C_2H_6), and propane (C_3H_8) are the beginning of a series of compounds in which any two members in a sequence differ by one carbon atom and two hydrogen atoms—namely, a CH_2 unit. Consider the series in Figure 25.3.3. The sequence starts with C_3H_8, and a CH_2 unit is added in each step moving up the series. Any family of compounds in which adjacent

members differ from each other by a definite factor (here a CH_2 group) is called a homologous series. The members of such a series, called *homologs*, have properties that vary in a regular and predictable manner.

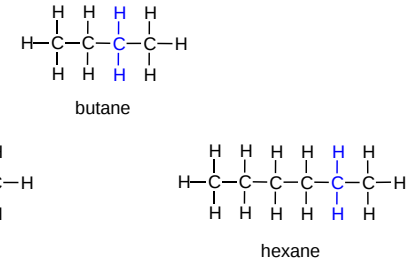


Figure 25.3.2: Members of a Homologous Series. Each succeeding formula incorporates one carbon atom and two hydrogen atoms more than the previous formula.

The homologous series allows us to write a general formula for alkanes: $C_nH_{2n\,+\,2}$. Using this formula, we can write a molecular formula for any alkane with a given number of carbon atoms. For example, an alkane with eight carbon atoms has the molecular formula $C_8H_{(2\,\times\,8)\,+\,2} = C_8H_{18}$.

Molecular Formulas

Alkanes are the simplest family of hydrocarbons - compounds containing carbon and hydrogen only. Alkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds. The first six alkanes are as follows:

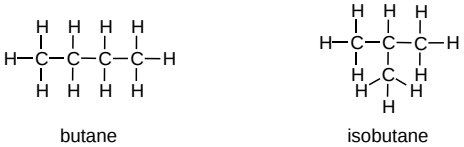
Table 2.2.1: Molecular formulas for small alkanes

methane	CH_4
ethane	C_2H_6
propane	C_3H_8
butane	C_4H_{10}
pentane	C_5H_{12}
hexane	C_6H_{14}

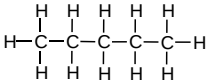
You can work out the formula of any of the alkanes using the general formula C_nH_{2n+2}

Isomerism

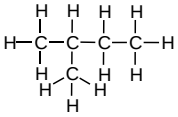
All of the alkanes containing 4 or more carbon atoms show structural isomerism, meaning that there are two or more different structural formulas that you can draw for each molecular formula. Isomers (from the Greek *isos* + *meros*, meaning "made of the same parts") are molecules that have the same molecular formula, but have a different arrangement of the atoms in space. Alkanes with 1-3 carbons, methane (CH_4), ethane (C_2H_6), and propane (C_3H_8,) do not exist in isomeric forms because there is only one way to arrange the atoms in each formula so that each carbon atom has four bonds. However, C_4H_{10}, has more than possible structure. The four carbons can be drawn in a row to form butane or the can branch to form isobutane. The two compounds have different properties—for example, butane boils at −0.5°C, while isobutane boils at −11.7°C.



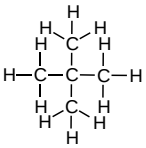
Likewise the molecular formula: C_5H_{12} has three possible isomer. The compound at the far left is pentane because it has all five carbon atoms in a continuous chain. The compound in the middle is isopentane; like isobutane, it has a one CH_3 branch off the second carbon atom of the continuous chain. The compound at the far right, discovered after the other two, was named neopentane (from the Greek *neos*, meaning “new”). Although all three have the same molecular formula, they have different properties, including boiling points: pentane, 36.1°C; isopentane, 27.7°C; and neopentane, 9.5°C.



pentane



isopentane



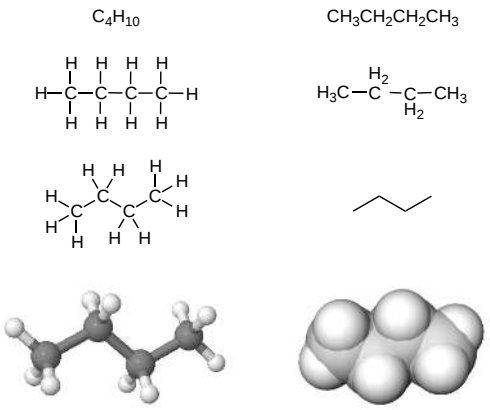
neopentane

Of the structures show above, butane and pentane are called **normal alkanes** or **straight-chain alkanes**, indicating that all contain a single continuous chain of carbon atoms and can be represented by a projection formula whose carbon atoms are in a straight line. The other structures, isobutane, isopentane, and neopentane are called called branched-chain alkanes. As the number of carbons in an akane increases the number of possible isomers also increases as shown in the table below.

Table 2.2.2: Number of isomers for hydrocarbons

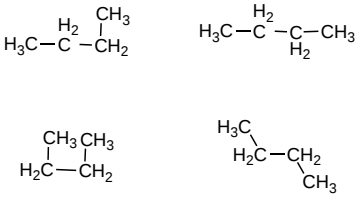
Molecular Formula	Number of Structural Isomers
CH_4	1
C_2H_6	1
C_3H_8	1
C_4H_{10}	2
C_5H_{12}	3
C_6H_{14}	5
C_7H_{16}	9
C_8H_{18}	18
C_9H_{20}	35
$C_{10}H_{22}$	75
$C_{14}H_{30}$	1858
$C_{18}H_{38}$	60,523
$C_{30}H_{62}$	4,111,846,763

Akanes can be represented in many different ways. The figure below shows some of the different ways straight-chain butane can be represented. Most often chemists refer to butane by the condensed structure $CH_3CH_2CH_2CH_3$ or *n*-C_4H_{10} where n denotes a normal straight alkane.



Note that many of these structures only imply bonding connections and do not indicate any particular geometry. The bottom two structures, referred to as "ball and stick" and "space filling" do show 3D geometry for butane. Because the four-carbon chain in butane may be bent in various ways the groups can rotate freely about the C–C bonds. However, this rotation does not change the

identity of the compound. It is important to realize that bending a chain does *not* change the identity of the compound; all of the following represent the same compound, butane:



The nomenclature of straight alkanes is based on the number of carbon atoms they contain. The number of carbons are indicated by a prefix and the suffix -ane is added to indicate the molecules is an alkane. The prefix for three carbons is prop so adding -ane, the IUPAC name for C_3H_8 is propane. Likewise, the prefix for six is hex so the name for the straight chain isomer of C_6H_{14} is called hexane. The first ten prefixes should be memorized, because these alkane names from the basis for naming many other organic compounds.

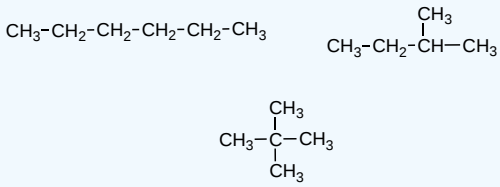
9.2.1" role="presentation" style="position:relative;" tabindex="0">

Table 2.2.3: The First 10 Straight-Chain Alkanes

Molecular Formula	Prefix	Condensed Structural Formula	Name
CH_4	Meth	CH_4	methane
C_2H_6	Eth	CH_3CH_3	ethane
C_3H_8	Prop	$CH_3CH_2CH_3$	propane
C_4H_{10}	But	$CH_3CH_2CH_2CH_3$	butane
C_5H_{12}	Pent	$CH_3CH_2CH_2CH_2CH_3$	pentane
C_6H_{14}	Hex	$CH_3(CH_2)_4CH_3$	hexane
C_7H_{16}	Hept	$CH_3(CH_2)_5CH_3$	heptane
C_8H_{18}	Oct	$CH_3(CH_2)_6CH_3$	octane
C_9H_{20}	Non	$CH_3(CH_2)_7CH_3$	nonane
$C_{10}H_{22}$	Dec	$CH_3(CH_2)_8CH_3$	decane

✔ Example 2.2.1: Chain Isomers in Pentane

Pentane, C_5H_{12}, has three chain isomers. If you think you can find any others, they are simply twisted versions of the ones below. If in doubt make some models.

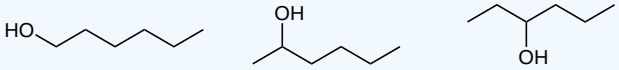


Exercises

? Exercise 2.2.1

Draw all of the isomers for $C_6H_{14}O$ that contain a 6 carbon chain and an alcohol (-OH) functional group.

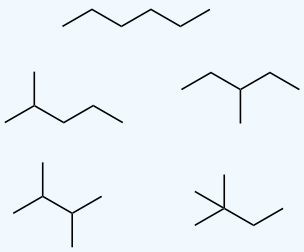
Answer



Exercise 2.2.2

Draw all possible isomers for C_6H_{14} (There are five total).

Answer



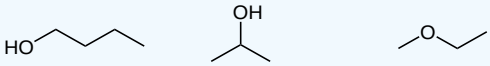
The top structure is when it is a 6 carbon chain. The middle row contains the 5 carbon chained isomers with branching at the 2nd and 3rd carbon. The bottom row contains the two 4 carbon chain isomers that can be drawn.

Exercise 2.2.3

Draw all possible isomers for C_3H_8.

Answer

The first structure is when an alcohol comes off the first carbon. The second structure is when the alcohol is coming off the central carbon. The third structure is the only possible ether form of C_3H_8.

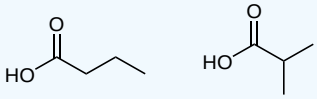


Exercise 2.2.4

Draw all possible isomers for $C_4H_8O_2$ that contain a carboxylic acid.

Answer

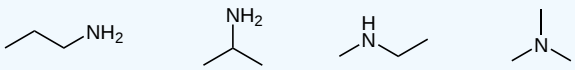
There are only 2 possibilities.



Exercise 2.2.5

Draw all possible isomers for C_3H_9N and indicate whether each amine is primary, secondary, or tertiary.

Answer

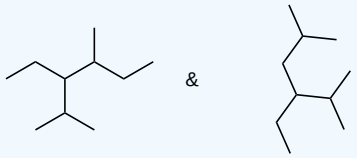


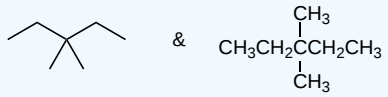
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The first and second structures are primary amines. The third structure is a secondary amine. The last structure is a tertiary amine.

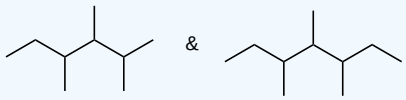
Exercise 2.2.6

Indicate whether each of the following sets are constitutional isomers, the same compound, or different compounds.

a) 

b) 

c) 

d) 

Answer

a) Both structures have formulas of $C_{10}H_{22}$ and have different connectivity which makes these **constitutional isomers**.

b) Both structures have formulas of C_7H_{16} and have the same connectivity which makes these the **same compound**.

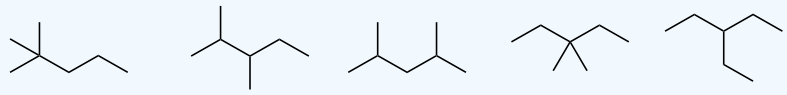
c) Both structure have formulas of C_7H_{16} and have different connectivity which makes these **constitutional isomers**.

d) The structure on the left has a formula of C_9H_{20} and the structure on the right has a formula of $C_{10}H_{22}$ so these are **different compounds**.

Exercise 2.2.7

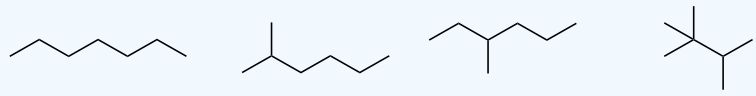
Draw the 5 constitutional isomers of C_7H_{16} (of the 9 total isomers possible) that have 5 carbons as the longest carbon chain length.

Answer



The 5 constitutional isomers with a 5 carbon chain length are shown above. Since there needs to be 7 carbons total, the 2 extra carbons are added as substituents. From left to right, the methyl group substitution pattern is 2,2, 2,3, 2,4, and 3,3, and the last one (on right) has a 3-ethyl substituent.

The other 4 possible constitutional isomers (with different length carbon chains) are shown below.



Contributors and Attributions

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- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Layne Morsch (University of Illinois Springfield)
- Dr. Krista Cunningham
- Dr. Zachary Sharrett (Sonoma State University)

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2.3: Alkyl Groups

Objectives

After completing this section, you should be able to

1. recognize and name any alkyl group that can be considered to have been formed by the removal of a terminal hydrogen atom from a straight-chain alkane containing ten or fewer carbon atoms.
2. explain what is meant by a primary, secondary, tertiary or quaternary carbon atom.
3. represent the various types of organic compounds using the symbol “R” to represent any alkyl group.

Key Terms

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

- alkyl group
- methyl group
- isopropyl group
- *sec*-butyl group
- isobutyl group
- *tert*-butyl group
- primary carbon
- secondary carbon
- tertiary carbon
- quaternary carbon

Study Notes

The differences among primary, secondary, tertiary and quaternary carbon atoms are explained in the following discussion. A convenient way of memorizing this classification scheme is to remember that a primary carbon atom is attached directly to only one other carbon atom, a secondary carbon atom is attached directly to two carbon atoms, and so on.

The **IUPAC** system requires first that we have names for simple unbranched chains and second, that we have names for simple alkyl groups that may be attached to the chains. An **alkyl group** is formed by removing one hydrogen from the alkane chain. The removal of this hydrogen results in a stem change from **-ane** to **-yl** to indicate an alkyl group. The removal of a hydrogen from methane, CH_4, creates a methyl group $-CH_3$. Likewise, the removal of a hydrogen from ethane, CH_3CH_3, creates an ethyl group $-CH_2CH_3$. The nomenclature pattern can continue to provide a series of straight-chain alkyl groups from straight chain alkanes with a hydrogen removed from the end. Note, the letter **R** is used to designate a generic (unspecified) alkyl group.

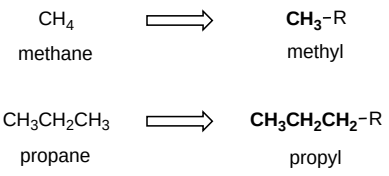


Table 2.3.2: Straight chain alkane and alkyl group names

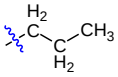
Alkane	Name	Alkyl Group	Name (Abbreviation)
CH_4	Methane	$-CH_3$	Methyl (Me)
CH_3CH_3	Ethane	$-CH_2CH_3$	Ethyl (Et)
$CH_3CH_2CH_3$	Propane	$-CH_2CH_2CH_3$	Propyl (Pr)
$CH_3CH_2CH_2CH_3$	Butane	$-CH_2CH_2CH_2CH_3$	Butyl (Bu)
$CH_3CH_2CH_2CH_2CH_3$	Pentane	$-CH_2CH_2CH_2CH_2CH_3$	Pentyl

Alkane	Name	Alkyl Group	Name (Abbreviation)
$CH_3CH_2CH_2CH_2CH_2CH_3$	Hexane	$-CH_2CH_2CH_2CH_2CH_2CH_3$	Hexyl

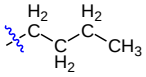
Prior to the systematic nomenclature developed for organic chemistry, prefixes were used to specify the connection point of straight-chain and branched-chain alkyl groups. Although the modern nomenclature system, discussed in the next section, is preferred these older terms are still often used, especially in solvents and reagents. Thus, an understanding of these prefixes is important to understanding organic chemistry. Notice that the total number of carbons in the alkyl subsistent is still indicated with the **prefix + yl**. For methyl and ethyl alkyl groups there is only one possible connection point so connection prefixes are not necessary. Starting with a three carbon alkyl group (propyl) the possibility of multiple connection points necessitates connection prefixes. These prefixes are often abbreviated with a letter which is italicized.

Normal (*n*)

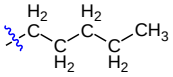
The prefix "n" is used to indicate a connection at the end of a straight-chain alkane. This prefix is not commonly used to just indicate alkyl subsistent as discussed above. However it is sometime used to indicate the connection of a functional group onto a straight alkane.



n-propyl
or propyl



n-butyl
or butyl



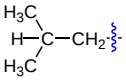
n-pentyl
or pentyl

Iso (*i*)

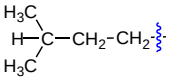
Starting with propyl alkyl groups there is the possibility of a connection other than the very end. The prefix "iso" implies that the connection ends with a $(CH_3)_2CH-$ group.



isopropyl
or *i*-propyl



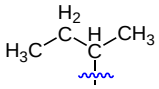
isobutyl
or *i*-butyl



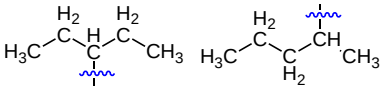
isopentyl
or *i*-pentyl

Secondary (*Sec*)

With butyl straight-chain alkyl groups there is the possibility of a connection on the second carbon from the end of the chain. These alkyl groups are given the prefix "*Sec.*" This is not used for pentyl or hexyl groups because there is more than one structure that are not identical that could be named as sec-pentyl or sec-hexyl.



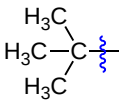
sec -butyl



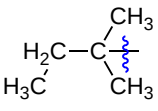
NOT *sec* -pentyl

Tertiary (*tert* or *t*)

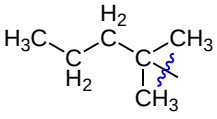
Starting with four carbon alkyl groups, there is an isomer which can have a connection to a tertiary carbon. These alkyl groups get the prefix "*t.*"



tert-butyl
or *t*-butyl



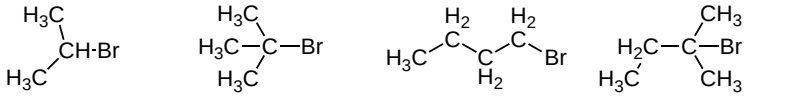
tert-pentyl
or *t*-pentyl



tert-hexyl
or *t*-hexyl

Example:

The naming system described above is often used to describe halogens which contain only a few carbons. The halogen is shown as bonded to the connection point of the alkyl group.



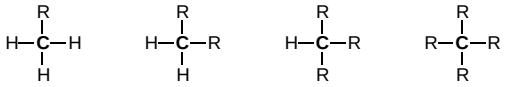
isopropyl bromide | *t*-butyl bromide | *n*-butyl bromide | *tert*-pentyl bromide

Classification of carbon atoms

Carbons have a special terminology to describe how many other carbons they are attached to. This allows for an easy description of branching in alkanes. Also, we will find that the number of carbons attached to a given atom will have subtle effects on its chemistry.

- Primary carbons (1°) attached to one other C atom.
- Secondary carbons (2°) are attached to two other C's.
- Tertiary carbons (3°) are attached to three other C's.
- Quaternary carbons (4°) are attached to four C's.

The figure below use the group "R" to represent an alkyl group of unspecified length. R typically used to represent alkyl groups but an also represent a part of a molecule which is either unspecified or not germane to the discussion.

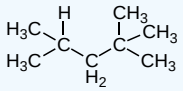


1° **C** | 2° **C** | 3° **C** | 4° **C**

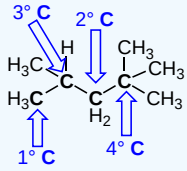
This terminology will be used repeatedly in organic chemistry to describe the number of carbons attached to a specific atom, however, the atom will not always a carbon.

Example 2.3.1

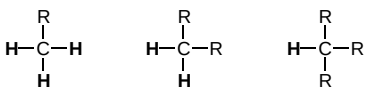
Please indicate the the number of 1°, 2°, 3°, and 4° carbons in the following molecule:



- The molecule has five Primary carbons (1°).
- The molecule has one Secondary carbon (2°).
- The molecule has one Tertiary carbon (3°).
- The molecule has one Quaternary carbon (4°)



Hydrogen atoms are also classified in this manner. A hydrogen atom attached to a primary carbon atom is called a primary hydrogen ect.

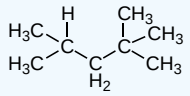


1° **H** | 2° **H** | 3° **H**

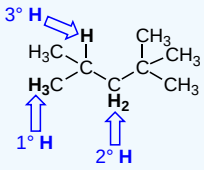
- Primary hydrogens (1°) are attached to carbons bonded to one other C atom
- Secondary hydrogens (2°) are attached to carbons bonded to two other C's
- Tertiary hydrogens (3°) are attached to carbons bonded to three other C's
- It is not possible to have a quaternary hydrogen (4°).

Example 2.3.2

Please indicate the the number of 1°, 2°, and 3°, hydrogens are in the following molecule:



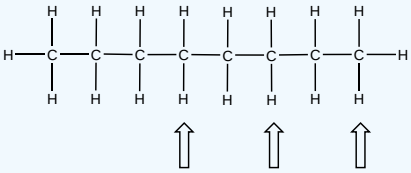
- The molecule has fifteen Primary (1°) hydrogens.
- The molecule has two Secondary (2°) hydrogens.
- The molecule has one Tertiary (3°) hydrogen.



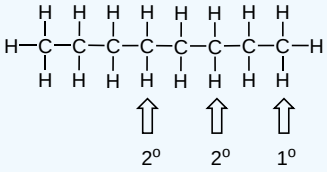
Exercises

Exercise 2.3.1

Determine whether the H's indicated in the following structure are 1°, 2°, or 3°.

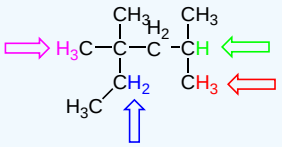


Answer

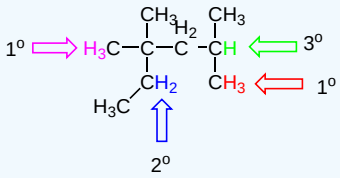


Exercise 2.3.2

Determine whether the H's indicated in the following structure is 1°, 2°, or 3°.

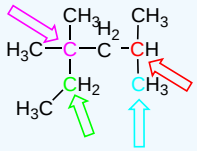


Answer

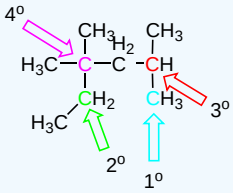


Exercise 2.3.3

Determine whether the carbons indicated in the structure below are 1°, 2°, 3°, or 4°.

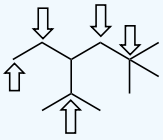


Answer

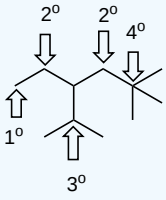


Exercise 2.3.4

Determine whether the carbons indicated in the structure below are 1°, 2°, 3°, or 4°.

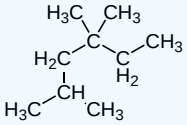


Answer



Exercise 2.3.5

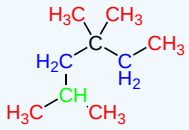
Please indicate the total number of each type 1°, 2°, 3°, and 4° carbons in the following molecule.



Answer

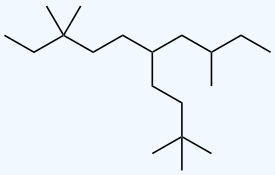
https://chem.libretexts.org/@go/page/396234

There are 5 primary (1°) C's, 2 secondary (2°) C's, 1 tertiary (3°) C and 1 quaternary (4°) C in the structure (seen color coded below).



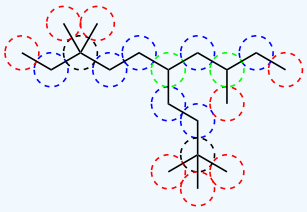
Exercise 2.3.6

Please indicate the total number of each type 1°, 2°, 3°, and 4° carbons in the following molecule.



Answer

There are 8 primary (1°) C's, 7 secondary (2°) C's, 2 tertiary (3°) C's and 2 quaternary (4°) C's in the structure (seen color coded below).



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2.4: Naming Alkanes

Objectives

After completing this section, you should be able to

1. provide the correct IUPAC name for any given alkane structure (Kekulé, condensed or shorthand).
2. draw the Kekulé, condensed or shorthand structure of an alkane, given its IUPAC name.

Key Terms

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

- IUPAC system

Study Notes

The IUPAC system of nomenclature aims to ensure

1. that every organic compound has a unique, unambiguous name.
2. that the IUPAC name of any compound conveys the structure of that compound to a person familiar with the system.

One way of checking whether the name you have given to an alkane is reasonable is to count the number of carbon atoms implied by the chosen name. For example, if you named a compound 3-ethyl-4-methylheptane, you have indicated that the compound contains a total of 10 carbon atoms—seven carbon atoms in the main chain, two carbon atoms in an ethyl group, and one carbon atom in a methyl group. If you were to check the given structure and find 11 carbon atoms, you would know that you had made a mistake. Perhaps the name you should have written was 3-ethyl-4,4-dimethylheptane!

When naming alkanes, a common error of beginning students is a failure to pick out the longest carbon chain. For example, the correct name for the compound shown below is 3-methylheptane, not 2-ethylhexane.

Remember that every substituent must have a number, and do not forget the prefixes: di, tri, tetra, etc.

You must use commas to separate numbers, and hyphens to separate numbers and substituents. Notice that 3-methylhexane is one word.

Hydrocarbons having no double or triple bond functional groups are classified as **alkanes** or **cycloalkanes**, depending on whether the carbon atoms of the molecule are arranged only in chains or also in rings. Although these hydrocarbons have no functional groups, they constitute the framework on which functional groups are located in other classes of compounds, and provide an ideal starting point for studying and naming organic compounds. The alkanes and cycloalkanes are also members of a larger class of compounds referred to as **aliphatic**. Simply put, aliphatic compounds are compounds that do not incorporate any aromatic rings in their molecular structure.

The following table lists the IUPAC names assigned to simple continuous-chain alkanes from C-1 to C-10. A common **"ane"** suffix identifies these compounds as alkanes. Longer chain alkanes are well known, and their names may be found in many reference and text books. The names **methane** through **decane** should be memorized, since they constitute the root of many IUPAC names. Fortunately, common numerical prefixes are used in naming chains of five or more carbon atoms.

Table 3.4.1 : Simple Unbranched Alkanes

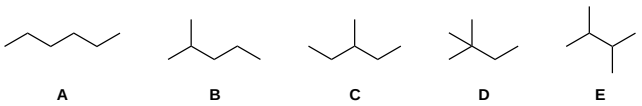
Name	Molecular Formula	Structural Formula	Isomers	Name	Molecular Formula	Structural Formula	Isomers

Name	Molecular Formula	Structural Formula	Isomers		Name	Molecular Formula	Structural Formula	Isomers
meth**ane**	CH_4	CH_4	1		hex**ane**	C_6H_{14}	$CH_3(CH_2)_4CH_3$	5
eth**ane**	C_2H_6	CH_3CH_3	1		hept**ane**	C_7H_{16}	$CH_3(CH_2)_5CH_3$	9
prop**ane**	C_3H_8	$CH_3CH_2CH_3$	1		oct**ane**	C_8H_{18}	$CH_3(CH_2)_6CH_3$	18
but**ane**	C_4H_{10}	$CH_3CH_2CH_2CH_3$	2		non**ane**	C_9H_{20}	$CH_3(CH_2)_7CH_3$	35
pent**ane**	C_5H_{12}	$CH_3(CH_2)_3CH_3$	3		dec**ane**	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	75

Some important behavior trends and terminologies

1. The formulas and structures of these alkanes increase uniformly by a CH_2 increment.
2. A uniform variation of this kind in a series of compounds is called **homologous**.
3. These formulas all fit the $\mathbf{C_nH_{2n+2}}$ rule. This is also the highest possible H/C ratio for a stable hydrocarbon.
4. Since the H/C ratio in these compounds is at a maximum, we call them **saturated** (with hydrogen).

Beginning with butane (C_4H_{10}), and becoming more numerous with larger alkanes, we note the existence of alkane isomers. For example, there are five C_6H_{14} isomers, shown below as abbreviated line formulas (**A** through **E**):



Although these distinct compounds all have the same molecular formula, only one (**A**) can be called hexane. How then are we to name the others?

The **IUPAC** system requires first that we have names for simple unbranched chains, as noted above, and second that we have names for simple alkyl groups that may be attached to the chains. Examples of some common **alkyl groups** are given in the following table. Note that the "ane" suffix is replaced by "**yl**" in naming groups. The symbol **R** is used to designate a generic (unspecified) alkyl group.

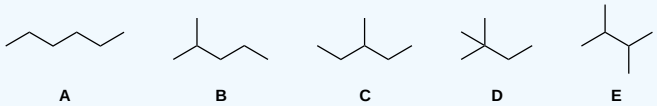
Table 3.4.2 : Alkyl Groups Names

Group	$CH_3–$	$C_2H_5–$	$CH_3CH_2CH_2–$	$(CH_3)_2CH–$	$CH_3CH_2CH_2CH_2–$	$(CH_3)_2CHCH_2–$	$CH_3CH_2CH(CH_3)–$	$(CH_3)_3C–$	R–
Name	Methyl	Ethyl	Propyl	Isopropyl	Butyl	Isobutyl	sec-Butyl	tert-Butyl	Alkyl

IUPAC Rules for Alkane Nomenclature

1. Find and name the longest continuous carbon chain.
2. Identify and name groups attached to this chain.
3. Number the chain consecutively, starting at the end nearest a substituent group.
4. Designate the location of each substituent group by an appropriate number and name.
5. Assemble the name, listing groups in alphabetical order.
6. The prefixes di, tri, tetra etc., used to designate several groups of the same kind, are not considered when alphabetizing.

Example 3.4.1 : Alkanes



The IUPAC names of the isomers of hexane are: **A** hexane **B** 2-methylpentane **C** 3-methylpentane **D** 2,2-dimethylbutane **E** 2,3-dimethylbutane

Halogen Groups

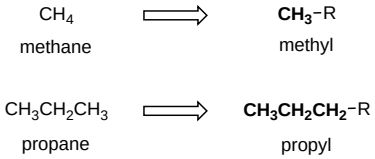
Halogen substituents are easily accommodated, using the names: fluoro (F-), chloro (Cl-), bromo (Br-) and iodo (I-).

Example 3.4.2 : Halogen Substitution

For example, $(CH_3)_2CHCH_2CH_2Br$ would be named 1-bromo-3-methylbutane. If the halogen is bonded to a simple alkyl group an alternative "alkyl halide" name may be used. Thus, C_2H_5Cl may be named chloroethane (no locator number is needed for a two carbon chain) or ethyl chloride.

Alkyl Groups

Alkanes can be described by the general formula C_nH_{2n+2}. An alkyl group is formed by removing one hydrogen from the alkane chain and is described by the formula C_nH_{2n+1}. The removal of this hydrogen results in a stem change from **-ane** to **-yl**. Take a look at the following examples.



The same concept can be applied to any of the straight chain alkane names provided in the table below.

Name	Molecular Formula	Condensed Structural Formula
Methane	CH_4	CH_4
Ethane	C_2H_6	CH_3CH_3
Propane	C_3H_8	$CH_3CH_2CH_3$
Butane	C_4H_{10}	$CH_3(CH_2)_2CH_3$
Pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$
Hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$
Heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$
Octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$
Nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$
Decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$
Undecane	$C_{11}H_{24}$	$CH_3(CH_2)_9CH_3$
Dodecane	$C_{12}H_{26}$	$CH_3(CH_2)_{10}CH_3$
Tridecane	$C_{13}H_{28}$	$CH_3(CH_2)_{11}CH_3$
Tetradecane	$C_{14}H_{30}$	$CH_3(CH_2)_{12}CH_3$
Pentadecane	$C_{15}H_{32}$	$CH_3(CH_2)_{13}CH_3$
Hexadecane	$C_{16}H_{34}$	$CH_3(CH_2)_{14}CH_3$
Heptadecane	$C_{17}H_{36}$	$CH_3(CH_2)_{15}CH_3$
Octadecane	$C_{18}H_{38}$	$CH_3(CH_2)_{16}CH_3$

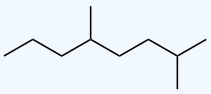
Name	Molecular Formula	Condensed Structural Formula
Nonadecane	$C_{19}H_{40}$	$CH_3(CH_2)_{17}CH_3$
Eicosane	$C_{20}H_{42}$	$CH_3(CH_2)_{18}CH_3$

Three Rules for Naming Alkanes

1. Choose the longest, most substituted carbon chain containing a functional group.
2. A carbon bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substituent present must have the lowest possible number.
3. Take the alphabetical order into consideration; that is, after applying the first two rules given above, make sure that your substituents and/or functional groups are written in alphabetical order.

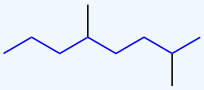
Example 3.4.3

What is the name of the follow molecule?

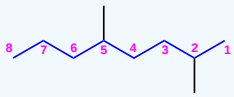


Solution

Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example does not contain any functional groups, so we only need to be concerned with choosing the longest, most substituted carbon chain. The longest carbon chain has been highlighted in blue and consists of eight carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number. Because this example does not contain any functional groups, we only need to be concerned with the two substitutes present, that is, the two methyl groups. If we begin numbering the chain from the left, the methyls would be assigned the numbers 4 and 7, respectively. If we begin numbering the chain from the right, the methyls would be assigned the numbers 2 and 5. Therefore, to satisfy the second rule, numbering begins on the right side of the carbon chain as shown below. This gives the methyl groups the lowest possible numbering.

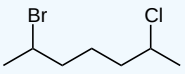


Rule 3: In this example, there is no need to utilize the third rule. Because the two substitutes are identical, neither takes alphabetical precedence with respect to numbering the carbons. This concept will become clearer in the following examples.

The name of this molecule is **2,5-dimethyloctane**

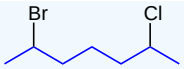
Example 3.4.4

What is the name of the follow molecule?



Solution

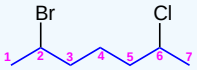
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine. The longest carbon chain has been highlighted in blue and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substituent present must have the lowest possible number. In this example, numbering the chain from either the left or the right would satisfy this rule. If we number the chain from the left, bromine and chlorine would be assigned the second and sixth carbon positions, respectively. If we number the chain from the right, chlorine would be assigned the second position and bromine would be assigned the sixth position. In other words, whether we choose to number from the left or right, the functional groups occupy the second and sixth positions in the chain. To select the correct numbering scheme, we need to utilize the third rule.



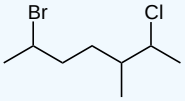
Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.



The name of this molecule is: **2-bromo-6-chloroheptane**

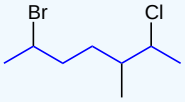
Example 3.4.5

What is the name of the follow molecule?

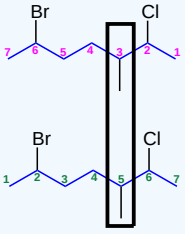


Solution

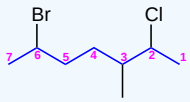
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine, and one substitute, the methyl group. The longest carbon chain has been highlighted in blue and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. After taking functional groups into consideration, any substitutes present must have the lowest possible carbon number. This particular example illustrates the **point of difference principle**. If we number the chain from the left, bromine, the methyl group and chlorine would occupy the second, fifth and sixth positions, respectively. This concept is illustrated in the second drawing below. If we number the chain from the right, chlorine, the methyl group and bromine would occupy the second, third and sixth positions, respectively, which is illustrated in the first drawing below. The position of the methyl, therefore, becomes a **point of difference**. In the first drawing, the methyl occupies the third position. In the second drawing, the methyl occupies the fifth position. To satisfy the second rule, we want to choose the numbering scheme that provides the lowest possible numbering of this substitute. Therefore, the first of the two carbon chains shown below is correct.



Therefore, the first numbering scheme is the appropriate one to use.



Once you have determined the correct numbering of the carbons, it is often useful to make a list, including the functional groups, substitutes, and the name of the parent chain.

Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.

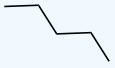
Parent chain: heptane Substitutents: 2-chloro 3-methyl 6-bromo

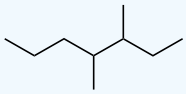
The name of this molecule is: **6-bromo-2-chloro-3-methylheptane**

Exercises

? Exercise 3.4.1

Give the proper IUPAC names of the following compounds.

a) 

b) 

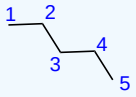
c) 

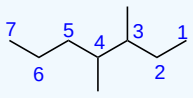
Answer

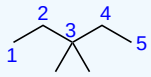
a) Since this structure is an unbranched alkane (all single bonds) with a 5 carbon chain length, its name would be **pentane**.

b) This alkane has a 7 carbon longest continuous chain length that we number from right to left to get the first methyl substituent we encounter to have the lowest possible number (3 versus being 4 if numbering from left to right). This causes it to have 2 methyl substituents at positions 3 & 4 so we would name it indicating those numbers and the prefix dimethyl which gives a proper IUPAC name of **3,4-dimethylheptane**.

c) This alkane has a 5 carbon longest continuous chain length (which could be numbered from left to right or right to left due to the symmetry at C-3). It has two methyl substituents off of C-3 so the proper IUPAC name is **3,3-dimethylpentane.**

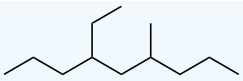
a) 

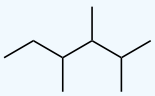
b) 

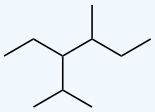
c) 

? Exercise 3.4.2

Give the proper IUPAC names of the following compounds.

a) 

b) 

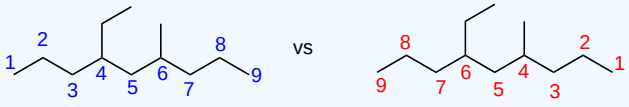
c) 

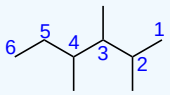
Answer

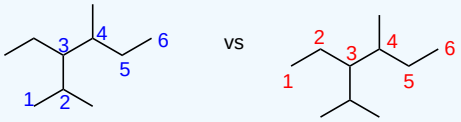
a) This alkane has a 9 carbon longest continuous chain length that we number from left to right (structure on left numbered in blue) to make the ethyl substituent be number 4. For the structure on the right (numbered in red) going from right to left, the methyl substituent is number 4. Since ethyl is higher in the alphabetical order, you want to make it have the lower number so the structure on the left (blue numbering) takes priority and the name is **4-ethyl-6-methylnonane**.

b) This alkane has a 6 carbon longest continuous chain length that we number from right to left to make the first methyl be C-2 (versus the opposite direction which would make the first methyl C-3). Since there are 3 methyl substituents at positions 2,3, & 4, this compound would have the name **2,3,4-trimethylhexane**.

c) This 6 carbon alkane can be numbered along different chains (see below) as well as in the opposite directions. This shows the two different chains that can be drawn (making the first substituent in that chain the lowest number). The structure on the left (numbered in blue) is the correct choice since it causes more substituents to be on the longest continuous chain (3 vs 2 in the structure on the right). This would make the IUPAC name of the structure **3-ethyl-2,4-dimethylhexane**. (Notice how ethyl takes priority over methyl and the di- is not considered for alphabetizing.)

a) 

b) 

c) 

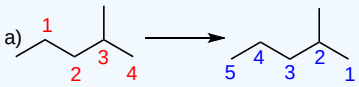
Exercise 3.4.3

All of the following names represent a compound that has been named improperly. Draw out the structure from the name and give the proper IUPAC name for the compounds.

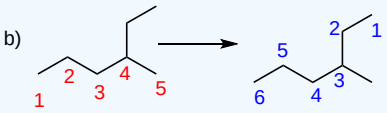
a. 1,3-dimethylbutane
b. 4-ethylpentane
c. 2-ethyl-3-methylpentane

Answer

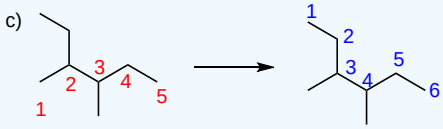
a) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), the correct name should be **2-methylpentane**.



b) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is 6 C's and we start the numbering on the end to the right to make the methyl substituent come off at C-3 (instead of beong at C-4 if we numbered it the opposite direction) the correct name should be **3-methyl hexane**.



c) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is 6 C's and since this molecule is symmetrical (between carbon 3 & 4), you can start the numbers from either end. In this case, we have methyl substituents coming off of carbons 3 & 4 so the proper name is **3,4-dimethyl hexane**.



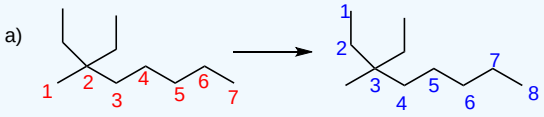
Exercise 3.4.4

All of the following names represent a compound that has been named improperly. Draw out the structure from the name and give the proper IUPAC name for the compounds.

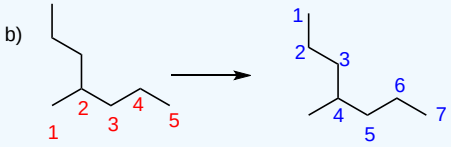
a. 2,2-diethylheptane
b. 2-propylpentane
c. 4,4-diethylbutane

Answer

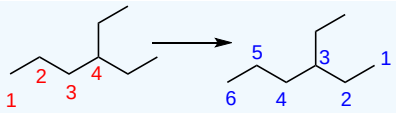
a) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is now 8 C's and you have an ethyl substituent at C-3 and a methyl substituent also at C-3 so the proper name is **3- ethyl-3-methyloctane**.



b) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is now 7 C's and since this molecule is symmetrical (at carbon 4), you can start the numbers from either end. There is a methyl substituent at C-4 so the proper name is **4-methylheptane**.



c) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right) going from right to left (to make the ethyl substituent have the lowest number possible), the correct name is **3-ethylhexane**

c) 

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2.5: Properties of Alkanes

Objectives

After completing this section, you should be able to

1. arrange a number of given straight-chain alkanes in order of increasing or decreasing boiling point or melting point.
2. arrange a series of isomeric alkanes in order of increasing or decreasing boiling point.
3. explain the difference in boiling points between a given number of alkanes.

Key Terms

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

- van der Waals force (also known as London Dispersion force)

Alkanes are not very reactive and have little biological activity; all alkanes are colorless and odorless non-polar compounds. The relative weak London dispersion forces of alkanes result in gaseous substances for short carbon chains, volatile liquids with densities around 0.7 g/mL for moderate carbon chains, and solids for long carbon chains. For molecules with the same functional groups, there is a direct relationship between the size and shape of molecules and the strength of the intermolecular forces (IMFs) causing the differences in the physical states.

Boiling Points

Table 2.5.1 describes some of the properties of some straight-chain alkanes. There is not a significant electronegativity difference between carbon and hydrogen, thus, there is not any significant bond polarity. The molecules themselves also have very little polarity. A totally symmetrical molecule like methane is completely non-polar, meaning that the only attractions between one molecule and its neighbors will be Van der Waals dispersion forces. These forces will be very small for a molecule like methane but will increase as the molecules get bigger. Therefore, the boiling points of the alkanes increase with molecular size.

For isomers, the more branched the chain, the lower the boiling point tends to be. Van der Waals dispersion forces are smaller for shorter molecules and only operate over very short distances between one molecule and its neighbors. It is more difficult for short, fat molecules (with lots of branching) to lie as close together as long, thin molecules.

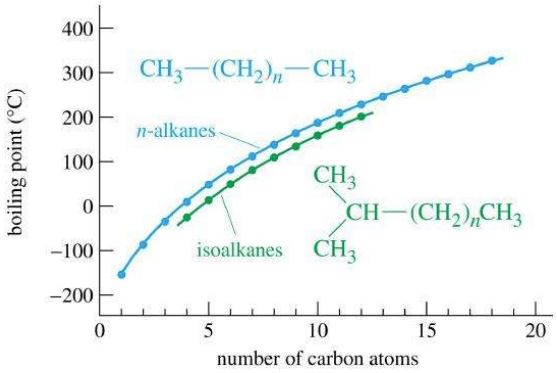
The boiling points shown are for the "straight chain" isomers of which there is more than one. The first four alkanes are gases at room temperature, and solids do not begin to appear until about $C_{17}H_{36}$, but this is imprecise because different isomers typically have different melting and boiling points.

Table 2.5.1: Physical Properties of Some Alkanes

Molecular Name	Formula	Melting Point (°C)	Boiling Point (°C)	Density (20°C)*	Physical State (at 20°C)
methane	CH_4	–182	–164	0.668 g/L	gas
ethane	C_2H_6	–183	–89	1.265 g/L	gas
propane	C_3H_8	–190	–42	1.867 g/L	gas
butane	C_4H_{10}	–138	–1	2.493 g/L	gas
pentane	C_5H_{12}	–130	36	0.626 g/mL	liquid
hexane	C_6H_{14}	–95	69	0.659 g/mL	liquid
octane	C_8H_{18}	–57	125	0.703 g/mL	liquid
decane	$C_{10}H_{22}$	–30	174	0.730 g mL	liquid

*Note the change in units going from gases (grams per liter) to liquids (grams per milliliter). Gas densities are at 1 atm pressure.

The boiling points for the "straight chain" isomers and isoalkanes isomers are shown to demonstrate that branching decreases the surfaces area, weakens the IMFs, and lowers the boiling point.



Example 2.5.1: Boiling Points of Alkanes

For example, the boiling points of the three isomers of C_5H_{12} are:

- pentane: 309.2 K
- 2-methylbutane: 301.0 K
- 2,2-dimethylpropane: 282.6 K

The slightly higher boiling points for the cycloalkanes are presumably because the molecules can get closer together because the ring structure makes them better able!

Exercise 2.5.1

For each of the following pairs of compounds, select the substance which you expect to have the higher boiling point:

a. octane and nonane.
b. octane and 2,2,3,3-tetramethylbutane.

Solution

a. nonane, since it has more atoms it will have greater IMF
b. octane, since it is not branched, the molecules can pack closer together increasing IMF

Solubility

Alkanes are virtually insoluble in water, but dissolve in organic solvents. However, liquid alkanes are good solvents for many other non-ionic organic compounds.

Solubility in Water

When a molecular substance dissolves in water, the following must occur:

- break the intermolecular forces within the substance. In the case of the alkanes, these are the Van der Waals dispersion forces.
- break the intermolecular forces in the water so that the substance can fit between the water molecules. In water, the primary intermolecular attractions are hydrogen bonds.

Breaking either of these attractions requires energy, although the amount of energy to break the Van der Waals dispersion forces in something like methane is relatively negligible; this is not true of the hydrogen bonds in water.

As something of a simplification, a substance will dissolve if there is enough energy released when new bonds are made between the substance and the water to compensate for what is used in breaking the original attractions. The only new attractions between the alkane and the water molecules are Van der Waals forces. These forces do not release a sufficient amount of energy to compensate for the energy required to break the hydrogen bonds in water. The alkane does not dissolve.

> This is a simplification because entropic effects are important when things dissolve.

Solubility in organic solvents

In most organic solvents, the primary forces of attraction between the solvent molecules are Van der Waals. Therefore, when an alkane dissolves in an organic solvent, the Van der Waals forces are broken and are replaced by new Van der Waals forces. The two processes more or less cancel each other out energetically; thus, there is no barrier to solubility.

? Exercise 2.5.1

For each of the following pairs of compounds, select the substance you expect to have the higher boiling point.

a. octane and nonane.
b. octane and 2,2,3,3-tetramethylbutane.

Answer

Nonane will have a higher boiling point than octane, because it has a longer carbon chain than octane. Octane will have a higher boiling point than 2,2,3,3-tetramethylbutane, because it branches less than 2,2,3,3-tetramethylbutane, and therefore has a larger "surface area" and more van der Waals forces.

Note: The actual boiling points are:

- nonane, 150.8°C
- octane, 125.7°C
- 2,2,3,3-tetramethylbutane, 106.5°C

Reactions of Alkanes

Alkanes undergo very few reactions. There are two important reactions that are still possible, combustion and halogenation. The halogenation reaction is very important in organic chemistry because it opens a gateway to further chemical reactions.

Combustion

Complete combustion (given sufficient oxygen) of any hydrocarbon produces carbon dioxide, water, and a significant amount of heat. Due to the exothermic nature of these combustion reactions, alkanes are commonly used as a fuel source (for example: propane for outdoor grills, butane for lighters). The hydrocarbons become harder to ignite as the molecules get bigger. This is because the larger molecules don't vaporize as easily. If the liquid is not very volatile, only those molecules on the surface can react with the oxygen. Larger molecules have greater Van der Waals attractions which makes it more difficult for them to break away from their neighbors and become a gas. An example combustion reaction is shown for propane:

$$\mathrm{C_3H_8 + O_2 \longrightarrow 3\,CO_2 + 4\,H_2O + 2044\,kJ/mol}$$

Halogenation

Halogenation is the replacement of one or more hydrogen atoms in an organic compound by a halogen (fluorine, chlorine, bromine or iodine). Unlike the complex transformations of combustion, the halogenation of an alkane appears to be a simple **substitution reaction** in which a C-H bond is broken and a new C-X bond is formed.

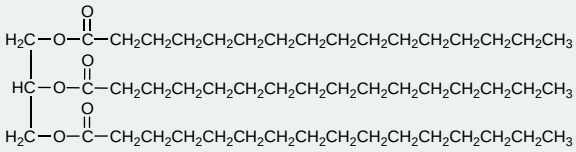
Since only two covalent bonds are broken (C-H & Cl-Cl) and two covalent bonds are formed (C-Cl & H-Cl), this reaction seems to be an ideal case for mechanistic investigation and speculation. However, one complication is that all the hydrogen atoms of an alkane may undergo substitution, resulting in a mixture of products, as shown in the following unbalanced equation. The relative amounts of the various products depend on the proportion of the two reactants used. In the case of methane, a large excess of the hydrocarbon favors formation of methyl chloride as the chief product; whereas, an excess of chlorine favors formation of chloroform and carbon tetrachloride.

$$\mathrm{CH_4 + Cl_2 \rightarrow CH_3Cl + CH_2Cl + CHCl_3 + CCl_4 + HCl}$$

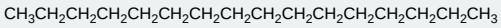
Looking Closer: An Alkane Basis for Properties of Other Compounds

An understanding of the physical properties of alkanes is important since petroleum and natural gas and the many products derived from them—gasoline, bottled gas, solvents, plastics, and more—are composed primarily of alkanes. This understanding is also vital because it is the basis for describing the properties of other organic and biological compound families. For example, large portions of the structures of lipids consist of nonpolar alkyl groups. Lipids include the dietary fats and fat like compounds called phospholipids and sphingolipids that serve as structural components of living tissues. These compounds have both polar and nonpolar groups, enabling them to bridge the gap between water-soluble and water-insoluble phases. This characteristic is essential for the selective permeability of cell membranes.

(a)



(b)



Tripalmitin (a), a typical fat molecule, has long hydrocarbon chains typical of most lipids. Compare these chains to hexadecane (b), an alkane with 16 carbon atoms.

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2.6: Conformations of Ethane

Objectives

After completing this section, you should be able to

1. explain the concept of free rotation about a carbon-carbon single bond.
2. explain the difference between conformational isomerism and structural isomerism.
3. draw the conformers of ethane using both sawhorse representation and Newman projection.
4. sketch a graph of energy versus bond rotation for ethane, and discuss the graph in terms of torsional strain.

Key Terms

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

- conformation (conformer, conformational isomer)
- dihedral angle
- eclipsed conformation
- Newman projection
- staggered conformation
- strain energy
- torsional strain (eclipsing strain)

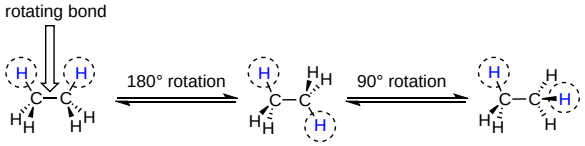
Study Notes

You should be prepared to sketch various conformers using both sawhorse representations and Newman projections. Each method has its own advantages, depending upon the circumstances. Notice that when drawing the Newman projection of the eclipsed conformation of ethane, you cannot clearly draw the rear hydrogens exactly behind the front ones. This is an inherent limitation associated with representing a 3-D structure in two dimensions.

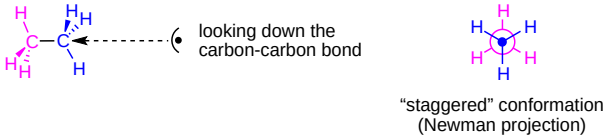
Conformational isomerism involves rotation about sigma bonds, and does not involve any differences in the connectivity of the atoms or geometry of bonding. Two or more structures that are categorized as conformational isomers, or **conformers**, are really just two of the exact same molecule that differ only in rotation of one or more sigma bonds.

Ethane Conformations

Although there are seven sigma bonds in the ethane molecule, rotation about the six carbon-hydrogen bonds does not result in any change in the shape of the molecule because the hydrogen atoms are essentially spherical. Rotation about the carbon-carbon bond, however, results in many different possible molecular conformations.



In order to better visualize these different conformations, it is convenient to use a drawing convention called the **Newman projection**. In a Newman projection, we look lengthwise down a specific bond of interest – in this case, the carbon-carbon bond in ethane. We depict the 'front' atom as a dot, and the 'back' atom as a larger circle.



The six carbon-hydrogen bonds are shown as solid lines protruding from the two carbons at 120°angles, which is what the actual tetrahedral geometry looks like when viewed from this perspective and flattened into two dimensions.

Figure 3.6.1: A 3D Model of Staggered Ethane.

The lowest energy conformation of ethane, shown in the figure above, is called the ‘staggered’ conformation. In the staggered conformation, all of the C-H bonds on the front carbon are positioned at an angle of 60° relative to the C-H bonds on the back carbon. This angle between a sigma bond on the front carbon compared to a sigma bond on the back carbon is called the dihedral angle. In this conformation, the distance between the bonds (and the electrons in them) is maximized. Maximizing the distance between the electrons decreases the electrostatic repulsion between the electrons and results in a more stable structure.

If we now rotate the front CH_3 group 60° clockwise, the molecule is in the highest energy ‘eclipsed' conformation, and the hydrogens on the front carbon are as close as possible to the hydrogens on the back carbon.



“eclipsed” conformation

This is the highest energy conformation because of unfavorable electrostatic repulsion between the electrons in the front and back C-H bonds. The energy of the eclipsed conformation is approximately 3 kcal/mol (12 kJ/mol) higher than that of the staggered conformation. **Torsional strain** (or eclipsing strain) is the name give to the energy difference caused by the increased electrostatic repulsion of eclipsing bonds.

Another 60° rotation returns the molecule to a second eclipsed conformation. This process can be continued all around the 360° circle, with three possible eclipsed conformations and three staggered conformations, in addition to an infinite number of variations in between. We will focus on the staggered and eclipsed conformers since they are, respectively, the lowest and highest energy conformers.

Unhindered (Free) Rotations Do Not Exist in Ethane

The carbon-carbon bond is not *completely* free to rotate – the 3 kcal/mol torsional strain in ethane creates a barrier to rotation that must be overcome for the bond to rotate from one staggered conformation to another. This rotational barrier is not large enough to prevent rotation except at extremely cold temperatures. So at normal temperatures, the carbon-carbon bond is constantly rotating. However, at any given moment the molecule is more likely to be in a staggered conformation - one of the rotational ‘energy valleys’ - than in any other conformer. The potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds, as shown in Figure 3.6.2.

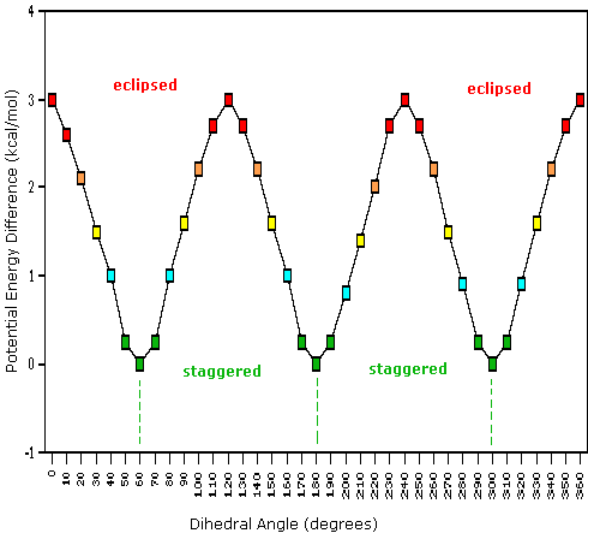


Figure 3.6.2: The potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds. Valleys in the graph represent the low energy staggered conformers, while peaks represent the higher energy eclipsed conformers.

Although the conformers of ethane are in rapid equilibrium with each other, the 3 kcal/mol energy difference leads to a substantial preponderance of staggered conformers (> 99.9%) at any given time. The animation below illustrates the relationship between ethane's potential energy and its dihedral angle

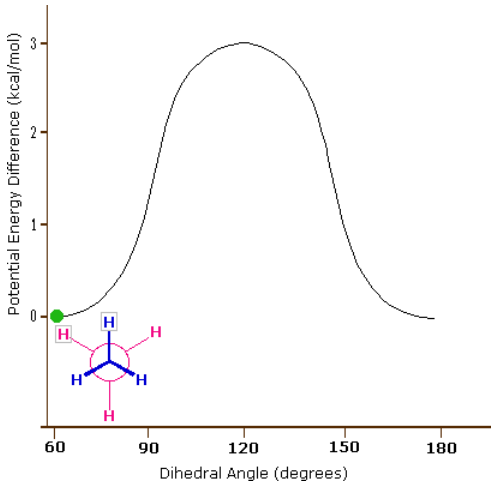


Figure 3.6.2: Animation of potential energy vs. dihedral angle in ethane

Exercises

1) What is the most stable rotational conformation of ethane and explain why it is preferred over the other conformation?

Solutions

1) Staggered, as there is less repulsion between the hydrogen atoms.

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2.7: Conformations of Other Alkanes

Objectives

After completing this section, you should be able to

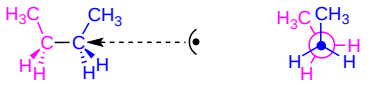
1. depict the staggered and eclipsed conformers of propane (or a similar compound) using sawhorse representations and Newman projections.
2. sketch a graph of energy versus bond rotation for propane (or a similar compound) and discuss the graph in terms of torsional strain.
3. depict the anti, gauche, eclipsed and fully eclipsed conformers of butane (or a similar compound), using sawhorse representations and Newman projections.
4. sketch a graph of energy versus C_2-C_3 bond rotation for butane (or a similar compound), and discuss it in terms of torsional and steric repulsion.
5. assess which of two (or more) conformers of a given compound is likely to predominate at room temperature from a semi-quantitative knowledge of the energy costs of the interactions involved.

Key Terms

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

- anti conformation
- gauche conformation
- eclipsed conformation
- steric repulsion (strain)

In butane, there are three rotating carbon-carbon sigma bonds to consider, but we will focus on the middle bond between C_2 and C_3. Below are two representations of butane in a conformation which puts the two CH_3 groups (C_1 and C_4) in the eclipsed position.

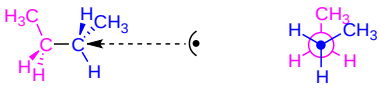


"eclipsed" (A)

Eclipsed interaction	Energy (kcal/mol)	Energy (kJ/mol)
H-H	1.0	4.0
H-CH_3	1.4	6.0
CH_3-CH_3	2.6	11.0

The CH_3-CH_3 groups create the significantly larger eclipsed interaction of 11.0 kJ/mol. There are also two H-H eclipsed interactions at 4.0 kJ/mol each to create a total of 2(4.0 kJ/mol) + 11.0 kJ/mol = 19.0 kJ/mol of strain. This is the highest energy conformation for butane, due to torsional strain caused by the electrostatic repulsion of electrons in the eclipsed bonds, but also because of another type of strain called '**steric repulsion'**, between the two rather bulky methyl groups. Steric strain comes about when two large groups, such as two methyl groups, try to occupy the same space. What results is a repulsive non-covalent interaction caused by their respective electron densities.

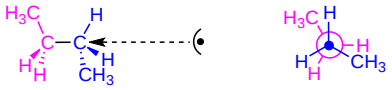
If we rotate the front, (blue) carbon by 60°clockwise, the butane molecule is now in a staggered conformation.



gauche

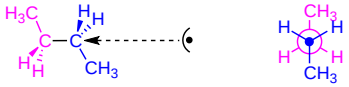
This is more specifically referred to as the '**gauche'** conformation of butane. Notice that although they are staggered, the two methyl groups are not as far apart as they could possibly be. There is still significant steric repulsion between the two bulky groups.

A further rotation of 60° gives us a second eclipsed conformation (B) in which both methyl groups are lined up with hydrogen atoms.



"eclipsed" (B)

Due to steric repulsion between methyl and hydrogen substituents, this eclipsed conformation B is higher in energy than the gauche conformation. However, because there is no methyl-to-methyl eclipsing, it is lower in energy than eclipsed conformation A. One more 60° rotation produces the **'anti'** conformation, where the two methyl groups are positioned opposite each other and steric repulsion is minimized.



anti

The anti conformation is the lowest energy conformation for butane. The diagram below summarizes the relative energies for the various eclipsed, staggered, and gauche conformations.

Figure* 2.7.1:* A 3D Structure of the Anti Butane Conformer.

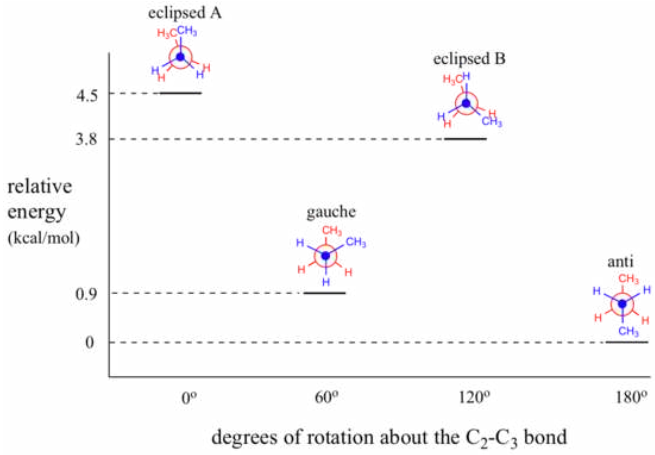


Figure 2.7.2: Potential curve vs dihedral angle of the C_2-C_3 bond of butane.

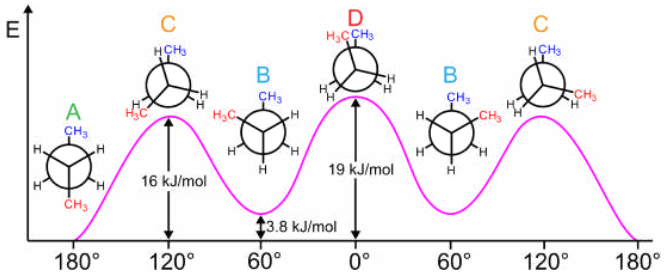
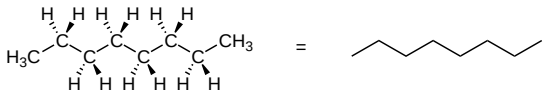


Figure 2.7.2: Newman projections of butane conformations & their relative energy differences (not total energies). Conformations form when butane rotates about one of its single covalent bond. Torsional/dihedral angle is shown on x-axis. Torsional/dihedral angle is shown on x-axis. Conformation names (according to IUPAC): **A**: anti-periplanar, anti or trans **B**: synclinal or gauche **C**: anticlinal or eclipsed **D**: syn-periplanar or cis. Source for conformation names & conformer classification: Pure & Appl. Chem., Vol. 68, No. 12, pp. 2193-2222, 1996. (Public Domain; Keministi).

At room temperature, butane is most likely to be in the lowest-energy anti conformation at any given moment in time, although the energy barrier between the anti and eclipsed conformations is not high enough to prevent constant rotation except at very low temperatures. For this reason (and also simply for ease of drawing), it is conventional to draw straight-chain alkanes in a zigzag form, which implies the anti conformation at all carbon-carbon bonds. For example octane is commonly drawn as:



octane

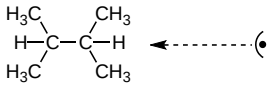
Drawing Newman Projections

Newman projections are a valuable method for viewing the relative positions of groups within molecule. Being able to draw the Newman projection for a given molecule is a valuable skill and will be used repeatedly throughout organic chemistry. Because organic molecules often contain multiple carbon-carbon bonds it is important to precisely know which bond and which direction is being sighted for the Newman projection. The details of the Newman projection change given the molecule but for typical alkanes a full conformational analysis involves a full 360° rotation in 60° increments. This will produce three staggered conformers and three eclipsed conformers. Typically, the staggered conformers are more stable and the eclipsed conformers are less stable. The least stable conformer will have the largest groups eclipsed while the most stable conformer will have the largest groups anti (180°) to each other.

Example

Draw the Newman projection of 2,3 dimethylbutane along the C_2-C_3 bond. Then determine the least stable conformation.

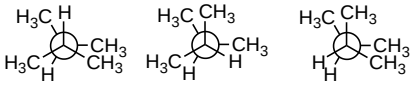
First draw the molecule and locate the indicated bond:



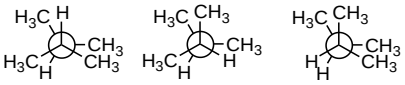
Because the question asks for the least stable conformation, focus on the three possible eclipsed Newman projections. Draw out three eclipsed Newman projections as a template. Because it is difficult to draw a true staggered Newman projection, it is common to show the bonds slightly askew.



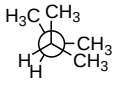
Place the substituents attached to the second carbon (C_3) on the back bonds of all three Newman projections. In this example they are 2 CH_3s and an H. Place the substituents in the same position on all three Newman projections.



Then place the substituents attached to the first carbon (C_2) on the front bonds of the Newman projection. In this example, the substituents are also 2 CH_3s and an H. Move the substituents through two 60° rotations to create the remaining two eclipsed Newman projections. Leave the substituents on the back carbon in place. Attempting to rotate the front and back carbons simultaneously is a common mistake and often leads to incorrect Newman projections.



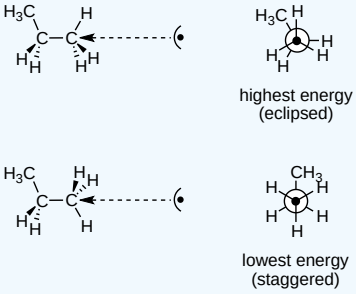
Compare the Newman projections by looking the eclipsed interactions. Remember that the order of torsional strain interactions are CH_3-CH_3 > CH_3-H > H-H. The third structure has two CH_3-CH_3 torsional interactions which will make it the least stable conformer of 2,3 dimethyl butane.



Example 2.7.1

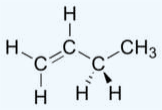
Draw Newman projections of the eclipsed and staggered conformations of propane, as if viewed down the C_1-C_2 bond.

Answer

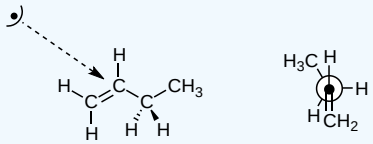


Example 2.7.2

Draw a Newman projection, looking down the C_2-C_3 bond, of 1-butene in the conformation shown below.



Answer



Exercises

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2.8: Gasoline - A Deeper Look

Objectives

After completing this section, you should be able to

1. describe the general nature of petroleum deposits, and recognize why petroleum is such an important source of organic compounds.
2. explain, in general terms, the processes involved in the refining of petroleum.
3. define the octane number of a fuel, and relate octane number to chemical structure.

Key Terms

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

- catalytic cracking
- catalytic reforming
- fractional distillation
- octane number (octane rating)

Study Notes

The refining of petroleum into usable fractions is a very important industrial process. In the laboratory component of this course, you will have the opportunity to compare this industrial process to the distillation procedure as it is performed in the student laboratory.

Petroleum

The petroleum that is pumped out of the ground is a complex mixture of several thousand organic compounds, including straight-chain alkanes, cycloalkanes, alkenes, and aromatic hydrocarbons with four to several hundred carbon atoms. The identities and relative abundance of the components vary depending on the source - Texas crude oil is somewhat different from Saudi Arabian crude oil. In fact, the analysis of petroleum from different deposits can produce a “fingerprint” of each, which is useful in tracking down the sources of spilled crude oil. For example, Texas crude oil is “sweet,” meaning that it contains a small amount of sulfur-containing molecules, whereas Saudi Arabian crude oil is “sour,” meaning that it contains a relatively large amount of sulfur-containing molecules.

Gasoline

Petroleum is converted to useful products such as gasoline in three steps: distillation, cracking, and reforming. Recall from Chapter 1 that distillation separates compounds on the basis of their relative volatility, which is usually inversely proportional to their boiling points. Part (a) in Figure 3.8.1 shows a cutaway drawing of a column used in the petroleum industry for separating the components of crude oil. The petroleum is heated to approximately 400°C (750°F) and becomes a mixture of liquid and vapor. This mixture, called the feedstock, is introduced into the refining tower. The most volatile components (those with the lowest boiling points) condense at the top of the column where it is cooler, while the less volatile components condense nearer the bottom. Some materials are so nonvolatile that they collect at the bottom without evaporating at all. Thus the composition of the liquid condensing at each level is different. These different fractions, each of which usually consists of a mixture of compounds with similar numbers of carbon atoms, are drawn off separately. Part (b) in Figure 3.8.1 shows the typical fractions collected at refineries, the number of carbon atoms they contain, their boiling points, and their ultimate uses. These products range from gases used in natural and bottled gas to liquids used in fuels and lubricants to gummy solids used as tar on roads and roofs.

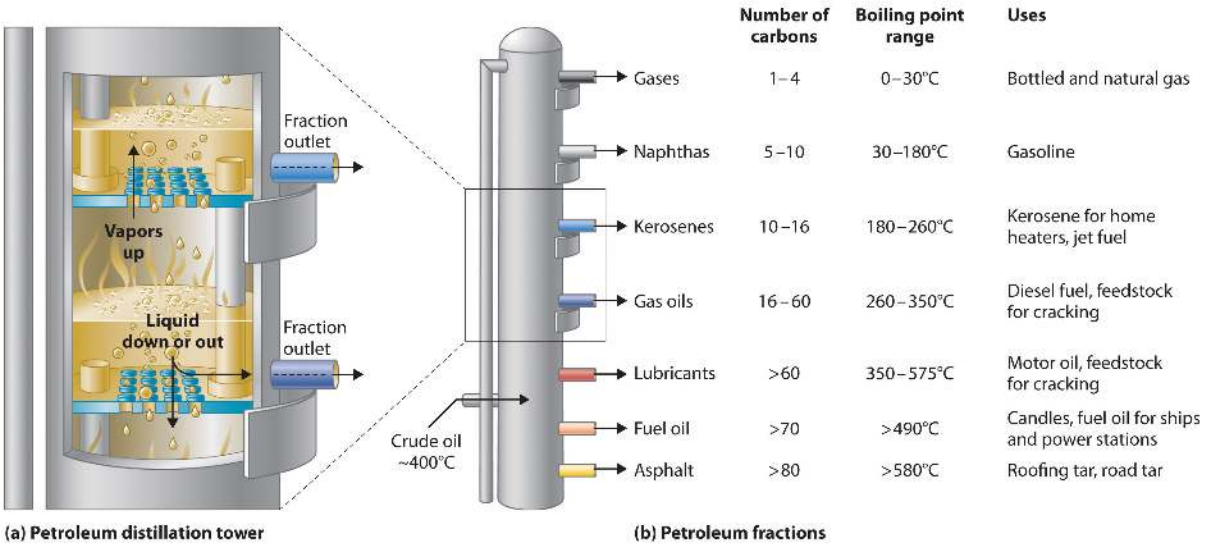


Figure 3.8.1: The Distillation of Petroleum. (a) This is a diagram of a distillation column used for separating petroleum fractions. (b) Petroleum fractions condense at different temperatures, depending on the number of carbon atoms in the molecules, and are drawn off from the column. The most volatile components (those with the lowest boiling points) condense at the top of the column, and the least volatile (those with the highest boiling points) condense at the bottom. (CC BY-NC-SA; anonymous)

The economics of petroleum refining are complex. For example, the market demand for kerosene and lubricants is much lower than the demand for gasoline, yet all three fractions are obtained from the distillation column in comparable amounts. Furthermore, most gasolines and jet fuels are blends with very carefully controlled compositions that cannot vary as their original feedstocks did. To make petroleum refining more profitable, the less volatile, lower-value fractions are converted to more volatile, higher-value mixtures that have carefully controlled formulas. The first process used to accomplish this transformation is cracking, in which the larger and heavier hydrocarbons in the kerosene and higher-boiling-point fractions are heated to temperatures as high as 900°C. High-temperature reactions cause the carbon–carbon bonds to break, which converts the compounds to lighter molecules similar to those in the gasoline fraction. Thus in cracking, a straight-chain alkane with a number of carbon atoms corresponding to the kerosene fraction is converted to a mixture of hydrocarbons with a number of carbon atoms corresponding to the lighter gasoline fraction. The second process used to increase the amount of valuable products is called reforming; it is the chemical conversion of straight-chain alkanes to either branched-chain alkanes or mixtures of aromatic hydrocarbons. Using metals such as platinum brings about the necessary chemical reactions. The mixtures of products obtained from cracking and reforming are separated by fractional distillation.

Octane Ratings

The quality of a fuel is indicated by its octane rating, which is a measure of its ability to burn in a combustion engine without knocking or pinging. Knocking and pinging signal premature combustion (Figure 3.8.2), which can be caused either by an engine malfunction or by a fuel that burns too fast. In either case, the gasoline-air mixture detonates at the wrong point in the engine cycle, which reduces the power output and can damage valves, pistons, bearings, and other engine components. The various gasoline formulations are designed to provide the mix of hydrocarbons least likely to cause knocking or pinging in a given type of engine performing at a particular level.

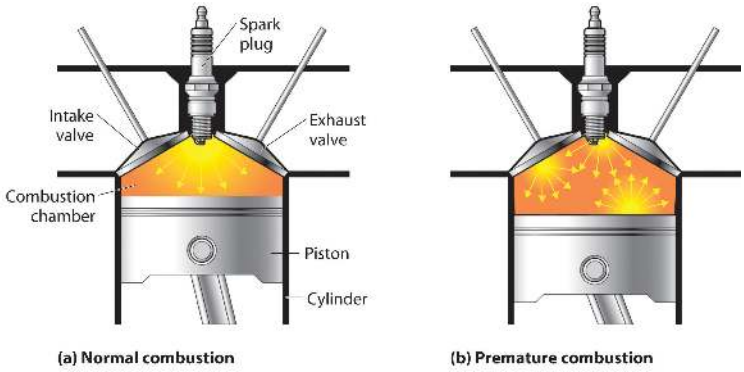


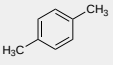
Figure 3.8.2: The Burning of Gasoline in an Internal Combustion Engine. (a) Normally, fuel is ignited by the spark plug, and combustion spreads uniformly outward. (b) Gasoline with an octane rating that is too low for the engine can ignite prematurely, resulting in uneven burning that causes knocking and pinging. (CC BY-NC-SA; anonymous)

The octane scale was established in 1927 using a standard test engine and two pure compounds: n-heptane and isooctane (2,2,4-trimethylpentane). n-Heptane, which causes a great deal of knocking on combustion, was assigned an octane rating of 0, whereas isooctane, a very smooth-burning fuel, was assigned an octane rating of 100. Chemists assign octane ratings to different blends of gasoline by burning a sample of each in a test engine and comparing the observed knocking with the amount of knocking caused by specific mixtures of n-heptane and isooctane. For example, the octane rating of a blend of 89% isooctane and 11% n-heptane is simply the average of the octane ratings of the components weighted by the relative amounts of each in the blend. Converting percentages to decimals, we obtain the octane rating of the mixture:

$$0.89(100) + 0.11(0) = 89 \tag{2.8.1}$$

As shown in Table 2.8.1, many compounds that are now available have octane ratings greater than 100, which means they are better fuels than pure isooctane. In addition, anti-knock agents, also called octane enhancers, have been developed. One of the most widely used for many years was **tetraethyl lead** [$(C_2H_5)_4Pb$], which at approximately 3 g/gal gives a 10–15-point increase in octane rating. Since 1975, however, lead compounds have been phased out as gasoline additives because they are highly toxic. Other enhancers, such as methyl t-butyl ether (MTBE), have been developed to take their place. They combine a high octane rating with minimal corrosion to engine and fuel system parts. Unfortunately, when gasoline containing MTBE leaks from underground storage tanks, the result has been contamination of the groundwater in some locations, resulting in limitations or outright bans on the use of MTBE in certain areas. As a result, the use of alternative octane enhancers such as ethanol, which can be obtained from renewable resources such as corn, sugar cane, and, eventually, corn stalks and grasses, is increasing.

Table 2.8.1: The Octane Ratings of Some Hydrocarbons and Common Additives

Name	Condensed Structural Formula	Octane Rating	Name	Condensed Structural Formula	Octane Rating
n-heptane	$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	0	*o*-xylene	skeletal structure of o-xylene.cdxml	107
n-hexane	$CH_3CH_2CH_2CH_2CH_2CH_3$	25	ethanol	CH_3CH_2OH	108
n-pentane	$CH_3CH_2CH_2CH_2CH_3$	62	*t*-butyl alcohol	$(CH_3)_3COH$	113
isooctane	$(CH_3)_3CCH_2CH(CH_3)_2$	100	*p*-xylene		116
benzene		106	methyl *t*-butyl ether	$H_3COC(CH_3)_3$	116
methanol	CH_3OH	107	toluene		118

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2.S: Organic Compounds- Alkanes and Their Stereochemistry (Summary)

Concepts & Vocabulary

12.1: Functional Groups

- **Functional groups** are atoms or small groups of atoms (two to four) that exhibit a characteristic reactivity.
- Functional groups have characteristic names that often carry over into the naming of compounds.
- The most common organic functional groups that will be encountered is this course are: alkanes, alkenes, alkynes, arenes, (alkyl and aryl) halides, alcohols, ethers, aldehydes, ketones, esters, carboxylic acids, acid chlorides, amides, amines, nitriles, nitro compounds, sulfides and sulfoxides.

12.2: Alkanes and Alkane Isomers

- Hydrocarbons are a common class of organic molecules that contain only carbon and hydrogen atoms.
- Alkanes are one type of hydrocarbon that contains only carbon-carbon and carbon hydrogen single bonds.
- Straight chain and branched alkanes have the generic formula C_nH_{2n+2}, where *n* is equal to the number of carbons. Cycloalkanes have the generic formula C_nH_{2n}.
- Structural isomers are molecules with the same molecular formula, but different structures.

12.3: Alkyl Groups

- Alkyl groups are small hydrocarbon chains attached to the parent alkane chain. The names of alkyl groups use the same prefixes to indicate the number of carbons (meth-, eth-, etc.), but use "-yl" as the ending, instead of "-ane".

12.4: Naming Alkanes

- The IUPAC System of nomenclature provides a set of rules for assigning every molecule a unique name.

12.5: Properties of Alkanes

- The boiling point of an alkane depends upon molecular weight and number of branches in the chain. Boiling points tend to increase with increasing molecular weight. Boiling points tend to decrease within a set of isomers as the number of branches increases.
- Alkanes and cycloalkanes are generally more soluble in organic solvents than in water.

12.6: Conformations of Ethane

- Rotation about the carbon-carbon sigma bonds in ethane results in different **rotational isomers** (also known as **conformational isomers** or **conformers**). **Newman projections** are a very common way of depicting conformers.
- The two most common conformers of ethane are called **staggered** and **eclipsed**. The staggered conformer is lower in energy (more stable) than the eclipsed conformer, because it has less **torsional strain**.

12.7: Conformations of Other Alkanes

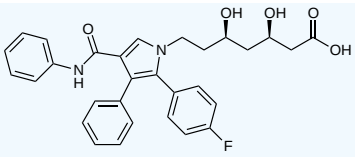
- Alkanes more complex than ethane, will have a greater variety of possible conformers. The **anti** and **gauche** conformers of butane are specific types of staggered conformations.

12.8: Gasoline - A Deeper Look

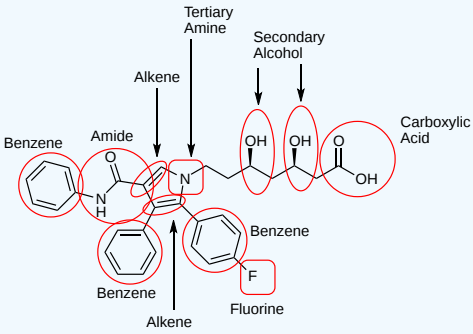
Summary Problems

? Exercise 2.S.1

Atorvastatin (Lipitor) is a synthetic pharmaceutical marketed by Pfizer for lowering blood cholesterol and is one of the top selling drugs in the world. Circle and label all functional groups in Lipitor. (Be sure to label any amines or alcohols as primary, secondary, or tertiary.)

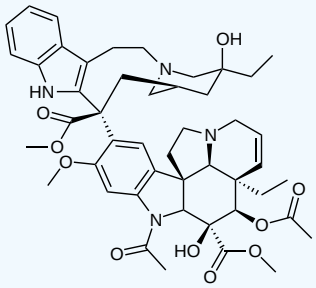


Answer

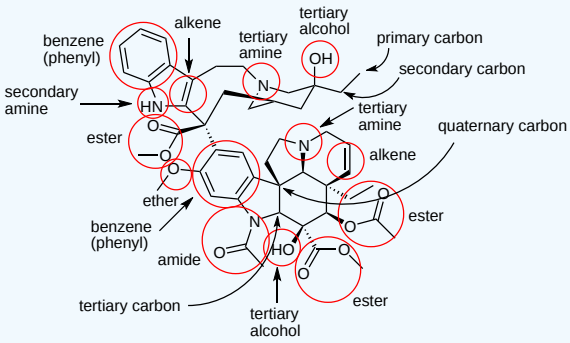


Exercise 2.S.2

Vincristine is a natural product that was originally isolated in 1958 and has been studied as an anticancer agent. Answer the following questions related to this molecule. a) Circle and label all functional groups. (Be sure to label any amines or alcohols as primary, secondary, or tertiary.) b) Clearly label one primary carbon, one secondary carbon, one tertiary carbon, and one quaternary carbon.

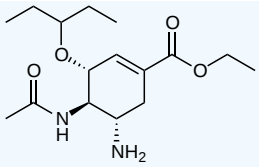


Answer

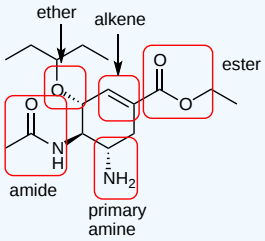


Exercise 2.S.3

Tamiflu (oseltamivir) is an anti-influenza medication that was discovered by Gilead Sciences and is marketed by the pharmaceutical company Genetech. Circle and label all functional groups in Tamiflu. (Be sure to label any amines or alcohols as primary, secondary, or tertiary.)



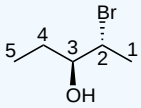
Answer



Notes: Alkanes are not functional groups, so there is no reason to circle groups like methyl or ethyl. (They are structural fragments.) Also, this molecule does not contain an aromatic ring. This is a cyclohexene ring. An aromatic ring is benzene and requires three double bonds in a six-membered ring.

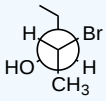
Exercise 2.S.4

For the following structure, a) Draw a Newman projection looking down the C2-C3 bond. (C2 should be in front.) b) Rotate the C2-C3 bond by 180 degrees (keep 3, 4, and 5 in the same orientation as the original structure). Draw the new skeletal structure and the new Newman projection looking down the C2-C3 bond. c) Label the Newman projections from parts a and b as staggered or eclipsed.



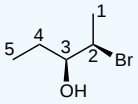
Answer

a)



staggered

b)





eclipsed

Skills to Master

- Skill 12.1 Identify the following functional groups that are present in a given organic molecule: alkanes, alkenes, alkynes, arenes, (alkyl and aryl) halides, alcohols, ethers, aldehydes, ketones, esters, carboxylic acids, acid chlorides, amides, amines, nitriles, and nitro compounds.
- Skill 12.2 Name and draw structures of straight chain alkanes up to ten carbons in length.
- Skill 12.3 Name and draw structures for all the structural isomers of a given molecular formula.
- Skill 12.4 Identify methyl, primary, secondary, tertiary, and quaternary carbons in organic structures.
- Skill 12.5 Provide the IUPAC name of any given alkane or cycloalkane structure.

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- Skill 12.6 Draw the structure of an alkane or cycloalkane given its IUPAC name.
- Skill 12.7 Arrange a series of alkanes in order of increasing or decreasing boiling point.
- Skill 12.8 Be able to draw Newman Projections of different conformers of alkanes.

Memorization Tasks (MT)

- MT 12.1 Memorize the name and structure of each of the common functional groups listed in Skill 3.1.
- MT 12.2 Memorize the names and be able to draw the first ten straight chain alkanes.
- MT 12.3 Memorize the structures and common names of the alkyl substitutent groups - isopropyl, *sec*-butyl, isobutyl,, and *tert*-butyl.

Contributors

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- Kevin M. Shea (Smith College)

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CHAPTER OVERVIEW

3: Stereochemistry at Tetrahedral Centers

This chapter introduces the concept of chirality, and discusses the structure of compounds containing one or two chiral centers. A convenient method of representing the three-dimensional arrangement of the atoms in chiral compounds is explained; furthermore, throughout the chapter , considerable emphasis is placed on the use of molecular models to assist in the understanding of the phenomenon of chirality. The chapter continues with an examination of stereochemistry—the three-dimensional nature of molecules. The subject is introduced using the experimental observation that certain substances have the ability to rotate plane-polarized light. Finally, certain reactions of alkenes are re-examined in the light of the new material encountered in this chapter.

3.1: Enantiomers and the Tetrahedral Carbon
3.2: The Reason for Handedness in Molecules - Chirality
3.3: Optical Activity
3.4: Pasteur's Discovery of Enantiomers
3.5: Sequence Rules for Specifying Configuration
3.6: Diastereomers
3.7: Racemic Mixtures and the Resolution of Enantiomers
3.8: Chirality in Nature and Chiral Environments
3.9: A Review of Isomerism
3.S: Stereochemistry at Tetrahedral Centers (Summary)

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3.1: Enantiomers and the Tetrahedral Carbon

Objectives

After completing this section, you should be able to

1. use molecular models to show that only a tetrahedral carbon atom satisfactorily accounts for the lack of isomerism in molecules of the type CH_2XY, and for the existence of optical isomerism in molecules of the type CHXYZ.
2. determine whether two differently oriented wedge-and-broken-line structures are identical or represent a pair of enantiomers.

Key Terms

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

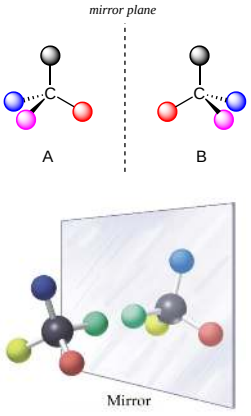
- enantiomer

Study Notes

Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. One of the most interesting types of isomer is the mirror-image stereoisomer, a non-superimposable set of two molecules that are mirror images of one another. The existence of these molecules are determined by a a concept known as **chirality**. The word “chiral” was derived from the Greek word for hand, because our hands are a good example of chirality since they are non-superimposable mirror images of each other.

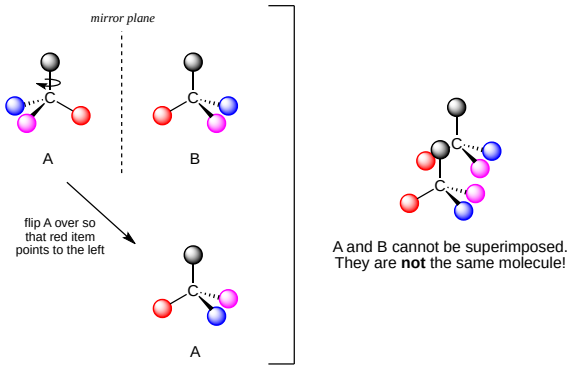
Chiral Molecules

The term **chiral**, from the Greek work for 'hand', refers to anything which cannot be superimposed on its own mirror image. Certain organic molecules are chiral meaning that they are not superimposable on their mirror image. Chiral molecules contain one or more **chiral centers**, which are almost always tetrahedral (sp^3-hybridized) carbons with four different substituents. Consider the molecule A below: a tetrahedral carbon, with four different substituents denoted by balls of four different colors.



The mirror image of A, which we will call B, is drawn on the right side of the figure, and an imaginary mirror is in the middle. Notice that every point on A lines up through the mirror with the same point on B: in other words, if A looked in the mirror, it would see B looking back.

Now, if we flip compound A over and try to superimpose it point for point on compound B, we find that we cannot do it: if we superimpose any two colored balls, then the other two are misaligned.



A is not superimposable on its mirror image (B), thus by definition A is a chiral molecule. It follows that B also is not superimposable on *its* mirror image (A), and thus it is also a chiral molecule.

A and B are called **stereoisomers or optical isomers**: molecules with the same molecular formula and the same bonding arrangement, but *a different arrangement of atoms in space*. **Enantiomers** are pairs of stereoisomers which are mirror images of each other: thus, A and B are enantiomers. It should be self-evident that a chiral molecule will always have one (and *only* one) enantiomer: enantiomers come in pairs. Enantiomers have identical physical properties (melting point, boiling point, density, and so on). However, enantiomers do differ in how they interact with polarized light (we will learn more about this soon) and they may also interact in very different ways with other chiral molecules - proteins, for example. We will begin to explore this last idea in later in this chapter, and see many examples throughout the remainder of our study of biological organic chemistry.

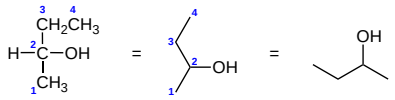
The Many Synonyms of the Chiral Carbon

Be aware - all of the following terms can be used to describe a chiral carbon.

chiral carbon = asymmetric carbon = optically active carbon = stereo carbon = stereo center = chiral center

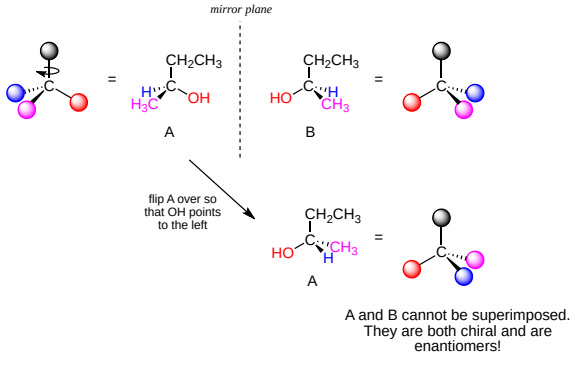
Let's apply our chirality discussion to real molecules.

Consider 2-butanol, drawn in two dimensions below.



2-butanol
(drawn in 2D)

Carbon #2 is a chiral center: it is sp^3-hybridized and tetrahedral (even though it is not drawn that way above), and the four substituents attached to is are different: a hydrogen (H) , a methyl ($-CH_3$) group, an ethyl ($-CH_2CH_3$) group, and a hydroxyl (OH) group. If the bonding at C_2 of 2-butanol is drawn in three dimensions and this structure called A. Then the mirror image of A can be drawn to form structure B.



When we try to superimpose A onto B, we find that we cannot do it. Because structure A and B are not superimposable on their mirror image they are both chiral molecules. Because A and B are different due only to the arrangement of atoms in space they are

stereoisomers. Because A and B are mirror images of each other they are also enantiomers. When looking at simplified line structures is clear that there are two distinct ways of drawing 2-butanol which only differ in their spatial arrangement around a chiral carbon.

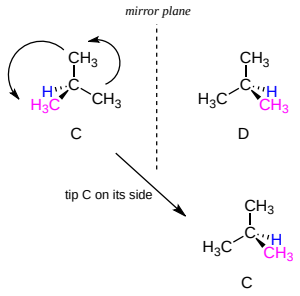


two enantiomers of 2-butanol

The 3D Structures of the Two Enantiomers of 2-Butanol

For comparison, 2-propanol, is an achiral molecule because is lacks a chiral carbon. Carbon #2 is bonded to two identical substituents (methyl groups), and so it is not a chiral carbon. Being achiral means that 2-propanol should be superimposable on its mirror image which is shown in the figure below. A more detailed explaination on why 2-propanol is achiral will be given in the next section.

2-propanol is achiral:



C and D can be superimposed.
They are the same molecule!

Stereoisomers

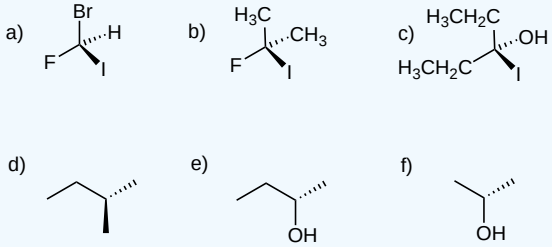
Stereoisomers have been defined as molecules with the same connectivity but different arrangements of the atoms in space. It is important to note that there are two types of stereoisomers: geometric and optical.

Optical isomers are molecules whose structures are mirror images but cannot be superimposed on one another in any orientation. Optical isomers have identical physical properties, although their chemical properties may differ in asymmetric environments. Molecules that are nonsuperimposable mirror images of each other are said to be chiral. 25.7.1a" id="MathJax-Element-1-Frame" role="presentation" style="position:relative;" tabindex="0">

Geometric isomers differ in the relative position(s) of substituents in a rigid molecule. Simple rotation about a C–C σ bond in an alkene, for example, cannot occur because of the presence of the π bond. The substituents are therefore rigidly locked into a particular spatial arrangement. Thus a carbon–carbon multiple bond, or in some cases a ring, prevents one geometric isomer from being readily converted to the other. The members of an isomeric pair are identified as either cis or trans, and interconversion between the two forms requires breaking and reforming one or more bonds. Because their structural difference causes them to have different physical and chemical properties, cis and trans isomers are actually two distinct chemical compounds.mers have the same connectivity, but different arrangements of atoms in space. Geometric isomers will be discussed in more detain in **Sections 7.4 and 7.5**.

? Exercise 3.1.1

Identify the following molecules as chiral or achiral.



https://chem.libretexts.org/@go/page/396255

Answer

a) chiral (4 different groups off C)

b) achiral (2 identical -CH_3 substituents off central C)

c) achiral (2 identical -CH_2CH_3 substituents off central C)

d) achiral (2 identical CH_3 substituents off carbon 2)

e) chiral (4 different groups off carbon 2)

f) achiral (2 identical CH_3 substituents off central C)

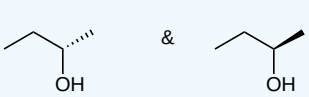
Exercise 3.1.2

Determine if the following sets of compounds in each group are enantiomers or the same compound.

a) 

b) 

c) 

d) 

Answer

a) enantiomers – non superimposable mirror images

b) same compound – when you rotate the molecule on the right it is identical to the one on the left

c) enantiomers – non superimposable mirror images

d) enantiomers – non superimposable mirror images

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- **24.7: Chirality in Organic Chemistry** is licensed CC BY-NC-SA 3.0.

3.2: The Reason for Handedness in Molecules - Chirality

Objectives

After completing this section, you should be able to

1. determine whether or not a compound is chiral, given its Kelulé, condensed or shorthand structure, with or without the aid of molecular models.
2. label the chiral centres (carbon atoms) in a given Kelulé, condensed or shorthand structure.

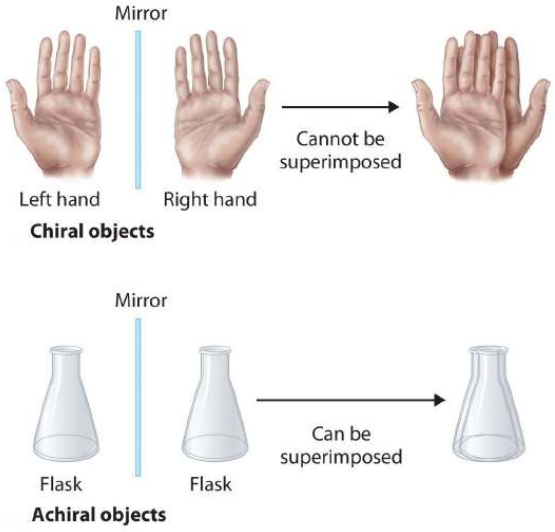
Key Terms

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

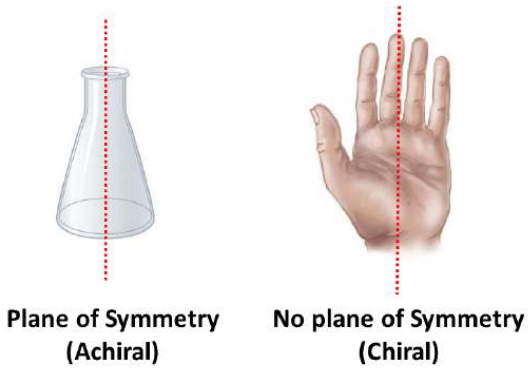
- achiral
- chiral
- chiral (stereogenic) centre
- plane of symmetry

Symmetry and Chirality

Molecules that are nonsuperimposable mirror images of each other are said to be chiral (pronounced “ky-ral,” from the Greek cheir, meaning “hand”). Examples of some familiar chiral objects are your hands. Your left and right hands are nonsuperimposable mirror images. (Try putting your right shoe on your left foot—it just doesn’t work.) An achiral object is one that can be superimposed on its mirror image, as shown by the superimposed flasks 25.7.1b in the figure below. .

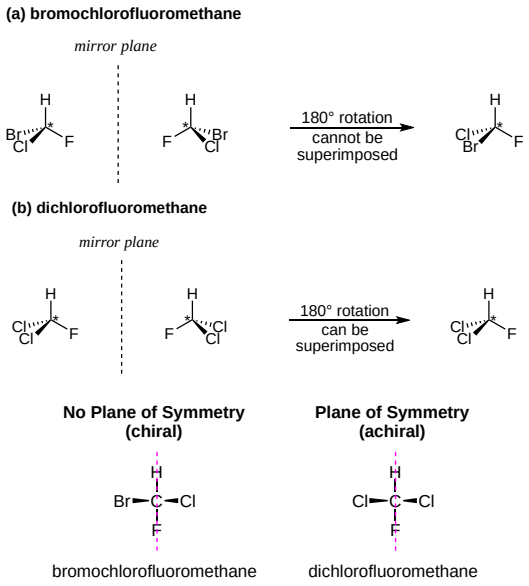


An an important questions is why is one chiral and the other not? The answer is that the flask has a plane of symmetry and your hand does not. A plane of symmetry is a plane or a line through an object which divides the object into two halves that are mirror images of each other. When looking at the flask, a line can be drawn down the middle which separates it into two mirror image halves. However, a similar line down the middle of a hand separates it into two non-mirror image halves. This idea can be used to predict chirality. If an object or molecule has a plane of symmetry it is achiral. If if lacks a plane of symmetry it is chiral.



Symmetry can be used to explain why a carbon bonded to four different substituents is chiral. When a carbon is bonded to fewer than four different substituents it will have a plane of symmetry making it achiral. A carbon atom that is bonded to four different substituents loses all symmetry, and is often referred to as an asymmetric carbon. The lack of a plane of symmetry makes the carbon chiral. The presence of a single chiral carbon atom sufficient to render the molecule chiral, and modern terminology refers to such groupings as chiral centers or stereo centers.

An example is shown in the bromochlorofluoromethane molecule shown in part (a) of the figure below. This carbon, is attached to four different substituents making it chiral. which is often designated by an asterisk in structural drawings. If the bromine atom is replaced by another chlorine to make dichlorofluoromethane, as shown in part (b) below, the molecule and its mirror image can now be superimposed by simple rotation. Thus the carbon is no longer a chiral center. Upon comparison, bromochlorofluoromethane lacks a plane of symmetry while dichlorofluoromethane has a plane of symmetry.

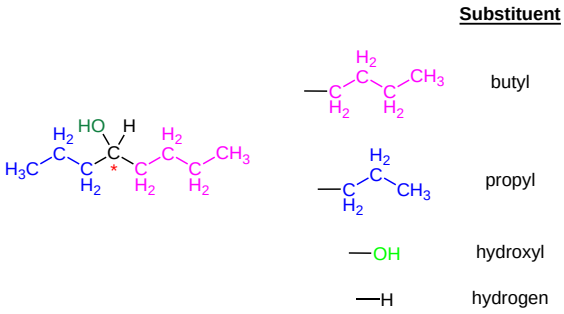


Identifying Chiral carbons

Identifying chiral carbons in a molecule is an important skill for organic chemists. The presence of a chiral carbon presents the possibility of a molecule having multiple stereoisomers. Most of the chiral centers we shall discuss in this chapter are asymmetric carbon atoms, but it should be recognized that other tetrahedral or pyramidal atoms may become chiral centers if appropriately substituted. Also, when more than one chiral center is present in a molecular structure, care must be taken to analyze their relationship before concluding that a specific molecular configuration is chiral or achiral. This aspect of stereoisomerism will be treated later. Because an carbon requires four different substituents to become asymmertric, it can be said, with few exceptions, that sp^2 and sp hybridized carbons involved in multiple bonds are achiral. Also, any carbon with more than one hydrogen, such as a -CH_3 or -CH_2- group, are also achiral.

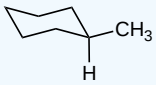
Looking for planes of symmetry in a molecule is useful, but often difficult in practice. It is difficult to illustrate on the two dimensional page, but you will see if you build models of these achiral molecules that, in each case, there is at least one **plane of symmetry**, where one side of the plane is the mirror image of the other. In most cases, the easiest way to decide whether a molecule is chiral or achiral is to look for one or more stereocenters - with a few rare exceptions, the general rule is that molecules with at least one stereocenter are chiral, and molecules with no stereocenters are achiral.

Determining if a carbon is bonded to four distinctly different substituents can often be difficult to ascertain. Remember even the slightest difference makes a substituent unique. Often these difference can be distant from the chiral carbon itself. Careful consideration and often the building of molecular models may be required. A good example is shown below. It may appear that the molecule is achiral, however, when looking at the groups directly attached to the possible chiral carbon, it is clear that they all different. The two alkyl groups are differ by a single -CH_2- group which is enough to consider them different.



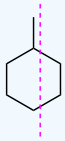
Example 3.2.1

Predict if the following molecule would be chiral or achiral:



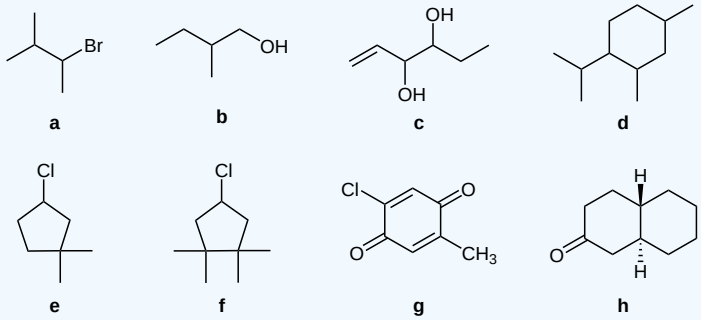
Answer

Achiral. When determining the chirality of a molecule, it best to start by locating any chiral carbons. An obvious candidate is the ring carbon attached to the methyl substituent. The question then becomes: does the ring as two different substituents making the substituted ring carbon chiral? With an uncertainty such as this, it is then helpful try to identify any planes of symmetry in the molecule. This molecule does have a plane of symmetry making the molecule achiral. The plane of symmetry would be easier see if the molecule were view from above. Typically, monosubstituted cycloalkanes have a similar plane of symmetry making them all achiral.

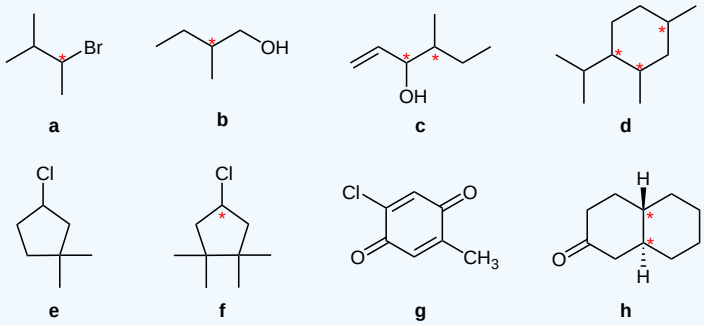


Exercise 5.2.1

Determine if each of the following molecules are chiral or achiral. For chiral molecules indicate any chiral carbons.



Answer

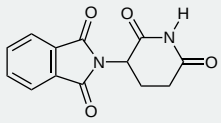


Explanation

Structures F and G are achiral. The former has a plane of symmetry passing through the chlorine atom and bisecting the opposite carbon-carbon bond. The similar structure of compound E does not have such a symmetry plane, and the carbon bonded to the chlorine is a chiral center (the two ring segments connecting this carbon are not identical). Structure G is essentially flat. All the carbons except that of the methyl group are sp^2 hybridized, and therefore trigonal-planar in configuration. Compounds C, D & H have more than one chiral center, and are also chiral.

Note

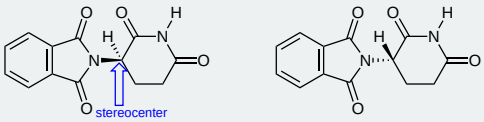
In the 1960's, a drug called thalidomide was widely prescribed in the Western Europe to alleviate morning sickness in pregnant women.



thalidomide

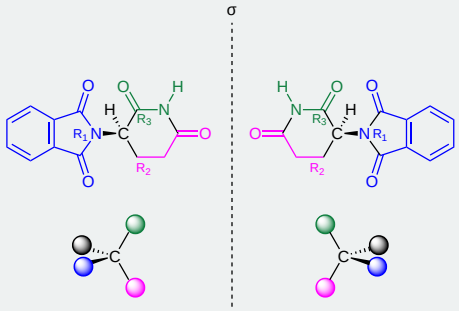
Thalidomide had previously been used in other countries as an antidepressant, and was believed to be safe and effective for both purposes. The drug was not approved for use in the U.S.A. It was not long, however, before doctors realized that something had gone horribly wrong: many babies born to women who had taken thalidomide during pregnancy suffered from severe birth defects.

Researchers later realized the problem lay in the fact that thalidomide was being provided as a mixture of two different isomeric forms.



effective isomer mutagenic isomer

One of the isomers is an effective medication, the other caused the side effects. Both isomeric forms have the same molecular formula and the same atom-to-atom connectivity, so they are not constitutional isomers. Where they differ is in the arrangement in three-dimensional space about one tetrahedral, sp^3-hybridized carbon. These two forms of thalidomide are **stereoisomers**. If you make models of the two stereoisomers of thalidomide, you will see that they too are mirror images, and cannot be superimposed.

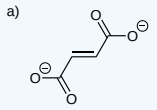


As a historical note, thalidomide was never approved for use in the United States. This was thanks in large part to the efforts of Dr. Frances Kelsey, a Food and Drug officer who, at peril to her career, blocked its approval due to her concerns about the lack of adequate safety studies, particularly with regard to the drug's ability to enter the bloodstream of a developing fetus. Unfortunately, though, at that time clinical trials for new drugs involved widespread and unregulated distribution to doctors and their patients across the country, so families in the U.S. were not spared from the damage caused.

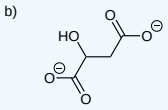
Very recently a close derivative of thalidomide has become legal to prescribe again in the United States, with strict safety measures enforced, for the treatment of a form of blood cancer called multiple myeloma. In Brazil, thalidomide is used in the treatment of leprosy - but despite safety measures, children are still being born with thalidomide-related defects.

Example 5.2.2

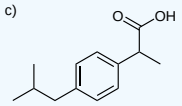
Label the molecules below as chiral or achiral, and locate all stereocenters.



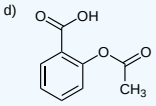
fumarate
(a citric acid cycle intermediate)



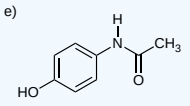
malate
(a citric acid cycle intermediate)



ibuprofen

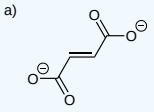


acetylsalicylic acid
(aspirin)

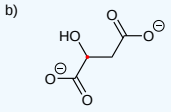


acetaminophen
(active ingredient in Tylenol)

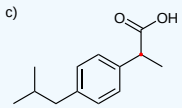
Answer



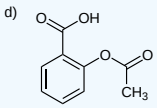
fumarate
(achiral)



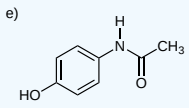
malate
(chiral)



ibuprofen
(chiral)



acetylsalicylic acid
(achiral)



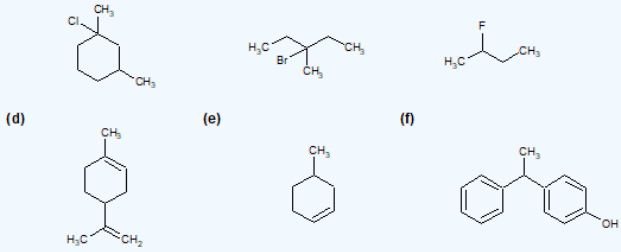
acetaminophen
(achiral)

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Exercise 5.2.2

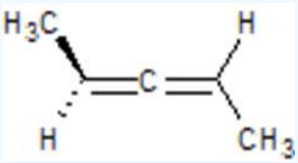
1) For the following compounds, star (*) each chiral center, if any.

(a) (b) (c)



(d) (e) (f)

2) Explain why the following compound is chiral.



3) Determine which of the following objects is chiral.

a) A Glove.

b) A nail.

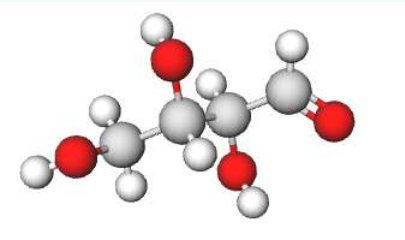
c) A pair of sunglasses.

d) The written word "Chiral".

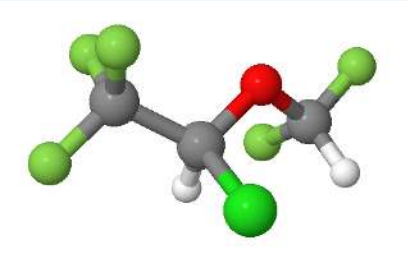
4) Place an "*" by all of the chrial carbons in the following molecules.

a)

Erythrose, a four carbon sugar.

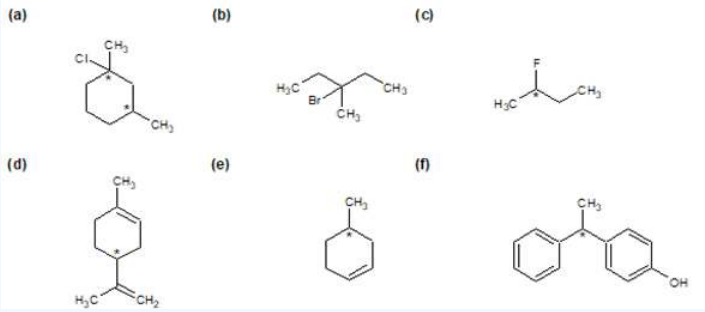


b) Isoflurane, an anestetic. Bright green = Chlorine, Pale green = Fluorine.



Answer

1)



2) Though the molecule does not contain a chiral carbon, it is chiral as it is non-superimposable on its mirror image due to its twisted nature (the twist comes from the structure of the double bonds needing to be at 90° angles to each other, preventing the molecule from being planar).

3)

a) Just as hands are chiral a glove must also be chiral.

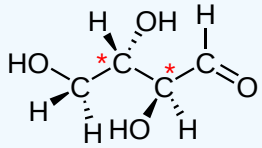
b) A nail has a plane of symmetry which goes down the middle making it a achiral.

c) A pair of sunglasses has a plane of symmetry which goes through the nose making it achiral.

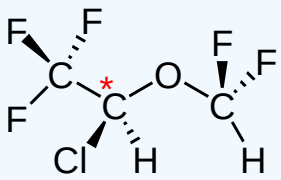
d) Most written words are chiral. Look one in a mirror to confirm this.

4

a)

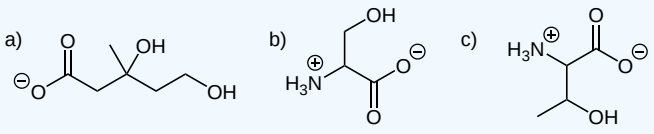


b)



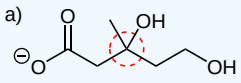
Exercise 5.2.3

Circle all of the carbon stereocenters in the molecules below.

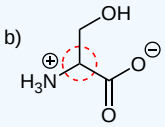


mevalonate serine threonine

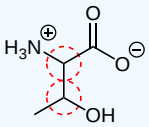
Answer

a) 

mevalonate

b) 

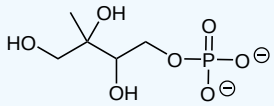
serine

c) 

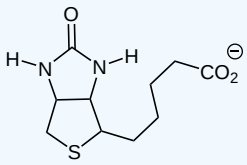
threonine

Exercise 5.2.4

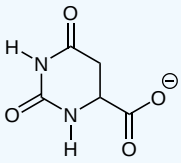
Circle all of the carbon stereocenters in the molecules below.

a) 

2-methylerythritol-4-phopshate

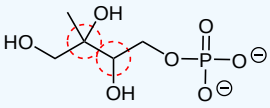
b) 

biotin

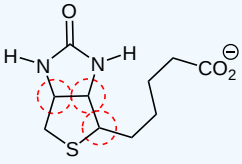
c) 

dihydroorotate

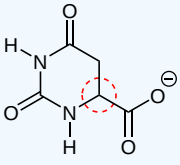
Answer

a) 

2-methylerythritol-4-phopshate

b) 

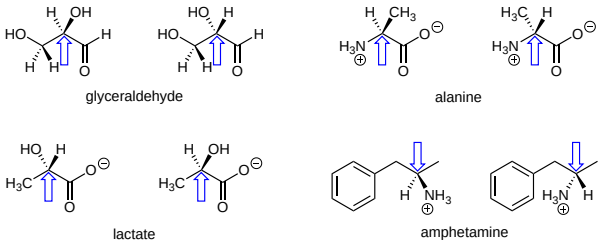
biotin

c) 

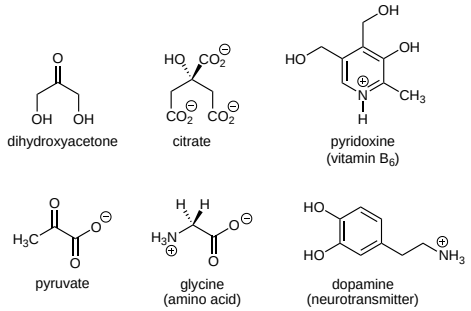
dihydroorotate

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Here are some more examples of chiral molecules that exist as pairs of enantiomers. In each of these examples, there is a single stereocenter, indicated with an arrow. (Many molecules have more than one stereocenter, but we will get to that that a little later!)



Here are some examples of molecules that are **achiral** (*not* chiral). Notice that none of these molecules has a stereocenter.

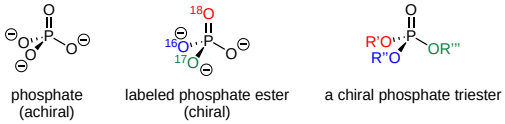


It is difficult to illustrate on the two dimensional page, but you will see if you build models of these achiral molecules that, in each case, there is at least one **plane of symmetry**, where one side of the plane is the mirror image of the other. Chirality is tied conceptually to the idea of asymmetry, and *any molecule that has a plane of symmetry cannot be chiral*. When looking for a plane of symmetry, however, we must consider all possible conformations that a molecule could adopt. Even a very simple molecule like ethane, for example, is asymmetric in many of its countless potential conformations – but it has obvious symmetry in both the eclipsed and staggered conformations, and for this reason it is achiral.

Looking for planes of symmetry in a molecule is useful, but often difficult in practice. In most cases, the easiest way to decide whether a molecule is chiral or achiral is to look for one or more stereocenters - with a few rare exceptions (see section 3.7B), the general rule is that molecules with at least one stereocenter are chiral, and molecules with no stereocenters are achiral. Carbon stereocenters are also referred to quite frequently as **chiral carbons**.

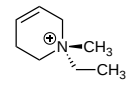
When evaluating a molecule for chirality, it is important to recognize that the question of whether or not the dashed/solid wedge drawing convention is used is irrelevant. Chiral molecules are sometimes drawn without using wedges (although obviously this means that stereochemical information is being omitted). Conversely, wedges may be used on carbons that are not stereocenters – look, for example, at the drawings of glycine and citrate in the figure above. Just because you see dashed and solid wedges in a structure, do not automatically assume that you are looking at a stereocenter.

Other elements in addition to carbon can be stereocenters. The phosphorus center of phosphate ion and organic phosphate esters, for example, is tetrahedral, and thus is potentially a stereocenter.

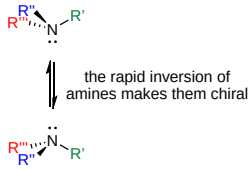


We will see in chapter 10 how researchers, in order to investigate the stereochemistry of reactions at the phosphate center, incorporated sulfur and/or ^{17}O and ^{18}O isotopes of oxygen (the 'normal' isotope is ^{16}O) to create chiral phosphate groups. Phosphate triesters are chiral if the three substituent groups are different.

Asymmetric quaternary ammonium groups are also chiral. Amines, however, are not chiral, because they rapidly invert, or turn 'inside out', at room temperature.



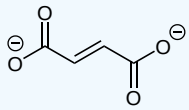
a chiral quaternary ammonium



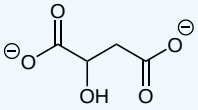
Exercise 5.2.5

Label the molecules below as chiral or achiral, and circle all stereocenters.

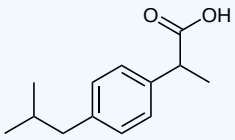
a) fumarate (a citric acid cycle intermediate)



b) malate (a citric acid cycle intermediate)

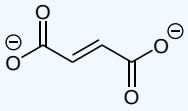


b) malate (a citric acid cycle intermediate)

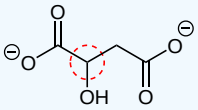


Answer

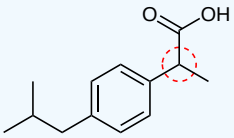
a) achiral (no stereocenters)



b) chiral



c) chiral

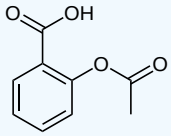


Exercise 5.2.6

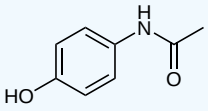
Label the molecules below as chiral or achiral, and circle all stereocenters.

a) acetylsalicylic acid (aspirin)

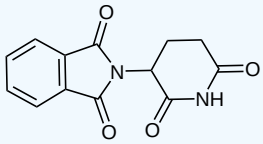
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b) acetaminophen (active ingredient in Tylenol)

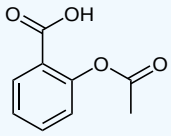


c) thalidomide (drug that caused birth defects in pregnant mothers in the 1960's)

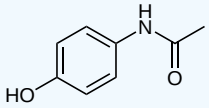


Answer

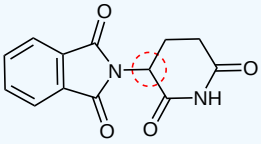
a) achiral (no stereocenters)



b) achiral (no stereocenters)

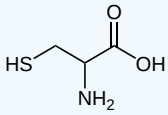


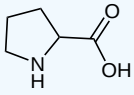
c) chiral



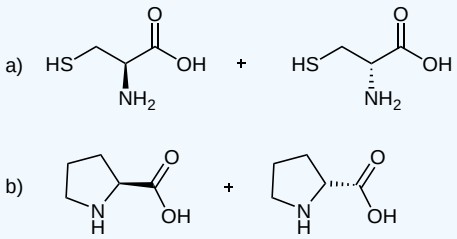
Exercise 5.2.7

Draw both enantiomers of the following chiral amino acids.

a) Cysteine 

b) Proline 

Answer



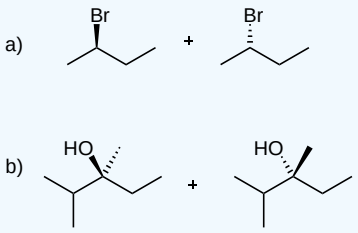
Exercise 5.2.8

Draw both enantiomers of the following compounds from the given names.

a) 2-bromobutane

b) 2,3-dimethyl-3-pentanol

Answer



Exercise 5.2.9

Which of the following body parts are chiral?

a) Hands b) Eyes c) Feet d) Ears

Answer

a) Hands- chiral since the mirror images cannot be superimposed (think of the example in the beginning of the section)

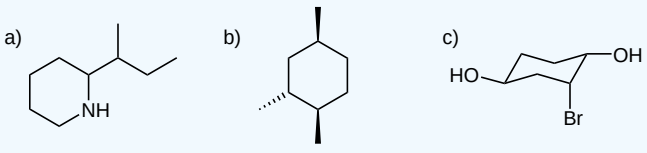
b) Eyes- achiral since mirror images that are superimposable

c) Feet- chiral since the mirror images cannot be superimposed (Does your right foot fit in your left shoe?)

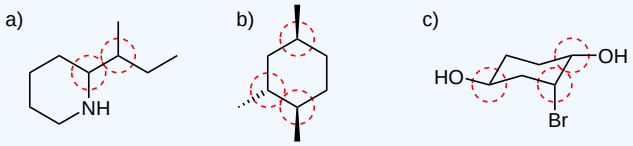
d) Ears- chiral since the mirror images cannot be superimposed

Exercise 5.2.10

Circle the chiral centers in the following compounds.



Answer

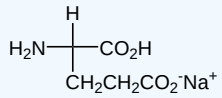


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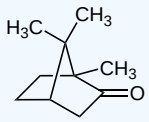
Exercise 5.2.11

Identify the chiral centers in the following compounds.

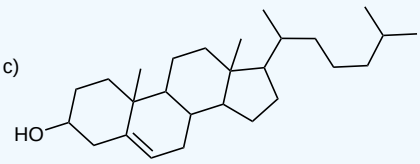
a)



b)

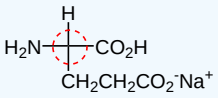


c)

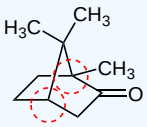


Answer

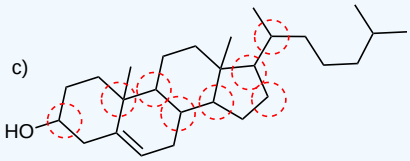
a)



b)



c)



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3.3: Optical Activity

Objectives

After completing this section, you should be able to

1. describe the nature of plane-polarized light.
2. describe the features and operation of a simple polarimeter.
3. calculate the specific rotation of a compound, given the relevant experimental data.

Key Terms

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

- analyzer
- dextrorotatory
- levorotatory
- optically active
- plane-polarized light
- polarimeter
- polarizer
- specific rotation, $[\alpha]_D^{20}$

Study Notes

A *polarizer* is a device through which only light waves oscillating in a single plane may pass. A *polarimeter* is an instrument used to determine the angle through which plane-polarized light has been rotated by a given sample. You will have the opportunity to use a polarimeter in the laboratory component of the course. An *analyzer* is the component of a polarimeter that allows the angle of rotation of plane-polarized light to be determined.

Specific rotations are normally measured at 20°C, and this property may be indicated by the symbol $[\alpha]_D^{20}$. Sometimes the solvent is specified in parentheses behind the specific rotation value, for example,

$$[\alpha]_D^{20} = +12^o \text{ (chloroform)}$$

For liquids, the specific rotation may be obtained using the neat liquid rather than a solution; in such cases the formula is

$$[\alpha]_D^{\text{temp}} \text{ (neat)} = \alpha \times l \times d$$

where α is the observed rotation, l is the path length of the cell (measured in decimetres, dm), and d is the density of the liquid.

Identifying and distinguishing enantiomers is inherently difficult, since their physical and chemical properties are largely identical. Fortunately, a nearly two hundred year old discovery by the French physicist Jean-Baptiste Biot has made this task much easier. This discovery disclosed that the right- and left-handed enantiomers of a chiral compound perturb plane-polarized light in opposite ways. This perturbation is unique to chiral molecules, and has been termed **optical activity**.

Polarimetry

Plane-polarized light is created by passing ordinary light through a polarizing device, which may be as simple as a lens taken from polarizing sun-glasses. Such devices transmit selectively only that component of a light beam having electrical and magnetic field vectors oscillating in a single plane. The plane of polarization can be determined by an instrument called a **polarimeter** (Figure 3.3.1).

Monochromatic (single wavelength) light, is polarized by a fixed polarizer next to the light source. A sample cell holder is located in line with the light beam, followed by a movable polarizer (the analyzer) and an eyepiece through which the light intensity can be observed. In modern instruments an electronic light detector takes the place of the human eye. In the absence of a sample, the light

intensity at the detector is at a maximum when the second (movable) polarizer is set parallel to the first polarizer (α = 0º). If the analyzer is turned 90º to the plane of initial polarization, all the light will be blocked from reaching the detector.

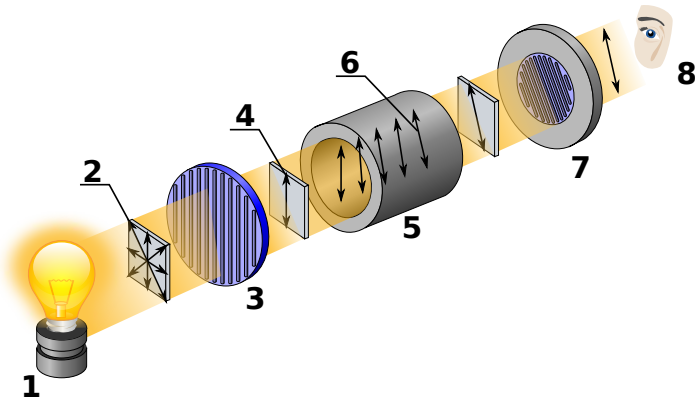


Figure 3.3.1: Operating principle of an optical polarimeter. 1. Light source 2. Unpolarized light 3. Linear polarizer 4. Linearly polarized light 5. Sample tube containing molecules under study 6. Optical rotation due to molecules 7. Rotatable linear analyzer 8. Detector. (CC BY-SA 3.0 Unported; Kaidor via Wikipedia)

Chemists use polarimeters to investigate the influence of compounds (in the sample cell) on plane polarized light. Samples composed only of achiral molecules (e.g. water or hexane), have no effect on the polarized light beam. However, if a single enantiomer is examined (all sample molecules being right-handed, or all being left-handed), the plane of polarization is rotated in either a clockwise (positive) or counter-clockwise (negative) direction, and the analyzer must be turned an appropriate matching angle, **α**, if full light intensity is to reach the detector. In the above illustration, the sample has rotated the polarization plane clockwise by +90º, and the analyzer has been turned this amount to permit maximum light transmission.

The observed rotations (α) of enantiomers are opposite in direction. One enantiomer will rotate polarized light in a clockwise direction, termed **dextrorotatory** or (+), and its mirror-image partner in a counter-clockwise manner, termed **levorotatory** or (–). The prefixes dextro and levo come from the Latin *dexter*, meaning right, and *laevus*, for left, and are abbreviated *d* and *l* respectively. If equal quantities of each enantiomer are examined , using the same sample cell, then the magnitude of the rotations will be the same, with one being positive and the other negative. To be absolutely certain whether an observed rotation is positive or negative it is often necessary to make a second measurement using a different amount or concentration of the sample. In the above illustration, for example, α might be –90º or +270º rather than +90º. If the sample concentration is reduced by 10%, then the positive rotation would change to +81º (or +243º) while the negative rotation would change to –81º, and the correct α would be identified unambiguously.

Since it is not always possible to obtain or use samples of exactly the same size, the observed rotation is usually corrected to compensate for variations in sample quantity and cell length. Thus it is common practice to convert the observed rotation, α, to a **specific rotation**, by the following formula:

$$[\alpha]_D = \frac{\alpha}{lc} \tag{5.3.1}$$

where

- $[\alpha]_D$ is the specific rotation
- l is the cell length in dm
- c is the concentration in g/ml
- D designates that the light used is the 589 line from a sodium lamp

Compounds that rotate the plane of polarized light are termed **optically active**. Each enantiomer of a stereoisomeric pair is optically active and has an equal but opposite-in-sign specific rotation. Specific rotations are useful in that they are experimentally determined constants that characterize and identify pure enantiomers. For example, the lactic acid enantiomers have the following specific rotations:

- Carvone from caraway: $[\alpha]_D^{20} = +62.5^o$ (this isomer may be referred to as (+)-carvone or d-carvone)
- Carvone from spearmint: $[\alpha]_D^{20} = -62.5^o$ (this isomer may be referred to as (–)-carvone or l-carvone)

and carvone enantiomers have the following specific rotations:

- Lactic acid from muscle tissue: $[\alpha]_D^{20} = +2.5^o$ (this isomer may be referred to as (+)-lactic acid or d-lactic acid)
- Lactic acid from sour milk: $[\alpha]_D^{20} = -2.5^o$ (this isomer may be referred to as (–)-lactic acid or l-lactic acid)

A 50:50 mixture of enantiomers has no observable optical activity. Such mixtures are called **racemates** or racemic modifications, and are designated (±). When chiral compounds are created from achiral compounds, the products are racemic unless a single enantiomer of a chiral co-reactant or catalyst is involved in the reaction. The addition of HBr to either cis- or trans-2-butene is an example of racemic product formation (the chiral center is colored red).

$$CH_3CH{=}CHCH_3 + HBr \longrightarrow (\pm)CH_3CH_2\color{red}{C}HBrCH_3$$

Chiral organic compounds isolated from living organisms are usually optically active, indicating that one of the enantiomers predominates (often it is the only isomer present). This is a result of the action of chiral catalysts we call enzymes, and reflects the inherently chiral nature of life itself. Chiral synthetic compounds, on the other hand, are commonly racemates, unless they have been prepared from enantiomerically pure starting materials.

There are two ways in which the condition of a chiral substance may be changed:

1. A racemate may be separated into its component enantiomers. This process is called **resolution**.
2. A pure enantiomer may be transformed into its racemate. This process is called **racemization**.

Enantiomeric Excess

The "optical purity" is a comparison of the optical rotation of a pure sample of unknown stereochemistry versus the optical rotation of a sample of pure enantiomer. It is expressed as a percentage. If the sample only rotates plane-polarized light half as much as expected, the optical purity is 50%.

$$\%\ \text{optical purity} = \frac{\text{specific rotation of mixture}}{\text{specific rotation of pure enantiomer}} \times 100\%$$

Because *R* and *S* enantiomers have equal but opposite optical activity, it naturally follows that a 50:50 racemic mixture of two enantiomers will have no observable optical activity. If we know the specific rotation for a chiral molecule, however, we can easily calculate the ratio of enantiomers present in a mixture of two enantiomers, based on its measured optical activity. When a mixture contains more of one enantiomer than the other, chemists often use the concept of **enantiomeric excess (ee)** to quantify the difference. Enantiomeric excess can be expressed as:

$$ee = \frac{(\%\ \text{more abundant enantiomer} - 50) \times 100\%}{50}$$

For example, a mixture containing 60% *R* enantiomer (and 40% *S* enantiomer) has a 20% enantiomeric excess of R: ((60-50) x 100) / 50 = 20 %.

? Exercise 3.3.1

The specific rotation of (*S*)-carvone is (+)61°, measured 'neat' (pure liquid sample, no solvent). The optical rotation of a neat sample of a mixture of *R* and *S* carvone is measured at (-)23°. Which enantiomer is in excess, and what is its ee? What are the percentages of (*R*)- and (*S*)-carvone in the sample?

Answer

The observed rotation of the mixture is levorotary (negative, counter-clockwise), and the specific rotation of the pure *S* enantiomer is given as dextrorotary (positive, clockwise), meaning that the pure *R* enantiomer must be levorotary, and the mixture must contain more of the *R* enantiomer than of the *S* enantiomer.

Rotation (*R*/*S* Mix) = [Fraction(*S*) × Rotation (*S*)] + [Fraction(*R*) × Rotation (*R*)]

Let Fraction (*S*) = x, therefore Fraction (*R*) = 1 – x.

Rotation (*R*/*S* Mix) = x[Rotation (*S*)] + (1 – x)[Rotation (*R*)].

–23 = x(+61) + (1 – x)(–61)

Solve for x: x = 0.3114 and (1 – x) = 0.6885

Therefore the percentages of (*R*)- and (*S*)-carvone in the sample are 68.9% and 31.1%, respectively.

ee = [(% more abundant enantiomer – 50) × 100]/50. = [68.9 – 50) × 100]/50 = 37.8%.

Chiral molecules are often labeled according to the sign of their specific rotation, as in (S)-(+)-carvone and (R)-(-)-carvone, or (±)-carvone for the racemic mixture. However, there is no relationship whatsoever between a molecule's R/S designation and the sign of its specific rotation. Without performing a polarimetry experiment or looking in the literature, we would have no idea that (-)-carvone has the R configuration and (+)-carvone has the S configuration

Chiral molecules are often labeled according to the sign of their specific rotation, as in (S)-(+)-carvone and (R)-(-)-carvone, or (±)-carvone for the racemic mixture. However, there is no relationship whatsoever between a molecule's R/S designation and the sign of its specific rotation. Without performing a polarimetry experiment or looking in the literature, we would have no idea that (-)-carvone has the R configuration and (+)-carvone has the S configuration.

Separation of Chiral Compounds

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. For example, if a racemic mixture of a chiral alcohol is reacted with a enantiomerically pure carboxylic acid, the result is a mixture of diastereomers: in this case, because the pure (R) entantiomer of the acid was used, the product is a mixture of (R-R) and (R-S) diastereomeric esters, which can, in theory, be separated by their different physical properties. Subsequent hydrolysis of each separated ester will yield the 'resolved' (enantiomerically pure) alcohols. The used of this technique is known as chiral resolution.

? Exercise 3.3.2

A 3.20 g sample of morphine ($[\alpha]_D$ = -132) was dissolved in 10.0 mL of acetic acid ($[\alpha]_D$ = 0). If it is put into a sample tube with a path length of 2.00 cm, what would be its observed rotation (α)?

Answer

The specific rotation, $[\alpha]_D$ = (observed rotation, α (degrees))/ [(pathlength, *l* (dm)) x (concentration, c (g/cm^3))] = α/(*l* x c)

Solving for α, α = $[\alpha]_D$ x *l* x c

($[\alpha]_D$ = -132) x (*l* = 2.00 cm = 0.200 dm) x (c = 3.20 g / 10.0 cm^3 = 0.320 g/cm^3)

α = -132 x 0.200 dm x 0.320 g/cm^3 = -8.45 °

? Exercise 3.3.3

Is the morphine in the previous excercise dextrorotatory or levorotatory?

Answer

Since morphine has a (-) rotation, it indicates that it rotates light to the left (counterclockwise) and morphine is levorotatory.

? Exercise 3.3.4

Label the following compounds as dextrorotatory or levorotatory.

a. sucrose ($[\alpha]_D$ = + 66.7)
b. cholesterol ($[\alpha]_D$ = - 31.5)
c. cocaine ($[\alpha]_D$ = - 16)
d. chloroform ($[\alpha]_D$ = 0)

Answer

a. sucrose ($[\alpha]_D$ = + 66.7) dextrorotatory

b. cholesterol ($[\alpha]_D$ = - 31.5) levorotatory
c. cocaine ($[\alpha]_D$ = - 16) levorotatory
d. chloroform ($[\alpha]_D$ = 0) neither, not optically active

Exercise 3.3.5a

The specific rotation of (*S*)-carvone is (+) 61° when measured neat (pure liquid sample with no solvent). The optical rotation of a neat sample of a mixture of R and S carvone is measured at (-) 23 ^{o}.

a) Which enantiomer is in excess?

Answer

Since the pure *S* enantiomer ((+) 61°) is dextrorotatory (positive, clockwise), the *R* enantiomer must be levorotatory. The observed rotation of the mixture is levorotatory since its negative (counterclockwise). This means the mixture must contain more of the *R* enantiomer than the *S* enantiomer.

Exercise 3.3.5b

b) What are the percentages of (*S*)- and (*R*)- carvone in the sample mixture?

Answer

Optical rotation (α) of the (*R*/*S* mixture) = [fraction (*S*) x $[\alpha]_D$ (*S*)] + [fraction (*R*) x $[\alpha]_D$ (*R*)]

To determine the fraction of S and R, we make y = fraction (*S*) and 1 – y = fraction (*R*)

-23° = y x (61°) + (1 – y) x (-61°) solving for y: y = 0.3114 and (1-y) = 0.6885

Therefore the percentage of (*S*)-carvone is 31.1 % and (*R*)-carvone is 68.9 %

Exercise 3.3.5c

c) What is the ee (enantiomeric excess)?

Answer

ee = [(% more abundant isomer – 50) x 100]/50 = [(68.9 – 50) x100]/50 = 37.8 % ee

Exercise 3.3.6a

Determine the ee's of the following from the percentages

- 95 % (*R*)- tartaric acid and 5.0 % (*S*)- tartaric acid

Answer

[(95 – 50) x 100] / 50 = 90 % ee (*R*)-tartaric acid

Exercise 3.3.6b

Determine the ee's of the following from the percentages

- 75 % (*S*)- limonene and 25 % (*R*)- limonene

Answer

[(75 – 50) x 100] / 50 = 50 % ee (*S*)- limonene

Exercise 3.3.6c

Determine the ee's of the following from the percentages

- 85 % (*R*) cysteine

Answer

(85 – 50) x 100] / 50 = 70 % ee (*R*)-cysteine

Exercise 3.3.6d

Determine the ee's of the following from the percentages

- 50 % (*S*) alanine

Answer

(50 – 50) x 100] / 50 = 0 % ee, racemic mixture

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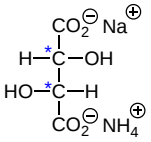
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3.4: Pasteur's Discovery of Enantiomers

Objective

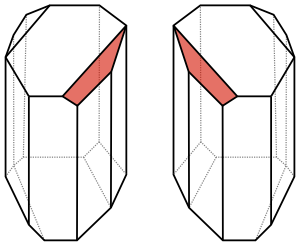
After completing this section, you should be able to discuss how the results of work carried out by Biot and Pasteur contributed to the development of the concept of the tetrahedral carbon atom.

Because enantiomers have identical physical and chemical properties in achiral environments, separation of the stereoisomeric components of a racemic mixture or racemate is normally not possible by the conventional techniques of distillation and crystallization. In some cases, however, the crystal habits of solid enantiomers and racemates permit the chemist (acting as a chiral resolving agent) to discriminate enantiomeric components of a mixture. As background for the following example, it is recommended that the section on crystal properties be reviewed. Tartaric acid, its potassium salt known in antiquity as "tartar", has served as the locus of several landmark events in the history of stereochemistry. In 1832 the French chemist Jean Baptiste Biot observed that tartaric acid obtained from tartar was optically active, rotating the plane of polarized light clockwise (**dextrorotatory**). An optically inactive, higher melting, form of tartaric acid, called racemic acid was also known.



sodium ammonium tartrate

A little more than a decade later, young Louis Pasteur conducted a careful study of the crystalline forms assumed by various salts of these acids. He noticed that under certain conditions, the sodium ammonium mixed salt of the racemic acid formed a mixture of enantiomorphic hemihedral crystals; a drawing of such a pair is shown below. Pasteur reasoned that the dissymmetry of the crystals might reflect the optical activity and dissymmetry of its component molecules. After picking the different crystals apart with a tweezer, he found that one group yielded the known dextrorotatory tartaric acid measured by Biot; the second led to a previously unknown levorotatory tartaric acid, having the same melting point as the dextrorotatory acid. Today we recognize that Pasteur had achieved the first resolution of a racemic mixture, and laid the foundation of what we now call stereochemistry.



Optical activity was first observed by the French physicist Jean-Baptiste Biot. He concluded that the change in direction of plane-polarized light when it passed through certain substances was actually a rotation of light, and that it had a molecular basis. His work was supported by the experimentation of Louis Pasteur. Pasteur observed the existence of two crystals that were mirror images in tartaric acid, an acid found in wine. Through meticulous experimentation, he found that one set of molecules rotated polarized light clockwise while the other rotated light counterclockwise to the same extent. He also observed that a mixture of both, a *racemic mixture* (or *racemic modification*), did not rotate light because the optical activity of one molecule canceled the effects of the other molecule. Pasteur was the first to show the existence of chiral molecules.

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3.5: Sequence Rules for Specifying Configuration

Objectives

After completing this section, you should be able to

1. assign Cahn-Ingold-Prelog priorities to a given set of substituents.
2. determine whether a given wedge-and-broken-line structure corresponds to an *R* or an *S* configuration, with or without the aid of molecular models.
3. draw the wedge-and-broken-line structure for a compound, given its IUPAC name, complete with *R* or *S* designation.
4. construct a stereochemically accurate model of a given enantiomer from either a wedge-and-broken-line structure or the IUPAC name of the compound, complete with *R* or *S* designation.

Key Terms

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

- absolute configuration
- *R* configuration
- *S* configuration

Study Notes

When designating a structure as *R* or *S*, you must ensure that the atom or group with the lowest priority is pointing away from you, the observer. The easiest way to show this is to use the wedge-and-broken-line representation. You can then immediately determine whether you are observing an *R* configuration or an *S* configuration.

To name the enantiomers of a compound unambiguously, their names must include the "handedness" of the molecule. The method for this is formally known as *R*/*S* nomenclature.

Introduction

The method of unambiguously assigning the handedness of molecules was originated by three chemists: R.S. Cahn, C. Ingold, and V. Prelog and, as such, is also often called the Cahn-Ingold-Prelog rules. In addition to the Cahn-Ingold system, there are two ways of experimentally determining the absolute configuration of an enantiomer:

1. X-ray diffraction analysis. Note that there is no correlation between the sign of rotation and the structure of a particular enantiomer.
2. Chemical correlation with a molecule whose structure has already been determined via X-ray diffraction.

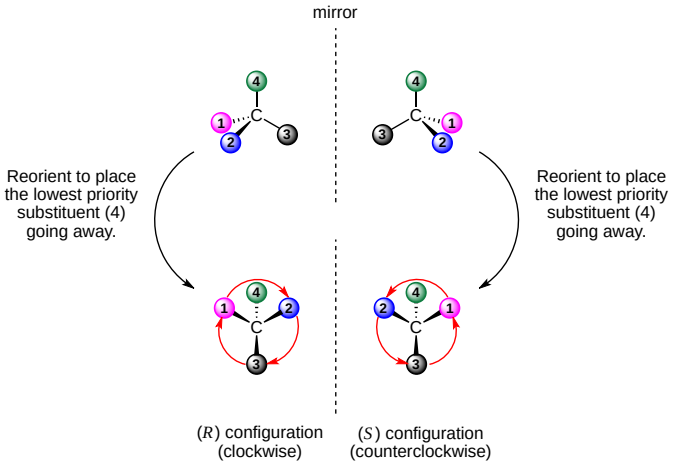
However, for non-laboratory purposes, it is beneficial to focus on the (*R*)/(*S*) system. The sign of optical rotation, although different for the two enantiomers of a chiral molecule,at the same temperature, **cannot** be used to establish the absolute configuration of an enantiomer; this is because the sign of optical rotation for a particular enantiomer may change when the temperature changes.

Stereocenters are labeled (*R*) or (*S*)

The "right hand" and "left hand" nomenclature is used to name the enantiomers of a chiral compound. The stereocenters are labeled as (*R*) or (*S*).

The **Cahn-Ingold-Prelog** rules of assign priorities the groups directly bonded to the chiral carbon. Having ranked the four groups attached to a chiral carbon, we describe the stereochemical configuration around the carbon by orienting the molecule so that the group with the lowest ranking (4) is given a dash bond to indicate it points directly away from us. We then look at the three remaining substituents, which now appear to radiate toward us which is shown by using wedge bonds. If a curved arrow drawn from the highest to second-highest to third-highest ranked substituent is clockwise, we say that the chirality center has the (R) configuration (Latin rectus, meaning “right”). If an arrow from is counterclockwise, the chirality center has the (S) configuration (Latin sinister, meaning “left”). To remember these assignments, think of a car’s steering wheel when making a Right (clockwise) turn. Note, the (R) or (S) configurations represent the two enantiomers of a chiral molecule. The (R) or (S) configuration is often

added as a prefix, in parenthesis, to a chiral molecule's name to indicate which enantiomer is being discussed (e.g., (R)-2-bromobutane). If more than chiral carbon is present in a chiral molecule, each carbon's number is included before the (R) or (S) configuration. Ex: (2R,4S,6R)-2-bromo-6-chloro-4-methylheptane.



Sequence Rules to Assign Priorities to Substituents

Before applying the (*R*) and (*S*) nomenclature to a stereocenter, the substituents must be prioritized according to the following rules:

Rule 1

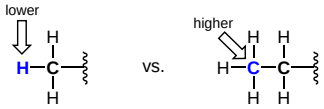
First, examine at the atoms directly attached to the stereocenter of the compound. A atom with a higher atomic number takes precedence over a atom with a lower atomic number. Hydrogen is the lowest possible priority atom, because it has the lowest atomic number.

1. The atom with higher atomic number has higher priority (I > Br > Cl > S > P > F > O > N > C > H).
2. When comparing isotopes, the atom with the higher mass number has higher priority [^{18}O > ^{16}O or ^{15}N > ^{14}N or ^{13}C > ^{12}C or T (^{3}H) > D (^{2}H) > H].

Rule 2

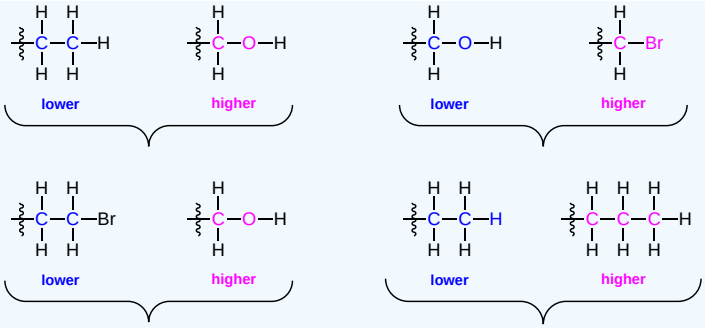
If there are two or more substituents which have the same element directly attached to chiral carbon, proceed along the substituent chains until a point of difference is found. Determine which of the chains has the first connection to an atom with the highest priority (the highest atomic number). That chain has the higher priority.

For example: an ethyl substituent takes priority over a methyl substituent. At the connectivity of the stereocenter, both have a carbon atom, which are equal in rank. Going down the chains, a methyl has only has hydrogen atoms attached to it, whereas the ethyl has two hydrogen atoms and a carbon atom. The carbon atom on the ethyl is the first point of difference and has a higher atomic number than hydrogen; therefore the ethyl takes priority over the methyl.



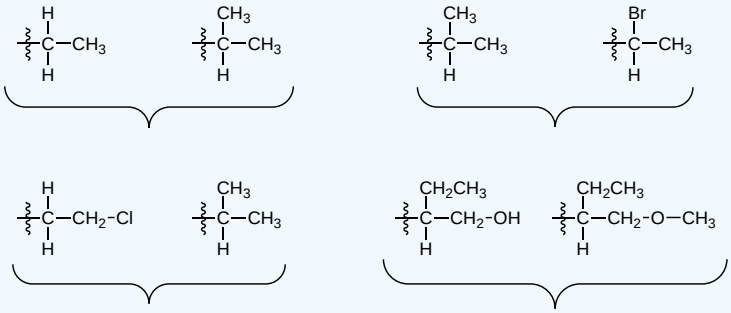
The "-H" (left) ranks lower than the "C-" (right) based on the relative molecular weights at the first point of difference.

Example 3.5.1



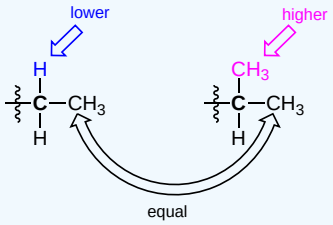
Worked Exercise 3.5.1

For the following pairs of substituents, determine which would have the higher and lower priority based on the **Cahn-Ingold-Prelog** rules. Explain your answer.



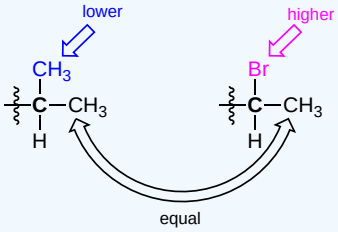
Answer

A 1-methylethyl substituent takes precedence over an ethyl substituent. Connected to the first carbon atom, ethyl only has one other carbon, whereas the 1-methylethyl has two carbon atoms attached to the first; this is the first point of difference. Therefore, 1-methylethyl ranks higher in priority than ethyl, as shown below:



The "C-" (right) ranks higher than the "H-" (left) based on the first point of difference and their relative atomic numbers.

However:

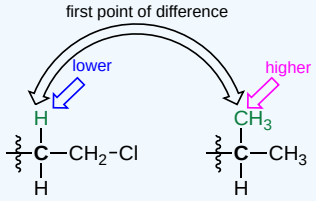


In this case, even though the bold carbon on the right structure has two connections to a non-hydrogen atom (C), it is the lower priority. This is because one of the atoms attached to the bold carbon on the left molecule

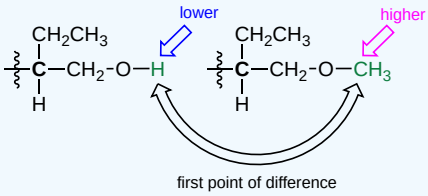
ranks higher than any of the atoms attached to the bold carbon on the right structure, since Br has a higher atomic number than C.

Caution!!

Keep in mind that priority is determined by the **first** point of difference along the two similar substituent chains. After the first point of difference, the rest of the chain is irrelevant.

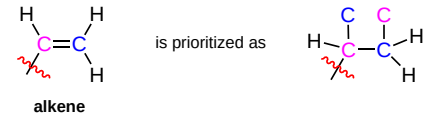


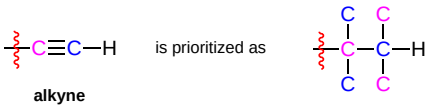
When looking for the first point of difference on similar substituent chains, one may encounter branching. If there is branching, choose the branch that is higher in priority. If the two substituents have similar branches, rank the elements within the branches until a point of difference.

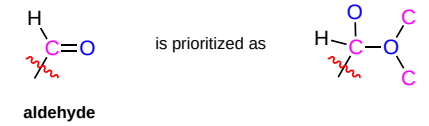


Rule 3

For assigning priority, multiple bonds are treated as if each bond of the multiple bond is bonded to a unique atom. For example, an alkene substituent (CH_2=CH-) has higher priority than an ethyl substituent (CH_3CH_2-). The alkene carbon priority is "two" bonds to carbon atoms and one bond to a hydrogen atom compared with the ethyl carbon that has only one bond to a carbon atom and two bonds to two hydrogen atoms. Similarly, alkyne substituent (HCC-) would have an even higher priority because the alkyne carbon is treated as if it is bonded to three carbons. This method remains the same with compounds containing a carbonyl (C=O) group. The carbon of an aldehyde substituent (O=CH-) is treated as if it is bonded to a hydrogen and two oxygen atoms.

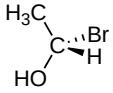






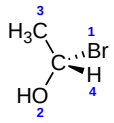
Determining (*R*) or (*S*) Configuration Using a Molecular Model

In order to demonstrate how to determine the (*R*)/(*S*) configuration of the chiral carbon in the following molecule using molecular models, first construct a model of the bromoethanol structure:

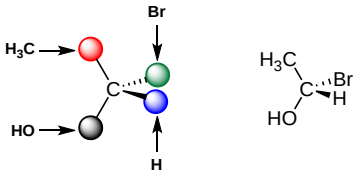


First make a molecular model of a tetrahedral carbon with four different substituents. In many cases, this will appear as a carbon with four bonds with a different colored ball attached to each bond.

For the molecule in question, determine the location of the chiral carbon and assign CIP priorities to the substituents. In this case, Br gets the highest priority because it has the highest atomic number. The O in the OH substituent gets priority 2 and the C in CH_3 gets priority 3. Lastly, H gets the lowest priority, 4, because it has the smallest atomic number.



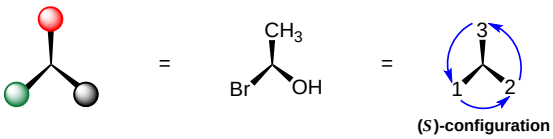
Now take your molecular model and orientate it to match the molecule in question. Remember in the dash/wedge representation, two regular bonds are in the plane of the page. The wedge bond is coming toward you and the dashed bond is going away from you. If you were to hold a piece of paper directly in front of you, the substituents with the regular bond should both be touching the piece of paper. The dashed bond should be pointing behind the piece of paper and the wedge bond should be pointing in front.



In this structure, the bromine is going away from you, the hydrogen is coming toward you and the hydroxide and methyl groups are in the plane of the page.

Then based on the position, assign each substituent on the chiral carbon a colored ball on your molecular model. In this case, bromine is going away so it is assigned the green ball. The hydrogen is coming toward you so it is assigned the blue ball. The last two substituents are in the plane of the page, however, the CH_3 is positioned higher so it is assigned the red ball which leaves OH being assigned the black ball.

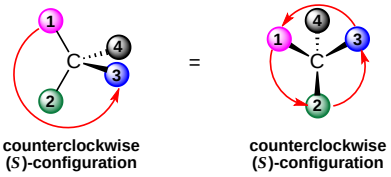
Lastly, grab onto the ball for the lowest priority substitutent, in this case the blue one, and point the other three substituents towards you. The three bonds should be angled towards you as if they all have wedge bonds. Assign the original substituents and their corresponding CIP priorities to the three colored balls. The green ball was assigned to bromine which was given priority one. The OH was assigned to the black ball and given priority two. The CH_3 was assigned to the red ball and given priority three. In this case the priorities are going counter clockwise so the chiral carbon has an ***(S)*** configuration.



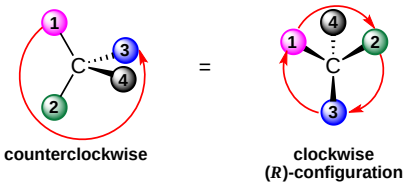
Determining (*R*) or (*S*) Configuration Without a Molecular Model

If a molecular model cannot be used there are a couple of simple methods which can be applied if the dash/wedge bond system is being used.

After assigning CIP priorities, if the lowest priority substituent (4) is on the dash bond the configuration of substituents 1-3 can be assigned directly. As shown in the figure below, the configuration of substituents 1-3 does not change when moving to sight down the bond of substituent 4. In both cases, substituents 1-3 are ordered in a counterclockwise fashion which gives the chiral carbon an (*S*) configuration.



The opposite is true if the lowest priority substituent (4) is on the wedge bond. As shown in the figure below, the configuration of substituents 1-3 is inverted when moving to sight down the bond of substituent 4. When the lowest priority substituent is on the wedge bond, the configuration of substituents 1-3 can be assigned directly only if the direction is inverted. i.e. clockwise = (*S*) and counterclockwise = (*R*).

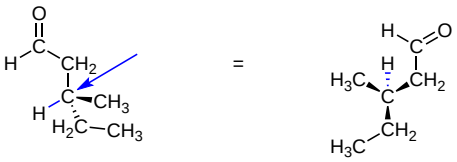


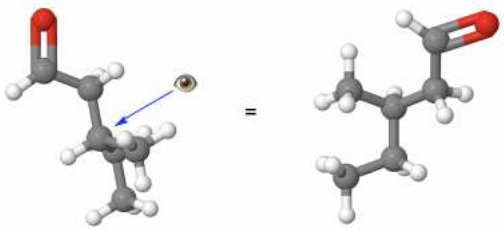
With the lowest priority group in front, drawing an arc from 1 to 2 to 3 gives the reverse of the configuration.

However, if the lowest priority substituent is on one of the regular bonds when the dash/wedge system is being used then configurations are best assigned by changing perspectives. This method can also be used if the three-dimensional configuration of the chiral carbon is represented. First, locate the chiral carbon and assign CIP priorities to its substituents. Then while perceiving the drawn molecule as a three-dimensional image, mentally change your perspective such that you are looking down the bond between the chiral carbon and the lowest CIP ranked substituent (#4). If done correctly, the bonds for substituents 1-3 should be coming towards you as wedge bonds. You can then follow the direction of the CIP priority numbers to determine the (*R*)/(*S*) configuration of the chiral carbon.



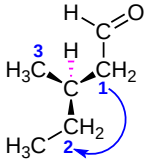
Locate the chiral carbon and assign CIP priorities to its substituents.





Mentally sight down the bond between the chiral carbon and the lowest CIP ranked substituent.

This bond is shown in magenta.



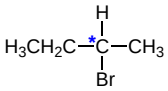
clockwise
(*R*)-configuration

Follow the direction of the CIP priority numbers to determine the (*R*)/(*S*) configuration.

Drawing the Structure of a Chiral Molecule from its Name

Draw the structure of (*S*)-2-Bromobutane:

1) Draw the basic structure of the molecule and determine the location of the chiral carbon.



2) Determine the chiral carbon's substituents and assign them a CIP priority.

-H (Priority 4)

-CH_3 (Priority 3)

-CH_2CH_3 (Priority 2)

-Br (Priority 1)

3) Draw the chiral carbon in a dash/wedge form and add the lowest priority substituent to the dash bond. In this case, the lowest priority substituent is -H.



4) Add the remaining substituents in a clockwise fashion for (*R*) and a counterclockwise fashion for (*S*).



clockwise
(*R*)-configuration

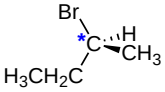


counterclockwise
(*S*)-configuration

The molecule posed in this question has an (*S*) configuration so the remaining substituents are added in a counterclockwise fashion.



counterclockwise
(*S*)-configuration



(*S*)-2-bromobutane

? Exercise 3.5.1

1) Orient the following so that the least priority (4) atom is paced behind, then assign stereochemistry ((*R*) or (*S*)).



2) Draw (*R*)-2-bromobutan-2-ol.

3) Assign (*R*)/(*S*) to the following molecule.



4) Which in the following pairs would have a higher CIP priority?

a. -H or -Cl
b. -Br or -I
c. $-CH_2OH$ or $-OCH_3$
d. $-CH_2CH_3$ or $-CH=CH_2$
e. $-NH_2$ or -OH

5) Rank the following substituents in order of their CIP priority:

a. -H, $-OCH_3$, $-CH_2OH$, -OH
b. -OH, $-CO_2H$, -CH=O, $-CH_2OH$
c. -CN, $-NH_2$, -CH=O, $-NHCH_3$
d. -SH, $-SCH_3$, -OH, $-OOCH_3$

6) Determine if the chiral carbon in the following molecules have an (*R*) or (*S*) configuration. Red = Oxygen & Blue = Nitrogen.

a)

b)

Answer

1) A is (*S*) and B is (*R*).



2)



3) The stereocenter is (*R*).

4)

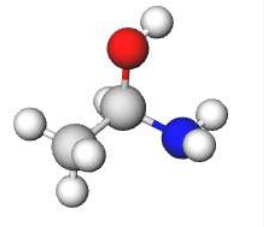
a. -Cl
b. -I
c. $-OCH_3$
d. $-CH=CH_2$
e. -OH

5) Rank the following substituents in order of their CIP priority:

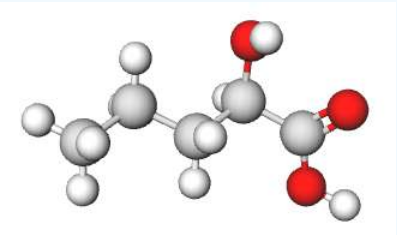
a. $-OCH_3$, -OH, $-CH_2OH$, -H,
b. -OH, $-CO_2H$, -CH=O, $-CH_2OH$
c. $-NHCH_3$, $-NH_2$, -CH=O, -CN
d. $-SCH_3$, -SH, $-OOCH_3$, -OH

6)

a) The chiral carbon is (*R*). The four substituents of the chiral carbon are -OH (1), $-NH_2$ (2), $-CH_3$ (3), and -H (4). Then looking down the lowest priority bond, you should roughly see what appears in the picture below. The substituents with priorities 1-3 are ordered in a clockwise fashion so the chiral carbon is (*R*).



b) The chiral carbon is (*S*). The four substituents of the chiral carbon are -CO_2H (1), -OH (2), -$CH_2CH_2CH_3$ (3), and -H (4). Then looking down the lowest priority bond, you should roughly see what appears in the picture below. The substituents with priorities 1-3 are ordered in a counterclockwise fashion so the chiral carbon is (*S*).



Exercise 3.5.2

Identify which substituent in the following sets has a higher ranking.

a. -H or -CH_3
b. -$CH_2CH_2CH_3$ or CH_2CH_3
c. -CH_2Cl or CH_2OH

Answer

a. **-CH_3**
b. **-$CH_2CH_2CH_3$**
c. **-CH_2Cl**

Exercise 3.5.3

Identify which substituent in the following sets has a higher ranking.

a. -NH_2 or -N=NH
b. -CH_2CH_2OH or -CH_2OH
c. -$CH=CH_2$ or -CH_2CH_3

Answer

a) **-N=NH**

b) **-CH_2OH**

c) **-$CH=CH_2$**

Exercise 3.5.4

Place the following sets of substituents in each group in order of lowest priority (1st) to highest priority (4th)

a. -NH_2, -F, -Br, -CH_3
b. -SH, -NH_2, -F, -H

Answer

a) $-CH_3 < -NH_2 < -F, < -Br$

b) $-H < -NH_2 < -F, < -SH$

Exercise 3.5.5

Place the following sets of substituents in each group in order of lowest priority (1st) to highest priority (4th)

a. $-CH_2CH_3$, -CN, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$
b. $-CH_2NH_2$, $-CH_2SH$, $-C(CH_3)_3$, -CN

Answer

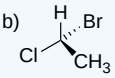
a) $-CH_2CH_3 < -CH_2CH_2OH < -CH_2CH_2CH_2OH, < -CN$

b) $-C(CH_3)_3 < -CH_2NH_2 < -CN < -CH_2SH$

Exercise 3.5.6

Assign the following chiral centers as (*R*) or (*S*).

a) 

b) 

c) 

Answer

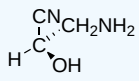
a) **(*S*)**: I > Br > F > H. The lowest priority substituent is going backwards so following the highest priority, it goes left (counterclockwise).

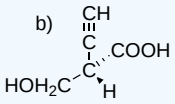
b) **(*R*)**: Br > Cl > CH_3 > H. Using a model kit, you need to rotate the H to the back position where the Br is. This causes the priority to go to the left (clockwise) when looking at it with the H in the back position. Alternatively, if you do not have a model kit, you can imagine the structure 3-dimensionally and since the lowest priority (H) is facing up (as drawn), if you look at it from below, starting with Br (1st priority) and moving towards Cl (2nd priority), you are moving right (clockwise) which represents (*R*) stereochemistry.

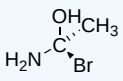
c) **Neither (*R*) or (*S*)**: Since there are two identical substituents (H's) the molecule is achiral and cannot be assigned (*R*) or (*S*).

Exercise 3.5.7

Assign the following chiral centers as (*R*) or (*S*).

a) 

b) 

c) 

Answer

a) **(*R*)**: OH > CN (C triple bonded to N) > CH_2NH_2 > H. The H needs to be moved to the back position which causes the priority to go to the right (clockwise) which indicates (*R*).

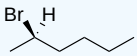
b) **(*S*)**: COOH > CH_2OH > C CH > H. Since the H is coming forward, you can assign the priority and it goes to the right (clockwise which would be (*R*)) but since the lowest priority is forward, you have to switch it to (*S*). Alternatively, you can rotate the molecule to put the lowest priority to the back and you'll see that it rotates left (or counterclockwise) for (*S*).

c) **(*S*)**: Br > OH > NH_2 > CH_3. Since the lowest priority is going back, you can follow the priority and see that it is going left (counterclockwise) and therefore (*S*).

Exercise 3.5.8

Draw the structure of (*R*)-2-bromohexane.

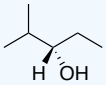
Answer



Exercise 3.5.9

Draw the structure of (*S*)-2-methyl-3-pentanol.

Answer



References

1. Schore and Vollhardt. *Organic Chemistry Structure and Function.* New York:W.H. Freeman and Company, 2007.
2. McMurry, John and Simanek, Eric. *Fundamentals of Organic Chemistry*. 6th Ed. Brooks Cole, 2006.

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3.6: Diastereomers

Objectives

After completing this section, you should be able to

1. calculate the maximum number of stereoisomers possible for a compound containing a specified number of chiral carbon atoms.
2. draw wedge-and-broken-line structures for all possible stereoisomers of a compound containing two chiral carbon atoms, with or without the aid of molecular models.
3. assign (*R*)/(*S*) configurations to wedge-and-broken-line structures containing two chiral carbon atoms, with or without the aid of molecular models.
4. determine, with or without the aid of molecular models, whether two wedge-and-broken-line structures containing two chiral carbon atoms are identical, represent a pair of enantiomers, or represent a pair of diastereomers.
5. draw the wedge-and-broken-line structure of a specific stereoisomer of a compound containing two chiral carbon atoms, given its IUPAC name and (*R*)/(*S*) configuration.

Key Terms

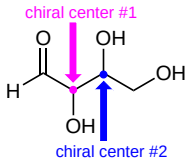
Make certain that you can define, and use in context, the key term below.

- diastereomer

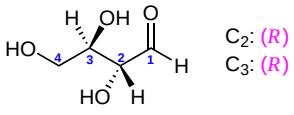
Diastereomers are two molecules which are stereoisomers (same molecular formula, same connectivity, different arrangement of atoms in space) but are *not* enantiomers. Unlike enantiomers which **are mirror images** of each other and **non-superimposable**, diastereomers are **not mirror images** of each other and **non-superimposable**. Diastereomers can have different physical properties and reactivity. They have different melting points and boiling points and different densities. In order for diastereomer stereoisomers to occur, a compound must have **two or more** stereocenters.

Introduction

So far, we have been analyzing compounds with a single chiral center. Next, we turn our attention to those which have multiple chiral centers. We'll start with some stereoisomeric four-carbon sugars with two chiral centers.



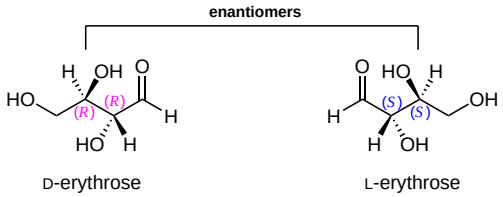
We will start with a common four-carbon sugar called D-erythrose.



D-erythrose

A note on sugar nomenclature: biochemists use a special system to refer to the stereochemistry of sugar molecules, employing names of historical origin in addition to the designators '*D*' and '*L*'. You will learn about this system if you take a biochemistry class. We will use the *D*/*L* designations here to refer to different sugars, but we won't worry about learning the system.

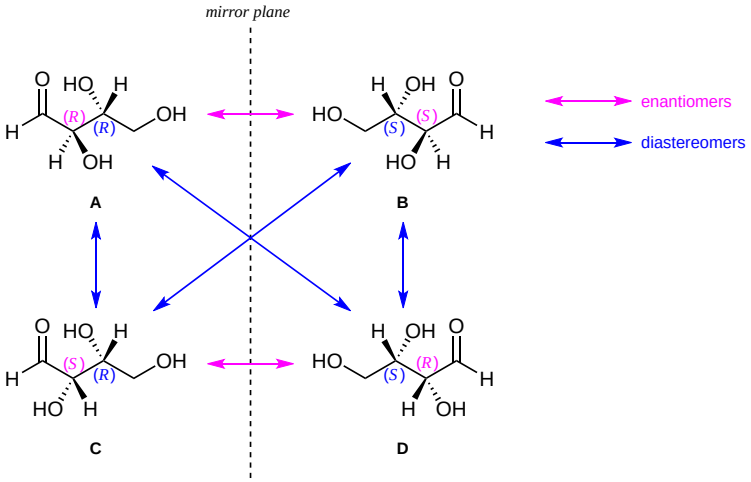
As you can see, *D*-erythrose is a chiral molecule: C_2 and C_3 are stereocenters, both of which have the (*R*) configuration. In addition, you should make a model to convince yourself that it is impossible to find a plane of symmetry through the molecule, regardless of the conformation. Does D-erythrose have an enantiomer? Of course it does – if it is a chiral molecule, it must. The enantiomer of erythrose is its mirror image, and is named L-erythrose (once again, you should use models to convince yourself that these mirror images of erythrose are not superimposable).



Notice that both chiral centers in L-erythrose both have the (*S*) configuration. To avoid confusion, we will simply refer to the different stereoisomers by capital letters.

Now let's consider all the possible stereoisomers.

Look first at compound A below. Both chiral centers in have the (*R*) configuration (you should confirm this for yourself!). The mirror image of Compound A is compound B, which has the (*S*) configuration at both chiral centers. If we were to pick up compound A, flip it over and put it next to compound B, we would see that they are *not* superimposable (again, confirm this for yourself with your models!). A and B are nonsuperimposable mirror images: in other words, enantiomers.



Now, look at compound C, in which the configuration is (*S*) at chiral center 1 and (*R*) at chiral center 2. Compounds A and C are stereoisomers: they have the same molecular formula and the same bond connectivity, but a different arrangement of atoms in space (recall that this is the definition of the term 'stereoisomer). However, they are *not* mirror images of each other (confirm this with your models!), and so they are *not* enantiomers. By definition, they are **diastereomers** of each other.

Notice that compounds C and B also have a diastereomeric relationship, by the same definition.

So, compounds A and B are a pair of enantiomers, and compound C is a diastereomer of both of them. Does compound C have its own enantiomer? Compound D is the mirror image of compound C, and the two are not superimposable. Therefore, C and D are a pair of enantiomers. Compound D is also a diastereomer of compounds A and B.

This can also seem very confusing at first, but there some simple shortcuts to analyzing stereoisomers:

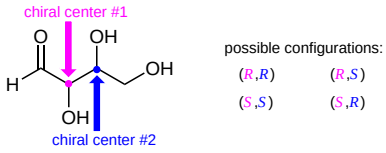
Stereoisomer Shortcuts

If ***all*** of the chiral centers are of opposite (*R*)/(*S*) configuration between two stereoisomers, they are enantiomers.

If ***at least one, but not all*** of the chiral centers are opposite between two stereoisomers, they are diastereomers.

> These shortcuts to not take into account the possibility of additional stereoisomers due to alkene groups: we will come to that later

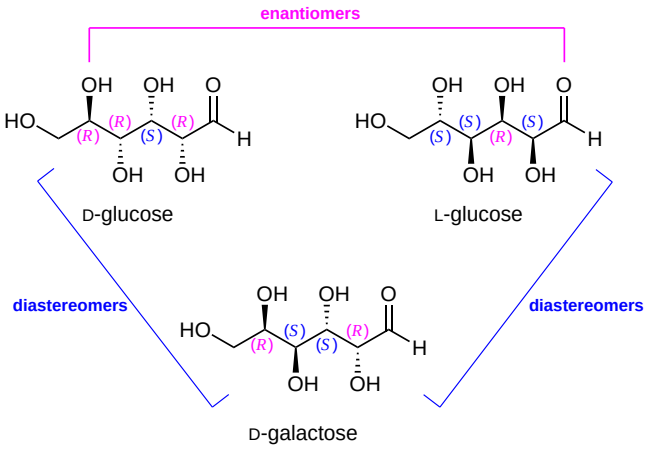
Here's another way of looking at the four stereoisomers, where one chiral center is associated with red and the other blue. Pairs of enantiomers are stacked together.



We know, using the shortcut above, that the enantiomer of (*R*,*R*) must be (*S*,*S*) - both chiral centers are different. We also know that (*R*,*S*) and (*S*,*R*) are diastereomers of (*R*,*R*), because in each case one - but not both - chiral centers are different.

Determining the Maximum Number of Stereoisomers for a Compound

In general, a structure with *n* stereocenters will have a maximum of 2^n different stereoisomers. (We are not considering, for the time being, the stereochemistry of double bonds – that will come later). For example, let's consider the glucose molecule in its open-chain form (recall that many sugar molecules can exist in either an open-chain or a cyclic form). There are two enantiomers of glucose, called D-glucose and L-glucose. The D-enantiomer is the common sugar that our bodies use for energy. It has $n = 4$ stereocenters, so therefore there are $2^n = 2^4 = 16$ possible stereoisomers (including D-glucose itself).

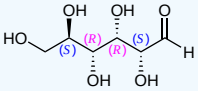


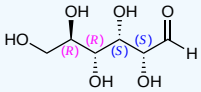
In L-glucose, all of the stereocenters are inverted relative to *D*-glucose. That leaves 14 diastereomers of D-glucose: these are molecules in which at least one, but not all, of the stereocenters are inverted relative to D-glucose. One of these 14 diastereomers, a sugar called *D*-galactose, is shown above: in D-galactose, one of four stereocenters is inverted relative to D-glucose. Diastereomers which differ in only one stereocenter (out of two or more) are called **epimers**. D-glucose and D-galactose can therefore be refered to as epimers as well as diastereomers.

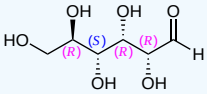
Example 3.6.1

- Draw the structure of L-galactose, the enantiomer of D-galactose.
- Draw the structure of two more diastereomers of D-glucose. One should be an epimer.

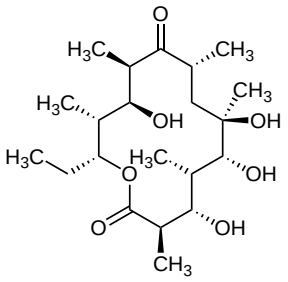
Answer


L-galactose


L-mannose
(epimer of D-glucose)


L-gulose
(diasteromer of D-glucose)

Erythronolide B, a precursor to the 'macrocyclic' antibiotic erythromycin, has 10 stereocenters. It's enantiomer is that molecule in which all 10 stereocenters are inverted.



erythronolide B

In total, there are $2^{10} = 1024$ stereoisomers in the erythronolide B family: 1022 of these are diastereomers of the structure above, one is the enantiomer of the structure above, and the last ***is*** the structure above.

We know that enantiomers have identical physical properties and equal but opposite degrees of specific rotation. Diastereomers, in theory at least, have different physical properties – we stipulate 'in theory' because sometimes the physical properties of two or more diastereomers are so similar that it is very difficult to separate them. In addition, the specific rotations of diastereomers are unrelated – they could be the same sign or opposite signs, and similar in magnitude or very dissimilar.

Exercise 3.6.1

Determine the number of stereoisomers a molecule can have with…

a. 3 chiral centers
b. 1 chiral center
c. 6 chiral centers

Answer

Since a molecule with n chiral centers can have 2^n stereoisomers…

a. $2^3 = 8$ possible stereoisomers
b. $2^1 = 2$ possible stereoisomers
c. $2^6 = 64$ possible stereoisomers

Exercise 3.6.2*a*

What is the relationship between enantiomers?

Answer

They are mirror images of each other and when 2 or more chiral centers are present, every stereocenter is the opposite in its enantiomer.

Exercise 3.6.2*b*

How does the stereochemistry in diastereomers differ from each other?

Answer

In diastereomers, one or more of the chiral centers is the opposite but they all can't be the opposite or else they'd be enantiomers.

Exercise 3.6.2c

What are epimers?

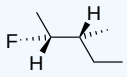
Answer

Epimers are when **only one** chiral center is the opposite (in molecules with 2 or more chiral centers) in its diastereomer.

Exercise 3.6.3a

Draw the structure of (2R,3R) 2-fluoro-3-methylhexane.

Answer

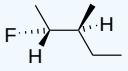


2R,3R

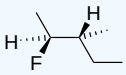
Exercise 3.6.3b

Draw both diastereomers of (2R,3R) 2-fluoro-3-methylhexane.

Answer



2R,3S

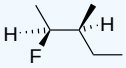


2S,3R

Exercise 3.6.3c

Draw the enantiomer of (2R,3R) 2-fluoro-3-methylhexane.

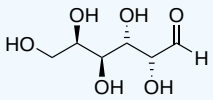
Answer



2S,3S

Exercise 3.6.4a

Draw the structure of L-galactose, the enantiomer of D-galactose.

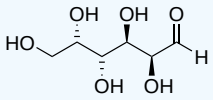


S, R, R, S

D-galactose

Answer

https://chem.libretexts.org/@go/page/396260



S, *R*, *R*, *S*

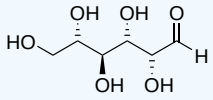
L-galactose

Exercise 3.6.4*b*

Draw a diastereomer of D-galactose that is an epimer.

Answer

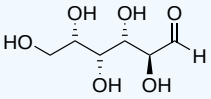
You can draw an epimer by drawing D-galactose with 1 (and only 1) of its chiral centers reversed. Here's an example when you switch only the first chiral center (in red). (There are 3 other epimers that could be drawn as long as you only swap a single chiral center in the diastereomer that you use.)



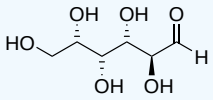
R, *R*, *R*, *S*

Exercise 3.6.4*c*

Identify if the following diastereomer of galactose is an epimer of D- galactose or L- galactose.



Answer

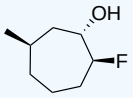


S, *R*, *S*, *S*

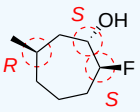
Since the diastereomer above only varies from L-galactose by 1 chiral center, the above is an epimer in relationship to L-galactose. Since it varies from D-galactose by 3 chiral centers, it is not an epimer but a diastereomer. Since not all of the chiral centers are swapped, it is not an enantiomer!

Exercise 3.6.5*a*

For the compound shown below, label each chiral center as R or S.



Answer



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Exercise 3.6.5b

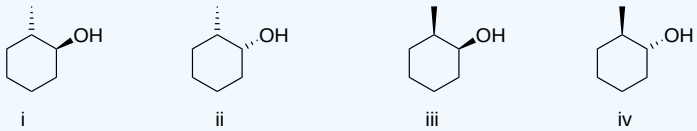
How many stereoisomers are possible for the compound in part a)?

Answer

Since there are 3 chiral centers, $2^3 = 8$ possible stereoisomers.

Exercise 3.6.6

Consider the stereoisomers below.



i ii iii iv

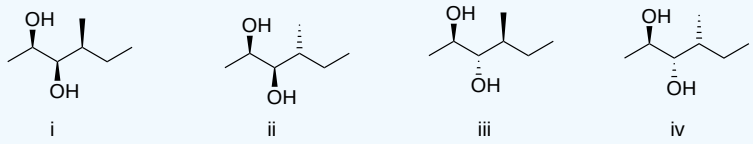
a. Which is/are an enantiomer of i?
b. Which is/are a diastereomer of ii?
c. Which is/are an epimer of i?

Answer

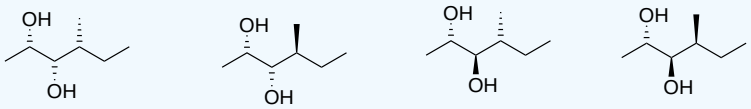
a. iv is an enantiomer of i since both chiral centers are switched and they are non superimposable mirror images.
b. i & iv are diastereomers of ii since they are stereoisomers that are not mirror images.
c. ii and iii are epimers of i since they are diastereomers with only 1 chiral center switched and the other one the same.

Exercise 3.6.7

Consider the 8 stereoisomers below.



i ii iii iv



v vi vii viii

a. Which is/are an enantiomer of i?
b. Which is/are a diastereomer of i?
c. Which is/are an epimer of i?

Answer

a. v is an enantiomer since all three chiral centers are switched and they are non superimposable mirror images.
b. ii, iii, iv, vi, vii & viii are diastereomers of i since they are stereoisomers that are not mirror images.
c. ii,iii & viii are epimers of i since they are diastereomers with only 1 chiral center switched and the other chiral centers the same.

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3.7: Racemic Mixtures and the Resolution of Enantiomers

Objectives

After completing this section, you should be able to

1. describe a common process for separating a mixture of enantiomers.
2. explain why racemic mixtures do not rotate plane-polarized light.

Key Terms

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

- racemic mixture (or racemate)
- resolve

Study Notes

A *racemic mixture* is a 50:50 mixture of two enantiomers. Because they are mirror images, each enantiomer rotates plane-polarized light in an equal but opposite direction and is optically inactive. If the enantiomers are separated, the mixture is said to have been *resolved*. A common experiment in the laboratory component of introductory organic chemistry involves the resolution of a racemic mixture.

The dramatic biochemical consequences of chirality are illustrated by the use, in the 1950s, of the drug Thalidomide, a sedative given to pregnant women to relieve morning sickness. It was later realized that while the (+)-form of the molecule, was a safe and effective sedative, the (−)-form was an active teratogen. The drug caused numerous birth abnormalities when taken in the early stages of pregnancy because it contained a mixture of the two forms.

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. For example, if a racemic mixture of a chiral alcohol is reacted with a enantiomerically pure carboxylic acid, the result is a mixture of diastereomers: in this case, because the pure (R) entantiomer of the acid was used, the product is a mixture of (R-R) and (R-S) diastereomeric esters, which can, in theory, be separated by their different physical properties. Subsequent hydrolysis of each separated ester will yield the 'resolved' (enantiomerically pure) alcohols. The used in this technique are known as 'Moscher's esters', after Harry Stone Moscher, a chemist who pioneered the method at Stanford University.

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called **resolution**. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. Reversing the first reaction then leads to the separated enantiomers plus the recovered reagent.

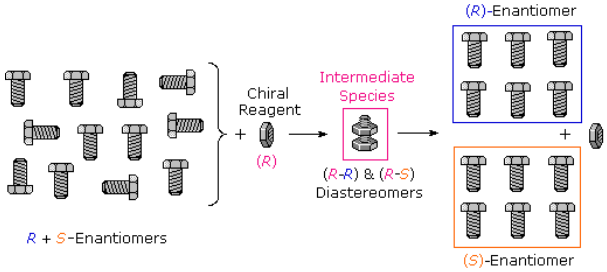


Figure 5.8.1:

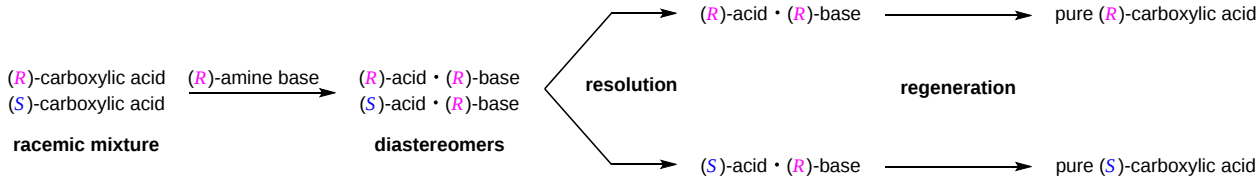
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Many kinds of chemical and physical reactions, including salt formation, may be used to achieve the diastereomeric intermediates needed for separation. Figure 5.8.1 illustrates this general principle by showing how a nut having a right-handed thread (R) could serve as a "reagent" to discriminate and separate a mixture of right- and left-handed bolts of identical size and weight. Only the two right-handed partners can interact to give a fully-threaded intermediate, so separation is fairly simple. The resolving moiety, i.e. the nut, is then removed, leaving the bolts separated into their right and left-handed forms. Chemical reactions of enantiomers are normally not so dramatically different, but a practical distinction is nevertheless possible.

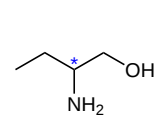
Because the physical properties of enantiomers are identical, they seldom can be separated by simple physical methods, such as fractional crystallization or distillation. It is only under the influence of another chiral substance that enantiomers behave differently, and almost all methods of resolution of enantiomers are based upon this fact. We include here a discussion of the primary methods of resolution.

Chiral Amines as Resolving Agents and Resolution of Racemic Acids

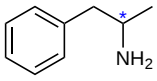
The most commonly used procedure for separating enantiomers is to convert them to a mixture of diastereomers that will have different physical properties: melting point, boiling point, solubility, and so on (Section 5-5). For example, if you have a racemic or (*R*)/(*S*) mixture of enantiomers of a carboxylic acid and convert this to a salt with a chiral amine base having the (*R*) configuration, the salt will be a mixture of two diastereomers, ((*R*)-acid • (*R*)-base) and ((*S*)-acid • (*R*)-base). These diastereomeric salts are *not* identical and they are not mirror images. Therefore they will differ to some degree in their physical properties, and a separation by physical methods, such as crystallization, may be possible. If the diastereomeric salts can be completely separated, the carboxylic acid regenerated from each salt will be either exclusively the (*R*) or the (*S*) enantiomer.



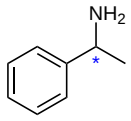
Resolution of chiral acids through the formation of diastereomeric salts requires adequate supplies of suitable chiral bases. Brucine, strychnine, and quinine frequently are used for this purpose because they are readily available, naturally occurring chiral bases. Simpler amines of synthetic origin, such as 2-amino-1-butanol, amphetamine, and 1-phenylethanamine, also can be used, but first they must be resolved themselves.



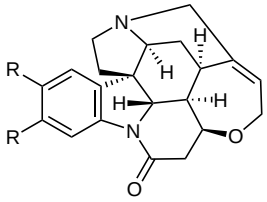
2-amino-1-butanol



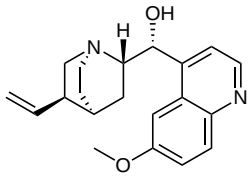
1-phenyl-2-propanamine
(amphetamine)



1-phenylethanamine



R = H,strychnine
R = OCH_3, brucine



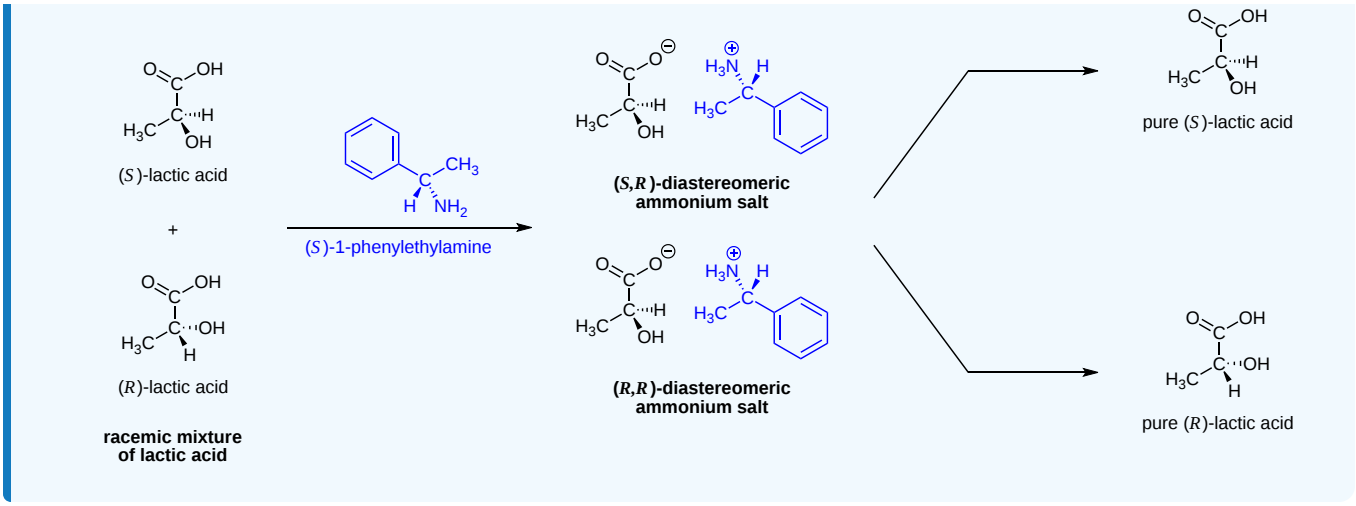
quinine
(antimicrobial)
(antimalarial)

? Worked Example 3.7.1

Show how (*S*)-1-phenylethylamine can be used to resolve a racemic mixture of lactic acid. Please draw all the structures involved.

Answer

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Resolution of Racemic Bases

Chiral acids, such as (+)-tartaric acid, (-)-malic acid, (-)-mandelic acid, and (+)-camphor- 10-sulfonic acid, are used for the resolution of a racemic base.

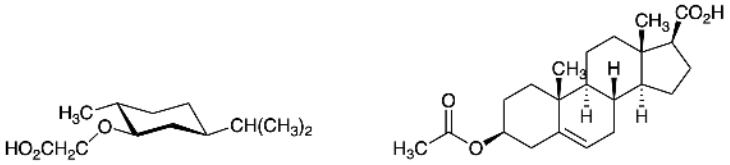


tartaric acid (2,3-dihydroxy-butanedioic acid) | malic acid (2-hydroxybutane-dioic acid) | mandelic acid (2-hydroxy-2-phenylethanoic acid) | camphor-10-sulfonic acid

The principle is the same as for the resolution of a racemic acid with a chiral base, and the choice of acid will depend both on the ease of separation of the diastereomeric salts and, of course, on the availability of the acid for the scale of the resolution involved. Resolution methods of this kind can be tedious, because numerous recrystallizations in different solvents may be necessary to progressively enrich the crystals in the less-soluble diastereomer. To determine when the resolution is complete, the mixture of diastereomers is recrystallized until there is no further change in the measured optical rotation of the crystals. At this stage it is hoped that the crystalline salt is a pure diastereomer from which one pure enantiomer can be recovered. The optical rotation of this enantiomer will be a maximum value if it is "optically" pure because any amount of the other enantiomer could only reduce the magnitude of the measured rotation α.

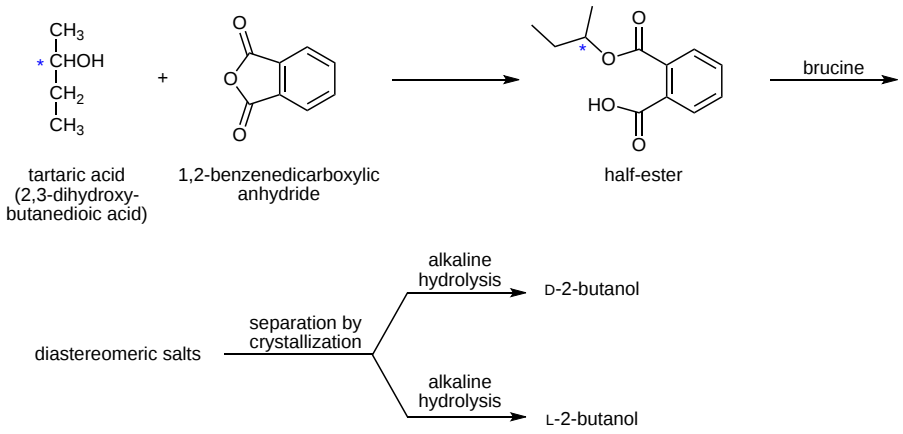
Resolution of Racemic Alcohols

To resolve a racemic alcohol, a chiral acid can be used to convert the alcohol to a mixture of diastereomeric esters. This is not as generally useful as might be thought because esters tend to be liquids unless they are very high-molecularweight compounds. If the diastereomeric esters are not crystalline, they must be separated by some other method than fractional crystallization (for instance, by chromatography methods, Section 9-2). Two chiral acids that are useful resolving agents for alcohols are:



menthoxyethanoic acid | 3-β-acetoxy-Δ^5-etienic acid

The most common method of resolving an alcohol is to convert it to a half-ester of a dicarboxylic acid, such as butanedioic (succinic) or 1,2-benzenedicarboxylic (phthalic) acid, with the corresponding anhydride. The resulting half-ester has a free carboxyl function and may then be resolvable with a chiral base, usually brucine:



Other Methods of Resolution

One of the major goals in the field of organic chemistry is the development of reagents with the property of "chiral recognition" such that they can affect a clean separation of enantiomers in one operation without destroying either of the enantiomers. We have not achieved that ideal yet, but it may not be far in the future. Chromatographic methods, whereby the stationary phase is a chiral reagent that adsorbs one enantiomer more strongly than the other, have been used to resolve racemic compounds, but such resolutions seldom have led to both pure enantiomers on a preparative scale. Other methods, called kinetic resolutions, are excellent when applicable. The procedure takes advantage of differences in reaction rates of enantiomers with chiral reagents. One enantiomer may react more rapidly, thereby leaving an excess of the other enantiomer behind. For example, racemic tartaric acid can be resolved with the aid of certain penicillin molds that consume the dextrorotatory enantiomer faster than the levorotatory enantiomer. As a result, almost pure (-)-tartaric acid can be recovered from the mixture:

$$(\pm)\text{-tartaric acid} + \text{mold} \rightarrow (-)\text{-tartaric acid} + \text{more mold}$$

The crystallization procedure employed by Pasteur for his classical resolution of (±)-tartaric acid (**Section 5.4**) has been successful only in a very few cases. This procedure depends on the formation of individual crystals of each enantiomer. Thus if the crystallization of sodium ammonium tartrate is carried out below 27", the usual racemate salt does not form; a mixture of crystals of the (+) and (-) salts forms instead. The two different kinds of crystals, which are related as an object to its mirror image, can be separated manually with the aid of a microscope and subsequently may be converted to the tartaric acid enantiomers by strong acid. A variation on this method of resolution is the seeding of a saturated solution of a racemic mixture with crystals of one pure enantiomer in the hope of causing crystallization of just that one enantiomer, thereby leaving the other in solution. Unfortunately, very few practical resolutions have been achieved in this way.

Predicating the Chirality of the Product of a Reaction

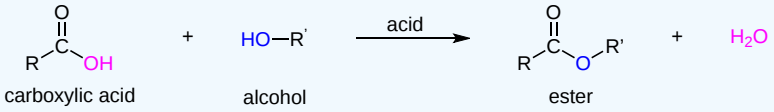
It important to understand the changes in chirality which occur during the formation of product during a reaction. A chiral reaction product, has the possibility of forming multiple stereoisomers which all need to be considered. Changes in chirality, if possible, will be discussed with each individual reaction as this textbook moves forward. Some possible situations which can occur are:

- **A new chiral carbon is formed during a reaction.** This commonly occurs when an sp^2 hybridized carbon in the reactant is converted to sp^3 hybridized chiral carbon in the product. When this occurs, a racemic mixture of the new chiral carbon is formed.
- **A chiral carbon is lost during a reaction.** This commonly occurs when an sp^3 hybridized chiral carbon in the reactant is converted to either a sp^2 or sp hybridized carbon in the product.
- **An enantiomerically pure starting material is converted to a racemic mixture in the product.** This commonly occurs when a sp^3 hybridized chiral carbon is temporarily converted to an sp^2 hybridized carbon during a reaction's mechanism. The chiral carbon is reformed as a racemic mixture.
- **Chiral carbons remain unchanged during a reaction.** If a chiral carbon is not directly involved in a reaction, it will move from a reactant to a product unchanged.

Determining if a chiral carbon is involved in a given reaction is vital for determining which of these four situations is occurring.

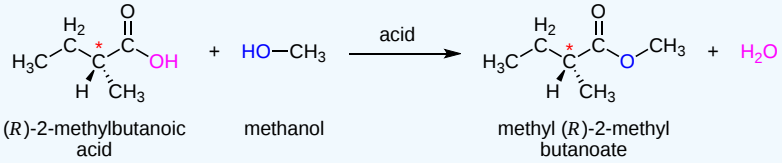
Worked Example 3.7.2

The following reaction involves the conversion of a carboxylic acid reacting with an alcohol to form an ester. If a pure sample of (R)-2-methylbutanoic acid is reacted with methanol to form an ester, what would be the stereochemistry of the product?



Answer

First it is important to identify the location of the chiral carbon and determine if it is directly involved in the reaction. In this case, the chiral carbon is not involved so the stereochemistry will be carried over into the product unchanged.



Exercise 3.7.1

Indicate the reagents you could use to resolve the following compounds. Show the reactions involved and specify the physical method you believe would be the best to separate the diastereomers of 1 -phenyl-2-propanamine.

Answer

You could react the 1-phenyl-2-propanamine racemic mixture with a chiral acid such as (+)-tartaric acid (*R*, *R*). The reaction will produce a mixture of diastereomeric salts (i.e. *R*, *R*, *R* and *S*, *R*, *R*). You can separate the diastereomers through crystallization and treat the salt with a strong base (e.g. KOH) to recover the pure enantiomeric amine.

Exercise 3.7.2

Indicate the reagents you would use to resolve the following and discuss the reactions involved and specify the physical method you believe would be the best to separate the diastereomers of 2,3-pentadienedioic acid.

Answer

You could react the 2,3-pentadienedioic acid mixture with a chiral base such as (*R*)-1-phenylethylamine. The reaction will produce a mixture of diastereomeric salts. Separate the diastereomers through crystallization and treat the resulting salt with strong acid (e.g. HCl) to recover the pure enantiomeric acid.

Exercise 3.7.3

Indicate the reagents you would use to resolve the following and discuss the reactions involved and specify the physical method you believe would be the best to separate the diastereomers of 1 -phenylethanol.

Answer

You could react the 1-phenylethanol mixture with 1,2-benzenedicarboxylic anhydride. The reaction will produce a mixture of diastereomeric salts. You could then separate the diastereomers through crystallization and then alkaline hydrolysis treatment should recover the pure enantiomeric alcohol.

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3.8: Chirality in Nature and Chiral Environments

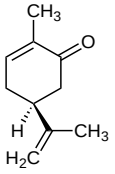
Objective

After completing this section, you should be able to explain how chiral molecules in nature can have such dramatically different biological properties.

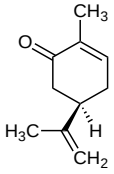
Some Chiral Organic Molecules

There are a number of important biomolecules that could occur as enantiomers, including amino acids and sugars. In most cases, only one enantiomer occurs naturally (although some fungi, for example, are able to produce mirror-image forms of these compounds). We will look later at some of these biomolecules, but first we will look at a compound that occurs naturally in both enantiomeric forms.

Carvone is a secondary metabolite. That means it is a naturally-occurring compound that is not directly connected to the very basic functions of a cell, such as self-replication or the production of energy. The role of secondary metabolites in nature is often difficult to determine. However, these compounds often play roles in self-defense, acting as deterrents against competitor species in a sort of small-scale chemical warfare scenario. They are also frequently used in communications; this role has been studied most extensively among insects, which use lots of compounds to send information to each other.



(S)-carvone
oil at 25 °C
bp: 230-231 °C
d: 0.965 g/mL
n: 1.4988
insol H_2O, misc EtOH, MeOH
$[\alpha]_D$ = +61.2°



(R)-carvone
oil at 25 °C
bp: 230-231 °C
d: 0.965 g/mL
n: 1.4988
insol H_2O, misc EtOH, MeOH
$[\alpha]_D$= −62.46°

Figure 3.8.1: The two naturally-occurring enantiomers of carvone.

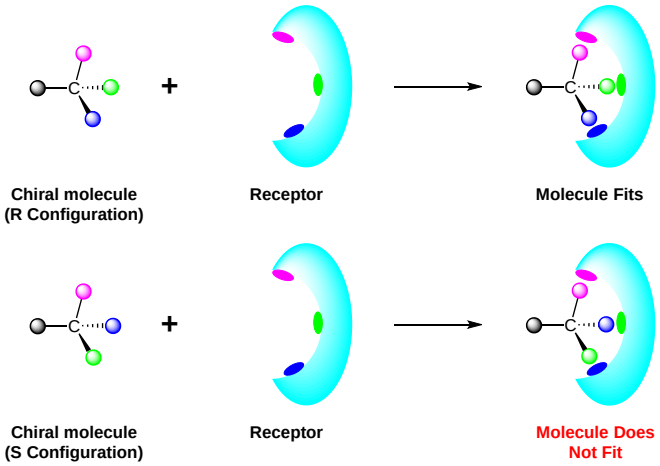
Carvone is produced in two enantiomeric forms. One of these forms, called (-)-carvone, is found in mint leaves, and it is a principal contributor to the distinctive odor of mint. The other form, (+)-carvone, is found in caraway seeds. This form has a very different smell, and is typically used to flavor rye bread and other Eastern European foods.

Note that (+)-carvone is another name for (S)-carvone. The (+) designation is based on its positive optical rotation value, which is experimentally measured. This means the (-)-carvone is (R)-carvone and would have a negative optical rotation value.

How different, exactly, are these two compounds, (+)- and (-)-carvone? Are they completely different isomers, with different physical properties? In most ways, the answer is no. These two compounds have the same appearance (colorless oil), the same boiling point (230 °C), the same refractive index (1.499) and specific gravity (0.965). However, they have optical rotations that are almost exactly opposite values.

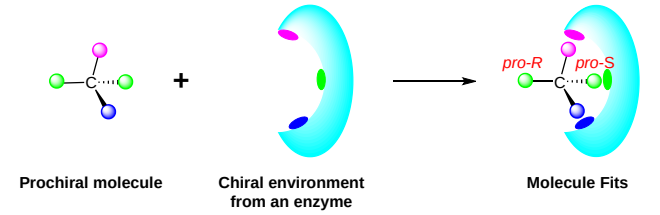
- Two enantiomers have the same physical properties.
- Enantiomers have opposite optical rotations.

Clearly they have different biological properties; since they have slightly different odors, they must fit into slightly different nasal receptors, signaling to the brain whether the person next to you is chewing a stick of gum or a piece of rye bread. This is much like how a left hand only fits into a left handed baseball glove and not into a right handed one. Receptors which allow for a biological effect, in this case to perceive a certain smell, are often chiral and will only allow one enantiomer of a chiral substrate to fit. An example of this is shown in the figure below. The receptor as a complementary three-dimension shape to allow the R configuration of the chiral substrate to fit. When the S configuration of the chiral substrate attempts to fit the configuration does not match that of the receptor as shown in the second drawing where the bottom two groups do not fit the receptor site.



Chiral Environments

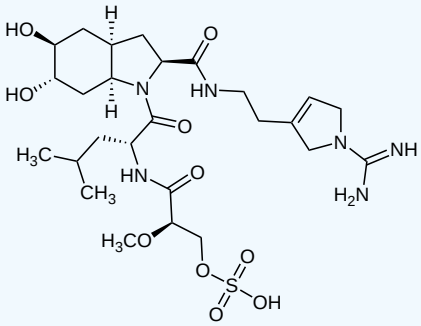
In the previous section, enzymes were shown to be capable of converting a prochiral substrate into a single enantiomer product. Enzymes can provides such an effect because they create a **chiral environment**. The figure below shows a prochiral substrate. The magenta and blue balls represent substituents while the two green balls represent two of the same substituent which is available for a given reaction. One of these substituents is *pro*-R and the other is *pro*-S. Without the presence of a chiral environment the two green substituents are chemically identical. However, as the prochiral molecule interacts with the chiral environment provided by an enzyme the two green substituents become chemically distinct. Despite being achiral, the prochiral molecule can only interact with the chiral environment in one specific position. The figure below shows that the *pro*-S green substituent of the prochiral molecule is protected by the enzyme, while the pro-R green substituent is exposed and can undergo a reaction. In this case the enzyme would provide a product that is predominantly the R enantiomer.



? Exercise 3.8.1

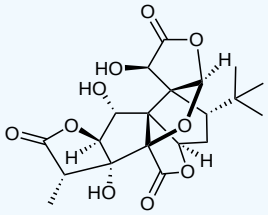
The following are three molecules found in nature. Please identify four chiral centers in each, mark them with asterisks, and identify each center as having a R or S configuration. Each molecule contains more than four chiral centers.

a) The following is the structure of dysinosin A, a potent thrombin inhibitor that consequently prevents blood clotting.

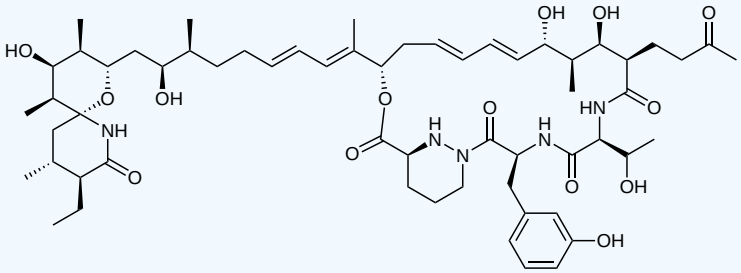


b) Ginkgolide B (below) is a secondary metabolite of the ginkgo tree, extracts of which are used in Chinese medicine.

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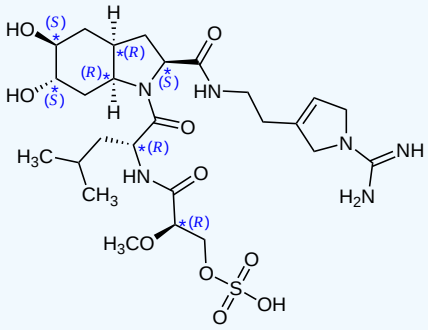


c) Sanglifehrin A, shown below, is produced by a bacteria that may be found in the soil of coffee plantations in Malawi. It is also a promising candidate for the treatment of organ transplant patients owing to its potent immuno-suppressant activity.

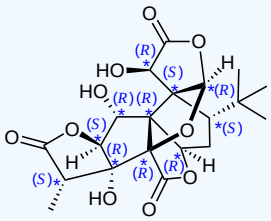


Answer

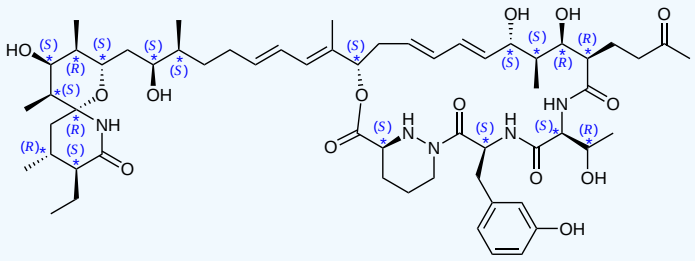
a)



b)



c)



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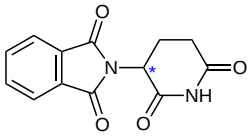


Figure \(\PageIndex{2}\): Thalidomide.

There are other reasons that we might concern ourselves with an understanding of enantiomers, apart from dietary and olfactory preferences. Perhaps the most dramatic example of the importance of enantiomers can be found in the case of thalidomide. Thalidomide was a drug commonly prescribed during the 1950's and 1960's in order to alleviate nausea and other symptoms of morning sickness. In fact, only one enantiomer of thalidomide had any therapeutic effect in this regard. The other enantiomer, apart from being therapeutically useless in this application, was subsequently found to be a teratogen, meaning it produces pronounced birth defects. This was obviously not a good thing to prescribe to pregnant women. Workers in the pharmaceutical industry are now much more aware of these kinds of consequences, although of course not all problems with drugs go undetected even through the extensive clinical trials required in the United States. Since the era of thalidomide, however, a tremendous amount of research in the field of synthetic organic chemistry has been devoted to methods of producing only one enantiomer of a useful compound and not the other. This effort probably represents the single biggest aim of synthetic organic chemistry through the last quarter century.

- Enantiomers may have very different biological properties.
- Obtaining enantiomerically pure compounds is very important in medicine and the pharmaceutical industry.

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3.9: A Review of Isomerism

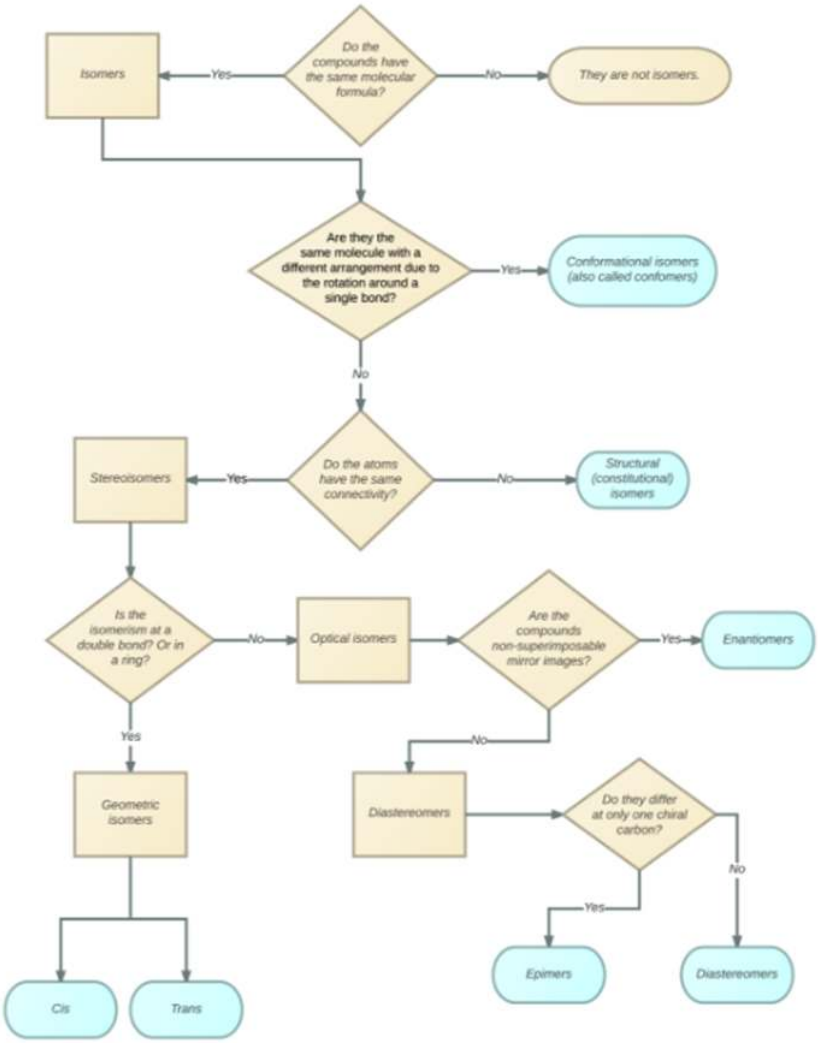
Objective

After completing this section, you should be able to explain the differences among constitutional (structural) isomers and stereoisomers (geometric isomers).

Key Terms

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

- constitutional
- (structural) isomers
- stereoisomers



Different types of isomers (Vladsinger)

Conformational Isomers

The C–C single bonds in ethane, propane, and other alkanes are formed by the overlap of an sp^3 hybrid orbital on one carbon atom with an sp^3 hybrid orbital on another carbon atom, forming a σ bond. Each sp^3 hybrid orbital is cylindrically symmetrical (all cross-sections are circles), resulting in a carbon–carbon single bond that is also cylindrically symmetrical about the C–C axis. Because

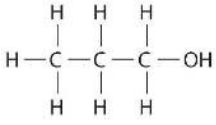
rotation about the carbon–carbon single bond can occur without changing the overlap of the sp^3 hybrid orbitals, there is no significant electronic energy barrier to rotation. Consequently, many different arrangements of the atoms are possible, each corresponding to different degrees of rotation. Differences in three-dimensional structure resulting from rotation about a σ bond are called differences in conformation, and each different arrangement is called a conformational isomer (or conformer).



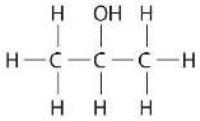
Conformational Isomers of Pentane

Structural Isomers

Unlike conformational isomers, which do not differ in connectivity, structural isomers differ in connectivity, as illustrated here for 1-propanol and 2-propanol. Although these two alcohols have the same molecular formula (C_3H_8O), the position of the –OH group differs, which leads to differences in their physical and chemical properties.

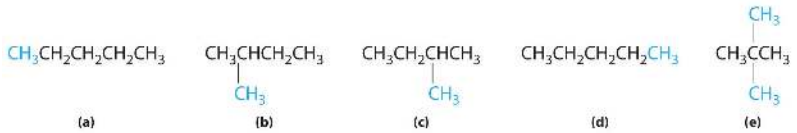


1-Propanol (*n*-propanol)



2-Propanol (isopropanol)

In the conversion of one structural isomer to another, at least one bond must be broken and reformed at a different position in the molecule. Consider, for example, the following five structures represented by the formula C_5H_{12}:



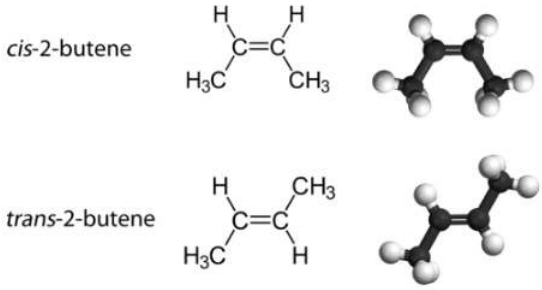
Of these structures, (a) and (d) represent the same compound, as do (b) and (c). No bonds have been broken and reformed; the molecules are simply rotated about a 180° vertical axis. Only three—n-pentane (a) and (d), 2-methylbutane (b) and (c), and 2,2-dimethylpropane (e)—are structural isomers. Because no bonds are broken in going from (a) to (d) or from (b) to (c), these alternative representations are not structural isomers. The three structural isomers—either (a) or (d), either (b) or (c), and (e)—have distinct physical and chemical properties.

Stereoisomers

Stereoisomers have the same connectivity in their atoms but a different arrangement in three-dimensional space. There are different classifications of stereoisomers depending on how the arrangements differ from one another. Notice that in the structural isomers, there was some difference in the connection of atoms. For example, 1-butene has a double bond followed by two single bonds while 2-butene has a single bond, then a double bond, then a single bond. A stereoisomer will have the same connectivity among all atoms in the molecule.

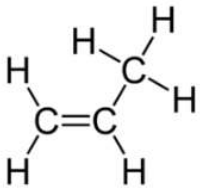
Geometric Isomers

With a molecule such as 2-butene, a different type of isomerism called geometric isomerism can be observed. **Geometric isomers** are isomers in which the order of atom bonding is the same but the arrangement of atoms in space is different. The double bond in an alkene is not free to rotate because of the nature of the bond. Therefore, there are two different ways to construct the 2-butene molecule (see figure below). The image below shows the two geometric isomers, called *cis*-2-butene and *trans*-2-butene.



Geometric Isomers of 2-Butene

The *cis* isomer has the two single hydrogen atoms on the same side of the molecule, while the *trans* isomer has them on opposite sides of the molecule. In both molecules, the bonding order of the atoms is the same. In order for geometric isomers to exist, there must be a rigid structure in the molecule to prevent free rotation around a bond. This occurs with a double bond or a ring. In addition, the two carbon atoms must each have two different groups attached in order for there to be geometric isomers. Propene (see figure below) has no geometric isomers because one of the carbon atoms (the one on the far left) involved in the double bond has two single hydrogens bonded to it.

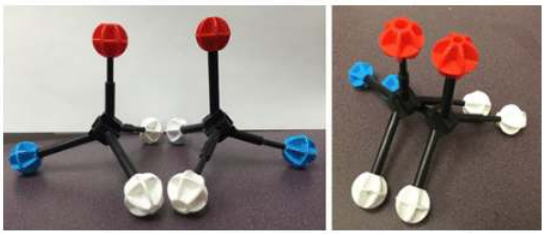


Physical and chemical properties of geometric isomers are generally different. As with alkenes, alkynes display structural isomerism beginning with 1-butyne and 2-butyne. However, there are no geometric isomers with alkynes because there is only one other group bonded to the carbon atoms that are involved in the triple bond.

Optical Isomers

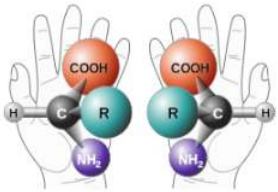
Stereoisomers that are not geometric isomers are known as optical isomers. Optical isomers differ in the placement of substituted groups around one or more atoms of the molecule. They were given their name because of their interactions with plane-polarized light. Optical isomers are labeled enantiomers or diastereomers.

Enantiomers are non-superimposable mirror images. A common example of a pair of enantiomers is your hands. Your hands are mirror images of one another but no matter how you turn, twist, or rotate your hands, they are not superimposable.



Two models that are mirror images and superimposable.

Since they are superimposable, they are the same molecule and are not isomers.



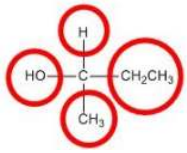
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Your hands and some molecules are mirror images but are not superimposable.

These pairs of molecules are called enantiomers.

:

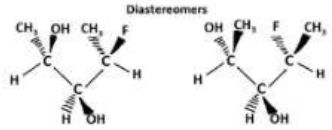
Objects that have non-superimposable mirror images are called **chiral**. When examining a molecule, carbon atoms with four unique groups attached are considered chiral. Look at the figure below to see an example of a chiral molecule. Note that we have to look beyond the first atom attached to the central carbon atom. The four circles indicate the four unique groups attached to the central carbon atom, which is chiral.



A chiral carbon has four unique groups attached to it

:

Another type of optical isomer are **diastereomers**, which are non-mirror image optical isomers. Diastereomers have a different arrangement around one or more atoms while some of the atoms have the same arrangement. As shown in the figure below, note that the orientation of groups on the first and third carbons are different but the second one remains the same so they are not the same molecule. The solid wedge indicates a group coming out of the page/screen towards you and the dashed line indicates that a group is going away from you "behind" the page/screen.



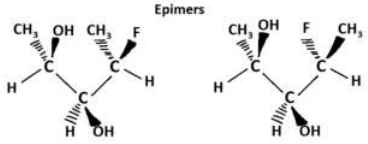
Diastereomers differ at one or more atom. These molecules are not mirror images and they are not superimposable.

They are optical isomers because they have the same connectivity between atoms but a different arrangement of substituent

groups.5.1.8" id="MathJax-Element-8-Frame" role="presentation" style="position:relative;" tabindex="0">

5.1.8" role="presentation" style="position:relative;" tabindex="0">

Epimers are a sub-group of diastereomers that differ at only one location. All epimers are diastereomers but not all diastereomers are epimers.



Epimers have a different arrangement around one atom, while arrangements around the other atoms are the same5.1.9" id="MathJax-Element-9-Frame" role="presentation" style="position:relative;" tabindex="0">

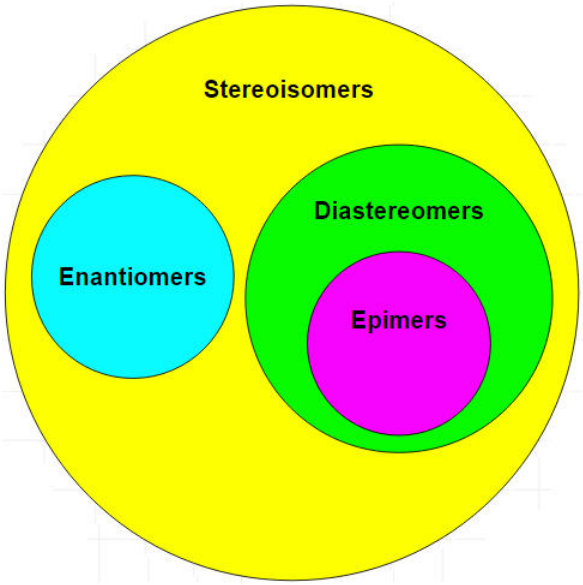
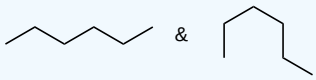


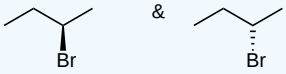
Diagram showing the division of stereoisomers (also known as optical isomers)

Exercise 3.9.1

What kind of isomers are the following pairs?

a) 

b) 

c) 

Answer

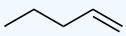
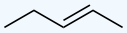
a) Since both structures have the same formula (C_6H_{12}) and they have the same connectivity, but are in a different arrangement of the atoms in space, they are conformational isomers.

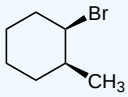
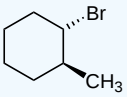
b) Since both structures have the same formula (C_2H_6O) but different connectivity, they are structural isomers.

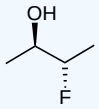
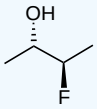
c) Since both structures have the same formula (C_3H_9Br) and the same connectivity but the structure on the left has *R* stereochemistry and the structure on the right has *S* stereochemistry, they are stereoisomers called enantiomers.

Exercise 3.9.2

What kind of isomers are the following pairs?

a)  & 

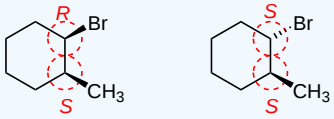
b)  & 

c)  & 

Answer

a) Since both structures have the same formula (C_2H_6O) but different connectivity of where the double bond is, they are structural isomers.

b) Both structures have the same formula and the same connectivity but the structure on the left has (*R*,*S*) stereochemistry and the structure on the right has (S,S) stereochemistry, they are stereoisomers that are diastereomers.

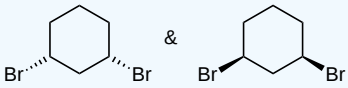


c) Both structures and have the same connectivity but their stereochemistry differs so they are stereoisomers. Since the one on the left is (R,S) and the one on the right is (S,R), they are non-super imposable mirror images of each other and enantiomers.



Exercise 3.9.3

What is the relationship between the following pairs?

a) 

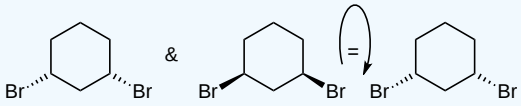
b) 

c) (*R*) – 2 chlorohexane & 1-chlorohexane

d) (2*R*, 3*R*) dichlorohexane & (2*S*, 3*R*) dichlorohexane

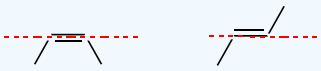
Answer

a) Both structures have the same connectivity and same chemical formula and when you rotate the structure on the right you can see that these are the same compound both with (R,S) stereochemistry.

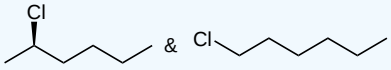


b)) Since both structures have the same formula (C_4H_8) and the same connectivity they are stereoisomers since they differ in what is known as cis/trans isomerism (covered more in Ch 7).Due to the pi bond between carbons 2 & 3, there is not free

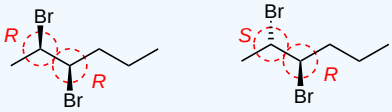
rotation between the C2-C3 bond so the structure on the left has the carbon chains on the same side of the double bond (cis) and the structure on the right has the carbon chains on opposite sides of the double bond (trans).



c) Looking at the structures below, you can see that they have the same formula ($C_6H_{13}Cl$) and different connectivity, so they are structural isomers.



d) Looking at the structures below, you can see that they have the same formula ($C_6H_{12}Br_2$) and the same connectivity, but the structure on the left is (*R*,*R*) and the structure on the right is (*S*,*R*) so since they differ by only one stereocenter, they are stereoisomers that are diastereomers (& epimers in this case).



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3.S: Stereochemistry at Tetrahedral Centers (Summary)

Concepts & Vocabulary

5.1: Enantiomers and the Tetrahedral Carbon

- Every molecule is either **chiral** (not superimposable on its mirror image) or **achiral** (superimposable on its mirror image).
- **Chiral** molecules do not have a plane of symmetry, while **achiral** molecules have one or more **planes of symmetry**.
- **Stereoisomers** vary by spatial arrangement of atoms but have the same atom connectivity.
- **Stereoisomers** that are mirror images of one another but are not superimposable are called **enantiomers**.

5.2: The Reason for Handedness in Molecules - Chirality

- A Tetrahedral carbon atom bonded to four different substituents is an **asymetric** carbon (also called a **stereocenter** or **chiral** carbon), which typically leads to a **chiral** molecule (meso compounds are the exception in section 5.7).

5.3: Optical Activity

- **Enantiomers** cause rotation of plane-polarized light in equal amounts in opposite directions. This is called **optical activity.** Clockwise rotation is called d**extrorotatory** (+) and counter-clockwise is called **levorotatory** (-).
- **Specific rotation** is the amount that a sample of a chemical rotates planne-polarized light. It can be used to calculate the purity of a mixture of **enantiomers** called the **enantiomeric excess**.
- **Resolution** is the separation of a mixture of **enatiomers**.
- **Racemates** are defined as a 50:50 mixture of **enantiomers**, resulting in a sample that is not **optically active**. The process of forming a **racemic** mixture is called **racemization**.

5.4: Pasteur's Discovery of Enantiomers

5.5: Sequence Rules for Specifying Configuration

- Use the CIP rules to determine the priority of each substituent attached to a **chiral** carbon to determine whether configuration is **R** or **S**. With the lowest priority group facing away from you, draw an arc connecting groups 1-2-3. If that arc is clockwise, the configuration is **R**. If counterclockwise, the configuration is **S**.

5.6: Diastereomers

- **Stereoisomers** that are not mirror images of one another are called **diastereomers**.
- **Diastereomers** have two or more **stereocenters**. The configurations of the **stereocenters** cannot be inverse of each other (example R,R and S,S) because that defines a pair of **enantiomers**.

5.7: Meso Compounds

- **Meso** compounds are **achiral** but have **chiral** centers. This is caused by having an internal **plane of symmetry** that allows the two molecules to be superimposable on one another and be **optically inactive**.

5.8: Racemic Mixtures and the Resolution of Enantiomers

- Each component of a **racemic** mixture rotates plane polarized light an equal amount in opposite directions, so there is no **optical activity**.
- **Racemic** mixtures can be separated into the component **enantiomers** by reaction with a **chiral** reagent, which will form **diastereomer** intermediates of the molecules which can then be separated. Following separation the **chiral** reagent is removed to yield the two pure **enantiomers**.

5.9: A Review of Isomerism

- There are several categories of **isomers** with the largest distinction between:
  - constitutional (structural) isomers that contain the same number of each atom but differ in connectivity
  - **stereoisomers** that have all the same atoms with the same connectivity, but only differ in how the atoms are arranged three dimensionally
- In addition to the **diastereomers** and **enantiomers** that have been discussed at length in this chapter, **stereoisomers** can also be:
  - cis/trans or E/Z isomers which differ by spatial arrangement around a double bond
  - conformational **isomers** (conformers) which occur due to free rotation of sigma bonds

5.10: Chirality at Nitrogen, Phosphorus, and Sulfur

- Nitrogen when bonded to three different atoms is **chiral**, however the lone pair of electrons moves freely between positions on the Nitrogen causing these molecules to become a **racemic** mixture.
- When bonded to four different atoms in quaternary ammonium salts, nitrogen atoms lead to **chiral** molecules.
- Organic phosphates with four different groups can also be **chiral**.

5.11: Prochirality

- When a carbon can be converted to a **chiral** center by changing only one of its attached groups, it is called **prochiral**.
- If a molecule has two hydrogens on the same atom and replacement of either one with deuterium would lead to **enantiomers**, the hydrogens are **enantiotopic**.
- Similarly if this replacement would lead to **diastereomer** molecules, the hydrogens are **diastereotopic**.
- If replacement of a hydrogen would not lead to a chiral center being created, they are termed **homotopic**.

5.12: Chirality in Nature and Chiral Environments

Skills to Master

- Skill 5.1 Identify stereocenters in molecular structures.
- Skill 5.2 Identify whether two structures are identical (not meso), constitutional isomers, enantiomers, diastereomers or meso and identical.
- Skill 5.3 Explain how plane polarized light is used to show optical activity.
- Skill 5.4 Calculate specific rotation from experimental data.
- Skill 5.5 Calculate optical purity and enantiomeric excess from experimental data.
- Skill 5.6 Determine configuration of stereocenters as R or S.
- Skill 5.7 Draw the enantiomer and diastereomers of a given compound with one or more stereocenters.
- Skill 5.8 Identify planes of symmetry in meso compounds.
- Skill 5.9 Describe a process for separating a mixture of enantiomers.
- Skill 5.10 Explain why racemic mixtures are optically inactive.
- Skill 5.11 Explain the difference between constitutional and stereoisomers.
- Skill 5.12 Give an example of a chiral center that is not carbon.

Memorization Tasks

MT 5.1 Memorize the rules for determining R and S configuration.

MT 5.2 Memorize the types of isomers and how to identify them.

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CHAPTER OVERVIEW

4: Organic Functional Groups

4.1: Organic Functional Groups
4.2: Generic (Abbreviated) Structures (aka R Groups)
4.3: Overview of the IUPAC Naming Strategy
4.4: Alkanes
4.5: Alkenes
4.6: Alcohols - Classification and Nomenclature
4.7: Ethers, Epoxides and Sulfides
4.8: Aldehydes and Ketones
4.9: Amines - Classification and Nomenclature
4.10: Benzene and its Derivatives
4.11: Carboxylic Acids

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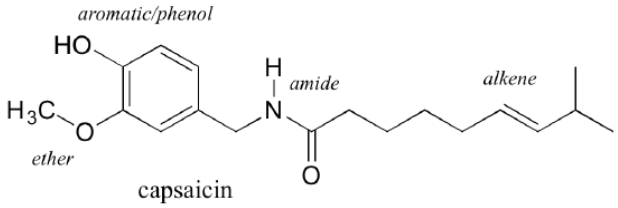
4.1: Organic Functional Groups

Learning Objective

- recognize and classify the common functional groups of organic chemistry (alkanes, alkenes, alkynes, alkyl halides, alcohols, amines, ethers, aldehydes, ketones, carboxylic acids, esters, and amides

Functional groups in organic compounds

Functional groups are structural units within organic compounds that are defined by specific bonding arrangements between specific atoms. The structure of capsaicin, the compound responsible for the heat in peppers, incorporates several functional groups, labeled in the figure below and explained throughout this section.

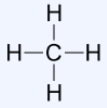


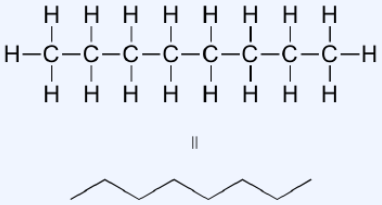
capsaicin

As we progress in our study of organic chemistry, it will become extremely important to be able to quickly recognize the most common functional groups, because *they are the key structural elements that define how organic molecules react*. For now, we will only worry about drawing and recognizing each functional group, as depicted by Lewis and line structures. Much of the remainder of your study of organic chemistry will be taken up with learning about how the different functional groups behave in organic reactions.

The 'default' in organic chemistry (essentially, the *lack* of any functional groups) is given the term **alkane**, characterized by single bonds between carbon and carbon, or between carbon and hydrogen. Methane, CH_4, is the natural gas you may burn in your furnace. Octane, C_8H_{18}, is a component of gasoline.

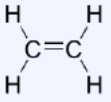
Alkanes

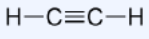

methane


octane

Alkenes (sometimes called **olefins**) have carbon-carbon double bonds, and **alkynes** have carbon-carbon triple bonds. Ethene, the simplest alkene example, is a gas that serves as a cellular signal in fruits to stimulate ripening. (If you want bananas to ripen quickly, put them in a paper bag along with an apple - the apple emits ethene gas, setting off the ripening process in the bananas). Ethyne, commonly called acetylene, is used as a fuel in welding blow torches.

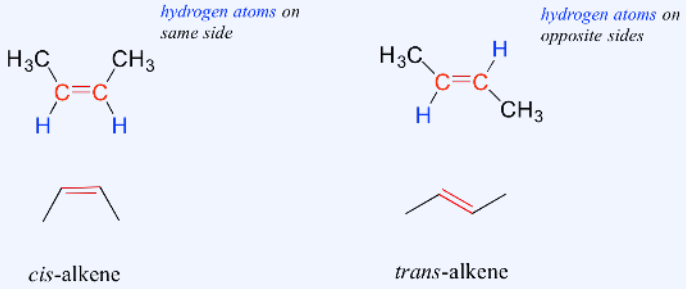
Alkenes and alkynes


ethene
(an alkene)


ethyne
(an alkyne)

Alkenes have trigonal planar electron geometry while alkynes have linear geometry. Furthermore, many alkenes can take two geometric forms: ***cis*** or ***trans***. The *cis* and *trans* forms of a given alkene are different molecules with different

physical properties there is a very high energy barrier to rotation about a double bond. In the example below, the difference between *cis* and *trans* alkenes is readily apparent.

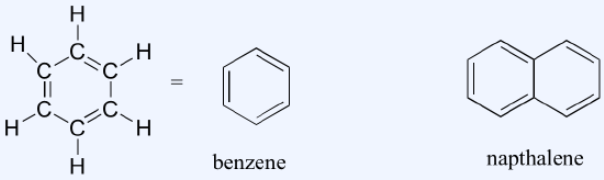


cis-alkene *trans*-alkene

Alkanes, alkenes, and alkynes are all classified as **hydrocarbons**, because they are composed solely of carbon and hydrogen atoms. Alkanes are said to be **saturated hydrocarbons**, because the carbons are bonded to the maximum possible number of hydrogens - in other words, they are *saturated* with hydrogen atoms. The double and triple-bonded carbons in alkenes and alkynes have fewer hydrogen atoms bonded to them - they are thus referred to as **unsaturated hydrocarbons**. As we will see in chapter 15, hydrogen can be added to double and triple bonds, in a type of reaction called 'hydrogenation'.

The **aromatic** group is exemplified by benzene (which used to be a commonly used solvent on the organic lab, but which was shown to be carcinogenic), and naphthalene, a compound with a distinctive 'mothball' smell. Aromatic groups are planar (flat) ring structures, and are widespread in nature. We will learn more about the structure and reactions of aromatic groups in chapters 2 and 14.

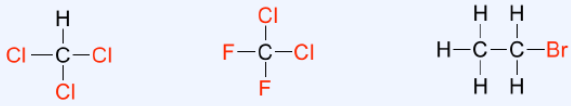
Aromatics



benzene napthalene

When the carbon of an alkane is bonded to one or more halogens, the group is referred to as a **alkyl halide** or **haloalkane**. Chloroform is a useful solvent in the laboratory, and was one of the earlier anesthetic drugs used in surgery. Chlorodifluoromethane was used as a refrigerant and in aerosol sprays until the late twentieth century, but its use was discontinued after it was found to have harmful effects on the ozone layer. Bromoethane is a simple alkyl halide often used in organic synthesis. Alkyl halides groups are quite rare in biomolecules.

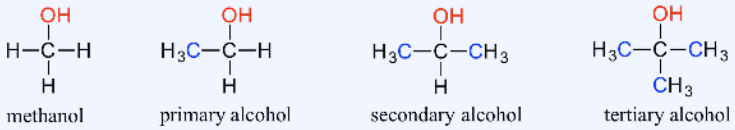
Haloalkanes

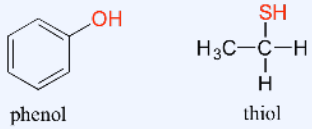


trichloromethane (chloroform) dichlorodifluoromethane (Freon-12) bromoethane

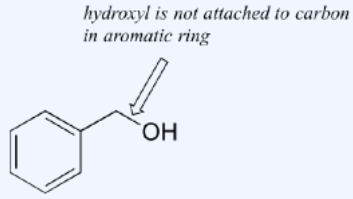
In the **alcohol** functional group, a carbon is single-bonded to an OH group (the OH group, by itself, is referred to as a **hydroxyl**). Except for methanol, all alcohols can be classified as primary, secondary, or tertiary. In a **primary alcohol**, the carbon bonded to the OH group is also bonded to only one other carbon. In a **secondary alcohol** and **tertiary alcohol,** the carbon is bonded to two or three other carbons, respectively. When the hydroxyl group is *directly* attached to an aromatic ring, the resulting group is called a **phenol**. The sulfur analog of an alcohol is called a **thiol** (from the Greek *thio*, for sulfur).

Alcohols, phenols, and thiols





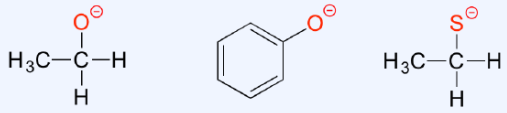
Note that the definition of a phenol states that the hydroxyl oxygen must be *directly* attached to one of the carbons of the aromatic ring. The compound below, therefore, is *not* a phenol - it is a primary alcohol.

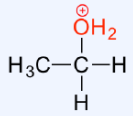


primary alcohol
(*not* a phenol)

The distinction is important, because as we will see later, there is a significant difference in the reactivity of alcohols and phenols.

The deprotonated forms of alcohols, phenols, and thiols are called **alkoxides**, **phenolates**, and **thiolates**, respectively. A protonated alcohol is an **oxonium** ion.

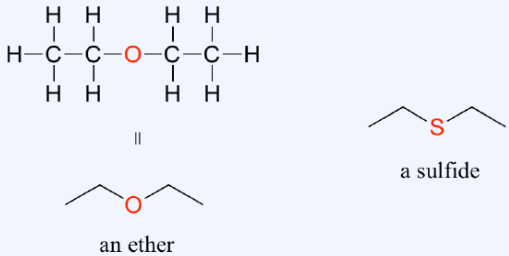




oxonium

In an **ether** functional group, a central oxygen is bonded to two carbons. Below is the structure of diethyl ether, a common laboratory solvent and also one of the first compounds to be used as an anesthetic during operations. The sulfur analog of an ether is called a **thioether** or **sulfide**.

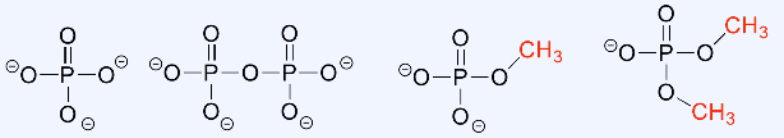
Ethers and sulfides



Phosphate and its derivative functional groups are ubiquitous in biomolecules. Phosphate linked to a single organic group is called a **phosphate ester**; when it has two links to organic groups it is called a

phosphate diester. A linkage between two phosphates creates a **phosphate anhydride**.

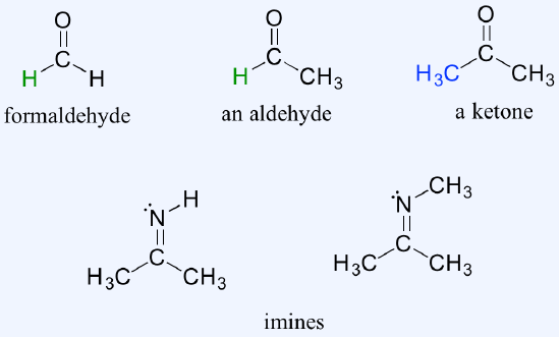
Organic phosphates



There are a number of functional groups that contain a carbon-oxygen double bond, which is commonly referred to as a **carbonyl**. **Ketones** and **aldehydes** are two closely related carbonyl-based functional groups that react in very similar ways. In a ketone, the carbon atom of a carbonyl is bonded to two other carbons. In an aldehyde, the carbonyl carbon is bonded on one side to a hydrogen, and on the other side to a carbon. The exception to this definition is formaldehyde, in which the carbonyl carbon has bonds to two hydrogens.

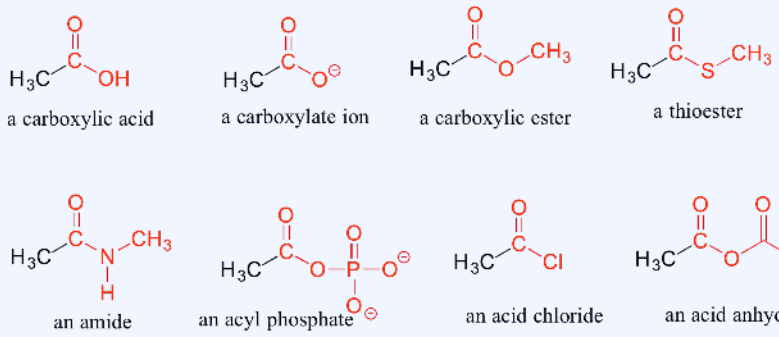
A group with a carbon-nitrogen double bond is called an **imine**, or sometimes a **Schiff base** (in this book we will use the term 'imine'). The chemistry of aldehydes, ketones, and imines will be covered in chapter 10.

Aldehydes, ketones, and imines

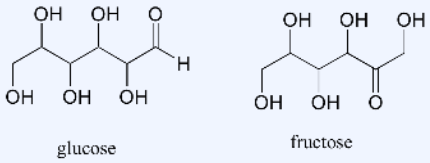


When a carbonyl carbon is bonded on one side to a carbon (or hydrogen) and on the other side to an oxygen, nitrogen, or sulfur, the functional group is considered to be one of the '**carboxylic acid derivatives**', a designation that describes a set of related functional groups. The eponymous member of this family is the **carboxylic acid** functional group, in which the carbonyl is bonded to a hydroxyl group. The conjugate base of a carboxylic acid is a **carboxylate**. Other derivatives are carboxylic esters (usually just called '**esters**'), **thioesters**, **amides**, **acyl phosphates**, **acid chlorides**, and **acid anhydrides**. With the exception of acid chlorides and acid anhydrides, the carboxylic acid derivatives are very common in biological molecules and/or metabolic pathways, and their structure and reactivity will be discussed in detail in chapter 11.

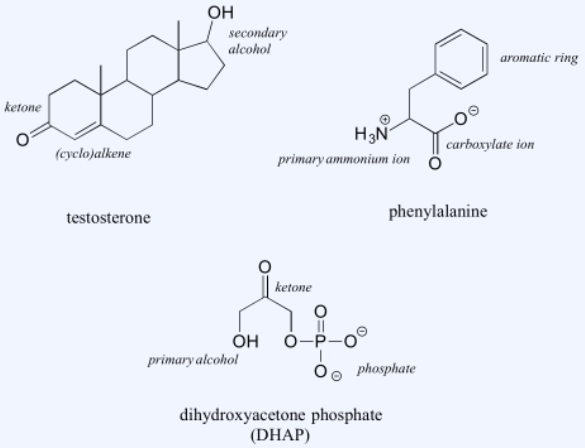
Carboxylic acid derivatives



A single compound often contains several functional groups, particularly in biological organic chemistry. The six-carbon sugar molecules glucose and fructose, for example, contain aldehyde and ketone groups, respectively, and both contain five alcohol groups (a compound with several alcohol groups is often referred to as a '**polyol**').



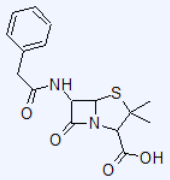
The hormone testosterone, the amino acid phenylalanine, and the glycolysis metabolite dihydroxyacetone phosphate all contain multiple functional groups, as labeled below.



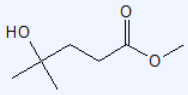
While not in any way a complete list, this section has covered most of the important functional groups that we will encounter in biological organic chemistry.

Exercise:

1. Identify the functional groups (other than alkanes) in the following organic compounds. State whether alcohols and amines are primary, secondary, or tertiary.



penicillin



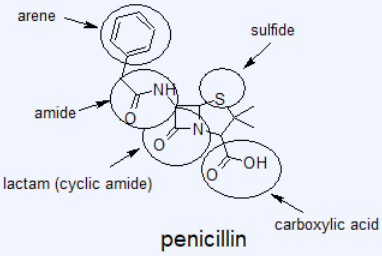


pyruvic acid

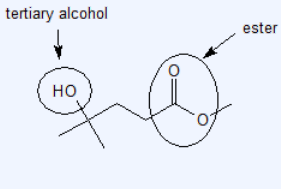


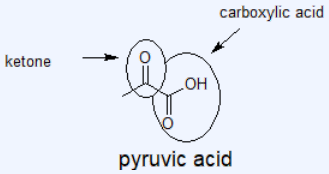
Solution

1.

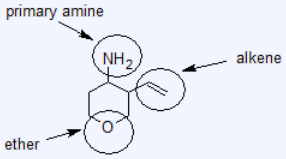


penicillin





pyruvic acid



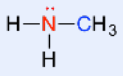
Amines are characterized by nitrogen atoms with single bonds to hydrogen and carbon. Just as there are primary, secondary, and tertiary alcohols, there are primary, secondary, and tertiary amines. Ammonia is a special case with no carbon atoms.

One of the most important properties of amines is that they are basic, and are readily protonated to form **ammonium** cations. In the case where a nitrogen has four bonds to carbon (which is somewhat unusual in biomolecules), it is called a quaternary ammonium ion.

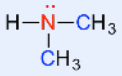
Amines



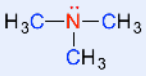
ammonia



a primary amine



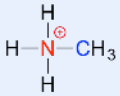
a secondary amine



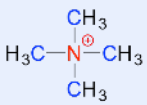
a tertiary amine



ammonium ion

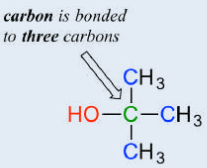


a primary ammonium ion

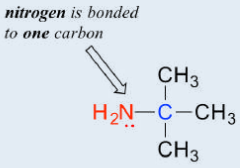


a quaternary ammonium ion

Note: Do not be confused by how the terms 'primary', 'secondary', and 'tertiary' are applied to alcohols and amines - the definitions are different. In alcohols, what matters is how many other carbons the alcohol *carbon* is bonded to, while in amines, what matters is how many carbons the *nitrogen* is bonded to.



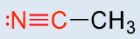
a *tertiary* alcohol



a *primary* amine

Finally, a **nitrile** group is characterized by a carbon triple-bonded to a nitrogen.

Nitriles



acetonitrile

Exercise

2. Draw one example of each compound that includes the specified structural features. Be sure to designate the location of all non-zero formal charges. All atoms should have complete octets (phosphorus may exceed the octet rule). There are many possible correct answers for these, so be sure to check your structures with your instructor or tutor.

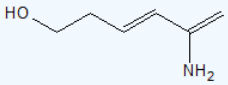
a) a compound with molecular formula $C_6H_{11}NO$ that includes alkene, secondary amine, and primary alcohol functional groups

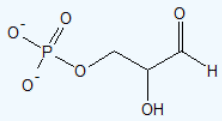
b) an ion with molecular formula $C_3H_5O_6P^{2-}$ that includes aldehyde, secondary alcohol, and phosphate functional groups.

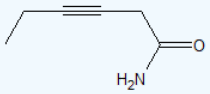
c) A compound with molecular formula C_6H_9NO that has an amide functional group, and does *not* have an alkene group.

Answer

2.

a) 

b) 

c) 

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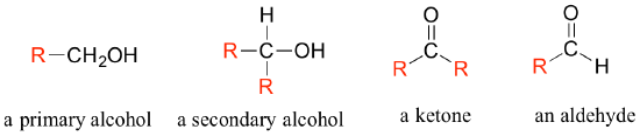
4.2: Generic (Abbreviated) Structures (aka R Groups)

Learning Objective

- use R groups to draw abbreviated, space saving forms of molecules.

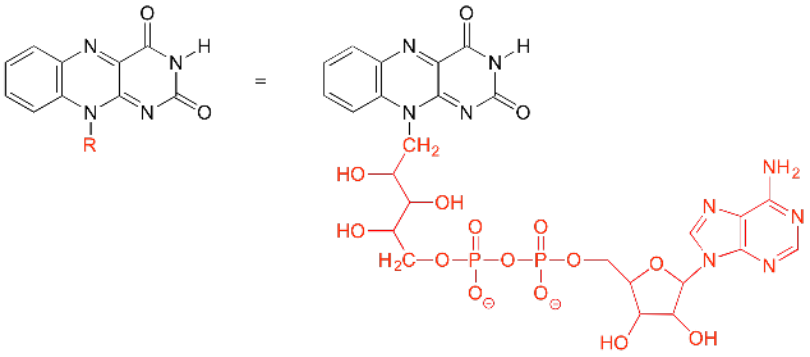
Drawing Generic (abbreviated) Organic Structures

In chapter 2, we learned to recognize and distinguish between organic functional groups. Often when drawing organic structures, chemists find it convenient to use the letter 'R' to designate part of a molecule outside of the region of interest. "R" represents the "Rest of the Molecule". If we just want to refer in general to a functional group without drawing a specific molecule, for example, we can use 'R groups' to focus attention on the group of interest:



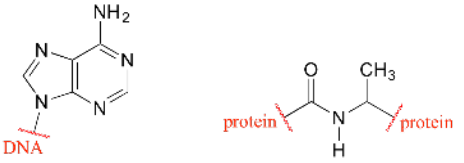
a primary alcohol | a secondary alcohol | a ketone | an aldehyde

The 'R' group is a convenient way to abbreviate the structures of large biological molecules, especially when we are interested in something that is occurring specifically at one location on the molecule. For example, in chapter 15 when we look at biochemical oxidation-reduction reactions involving the flavin molecule, we will abbreviate a large part of the flavin structure which does not change at all in the reactions of interest:



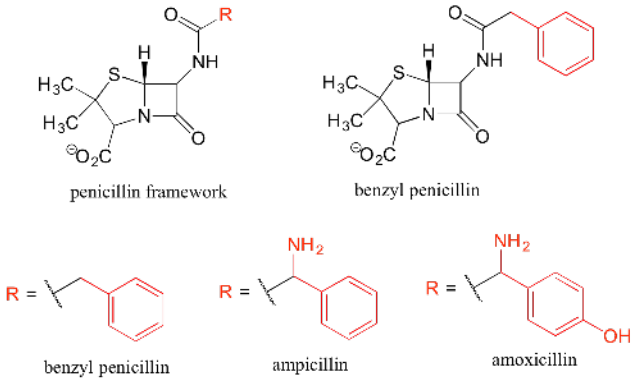
flavin adenine dinucleotide (FAD)

As an alternative, we can use a 'break' symbol to indicate that we are looking at a small piece or section of a larger molecule. This is used commonly in the context of drawing groups on large polymers such as proteins or DNA.



an adenine base in DNA | a small section of a protein

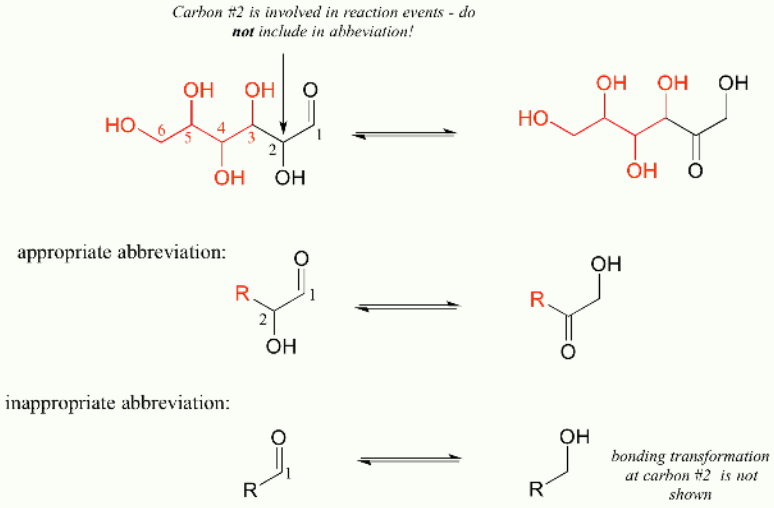
Finally, 'R' groups can be used to concisely illustrate a series of related compounds, such as the family of penicillin-based antibiotics.



Using abbreviations appropriately is a very important skill to develop when studying organic chemistry in a biological context, because although many biomolecules are very large and complex (and take forever to draw!), usually we are focusing on just one small part of the molecule where a change is taking place.

As a rule, *you should never abbreviate any atom involved in a bond-breaking or bond-forming event that is being illustrated:* only abbreviate that part of the molecule which is not involved in the reaction of interest.

For example, carbon #2 in the reactant/product below most definitely is involved in bonding changes, and therefore should not be included in the 'R' group.

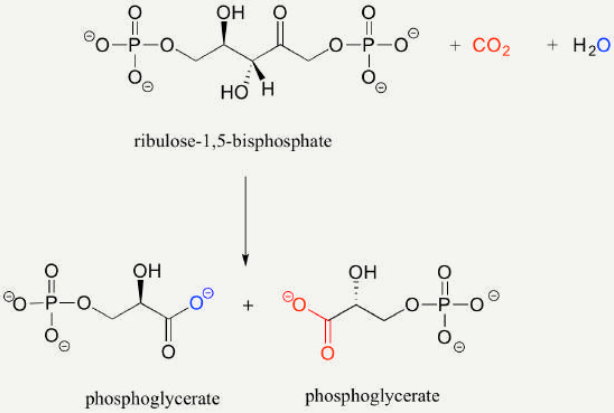


If you are unsure whether to draw out part of a structure or abbreviate it, the safest thing to do is to draw it out.

1. a) If you intend to draw out the chemical details of a reaction in which the methyl ester functional group of cocaine (see earlier figure) was converted to a carboxylate plus methanol, what would be an appropriate abbreviation to use for the cocaine structure (assuming that you *only* wanted to discuss the chemistry specifically occurring at the ester group)?

b) Below is the (somewhat complicated) reaction catalyzed by an enzyme known as 'Rubisco', by which plants 'fix' carbon dioxide. Carbon dioxide and the oxygen of water are

colored red and blue respectively to help you see where those atoms are incorporated into the products. Propose an appropriate abbreviation for the starting compound (ribulose 1,5-bisphosphate), using two different 'R' groups, R_1 and R_2.



Solutions to exercises

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4.3: Overview of the IUPAC Naming Strategy

learning objectives

- name alkanes, cycloalkanes, alkenes, alkynes, alkyl halides, ethers, alcohols, amines, benzene and its derivatives, aldehydes, ketones, amines, carboxylic acids, and carboxylic acid derivatives using IUPAC (systematic) and selected common name nomenclature
- draw the structure of alkanes, cycloalkanes, alkenes, alkynes, alkyl halides, ethers, alcohols, amines, benzene and its derivatives, aldehydes, ketones, amines, carboxylic acids, and carboxylic acid derivatives from the IUPAC (systematic) and selected common names

Overview of the IUPAC System for Naming Organic Compounds

The International Union of Pure and Applied Chemistry (IUPAC) has established the rules of nomenclature of all chemical compounds. IUPAC nomenclature can also be called "systematic" nomenclature because there is an overall system and structure to the names. This section provides an overview of the general naming strategy and structure for organic compounds.

Naming organic compounds according to the IU{AC system requires up to four pieces of information

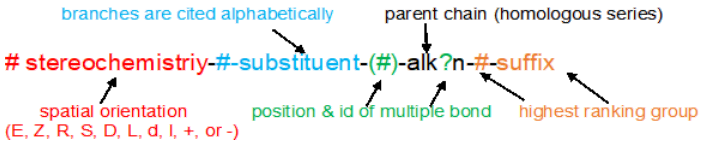
1. recognize & prioritize the functional group(s) present

2. identify & number the longest continuous carbon chain to give the highest ranking group the lowest possible number

3. cite the substituents (branches) alphabetically using the numbering determined above

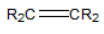
4. recognize & classify any stereochemistry (E/Z, R/S, cis/trans, etc)

With these four pieces of information, the IUPAC name is written using the format below. This same format applies to **ALL** the organic compounds.



Recognize & Prioritize the Functional Group(s) Present

The IUPAC Rules of Organic Nomenclature assume that the following table is understood and memorized.

Structure	Classification	Suffix Name	Substituent Name
higher priority 	Carboxylic acid	-oic acid	carboxy-
	Ester	-oate	alkoxycarbonyl-
	Amide	-amide	amido-
	Nitrile	-nitrile	cyano-
	Aldehyde	-al	formyl-
	Ketone	-one	oxo-
	Alcohol	-ol	hydroxy-
	Amine	-amine	amino-
	Alkene	-ene	alken-
	Alkyne	-yne	alkyn-
	Alkane*	-ane	alkyl-
	Ether*	---	alkoxy-
lower priority	Alkyl halide*	---	halo-

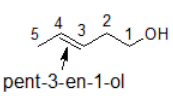
*Same overall priority, prioritize by structure as described in the appendix

Identify & Number the Longest Continuous Carbon Chain with the Highest Priority Group

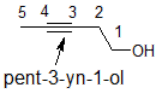
The longest continuous carbon chain (parent) is named using the Homologous Series, as well as any carbon branches. The suffixes and location within the name distinguish between the parent and the branches.

When Alkenes and Alkynes have Lower Priority

The hydrocarbon suffixes differ in the letter preceeding the "n". When alkenes and alkynes occur in compounds with higher priority functional groups, then the distinction between hydrocarbons is communicated with a single letter: "e", or "y" for alkenes and alkynes, respectively, An example is shown below to illustrate the application of this rule.



pent-3-en-1-ol



pent-3-yn-1-ol

substituents (branches) alphabetically

The major substituents are listed above and need to be memorized. There are a few additional substituents that will introduced later in the text.

Stereochemistry

Distinguishing spatial orientations of atoms (stereochemistry) are communicated at the beginning of the name using the appropriate symbols, such as E/Z, R/S, cis/trans, etc. This nomenclature will be discussed when it is possible for a functional group.

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4.4: Alkanes

learning objectives

- name alkanes using IUPAC (systematic) and selected common name nomenclature
- draw the structure of alkanes from IUPAC (systematic) and selected common names

Alkanes are hydrocarbons that can be described by the general formula C_nH_{2n+2}. They consist only of carbon and hydrogen and contain only single bonds. Alkanes are also known as "saturated hydrocarbons."

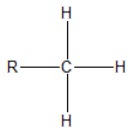
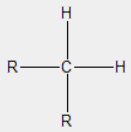
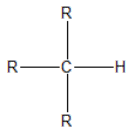
The following table contains the systematic names for the first twenty straight chain alkanes. It will be important to familiarize yourself with these names because they will be the basis for naming many other organic molecules throughout your course of study.

Name	Molecular Formula	Condensed Structural Formula
Methane	CH_4	CH_4
Ethane	C_2H_6	CH_3CH_3
Propane	C_3H_8	$CH_3CH_2CH_3$
Butane	C_4H_{10}	$CH_3(CH_2)_2CH_3$
Pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$
Hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$
Heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$
Octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$
Nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$
Decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$
Undecane	$C_{11}H_{24}$	$CH_3(CH_2)_9CH_3$
Dodecane	$C_{12}H_{26}$	$CH_3(CH_2)_{10}CH_3$
Tridecane	$C_{13}H_{28}$	$CH_3(CH_2)_{11}CH_3$
Tetradecane	$C_{14}H_{30}$	$CH_3(CH_2)_{12}CH_3$
Pentadecane	$C_{15}H_{32}$	$CH_3(CH_2)_{13}CH_3$
Hexadecane	$C_{16}H_{34}$	$CH_3(CH_2)_{14}CH_3$
Heptadecane	$C_{17}H_{36}$	$CH_3(CH_2)_{15}CH_3$
Octadecane	$C_{18}H_{38}$	$CH_3(CH_2)_{16}CH_3$
Nonadecane	$C_{19}H_{40}$	$CH_3(CH_2)_{17}CH_3$
Eicosane	$C_{20}H_{42}$	$CH_3(CH_2)_{18}CH_3$

Carbon Atom Classifications

To assign the prefixes sec-, which stands for secondary, and tert-, for tertiary, it is important that we first learn how to classify carbon atoms. If a carbon is attached to only one other carbon, it is called a primary carbon. If a carbon is attached to two other carbons, it is called a seconday carbon. A tertiary carbon is attached to three other carbons and last, a quaternary carbon is attached to four other carbons. These terms are summarixed with an example in the table below.

Classification	Example
methyl	CH_4

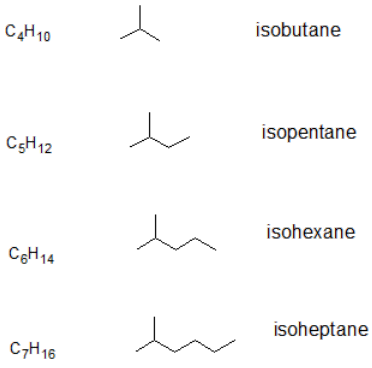
primary	
secondary	
tertiary	

Using Common Names with Branched Alkanes

Certain branched alkanes have common names that are still widely used today. These common names make use of prefixes, such as ***iso-***, ***sec-***, ***tert-***, and ***neo-***.

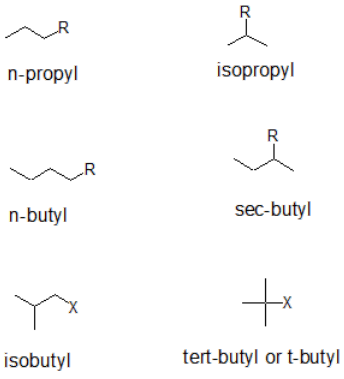
Isoalkanes

The prefix ***iso-***, which stands for isomer, is commonly given to 2-methyl alkanes. In other words, if there is methyl group located on the second carbon of a carbon chain, we can use the prefix ***iso-***. The prefix will be placed in front of the alkane name that indicates the *total* number of carbons as in isopentane which is the same as 2-methylbutane and isobutane which is the same as 2-methylpropane. The pattern is illustrated below

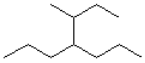


Sec- and Tert-alkanes

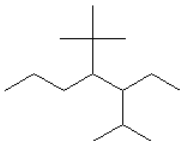
Secondary and tertiary alkanes can be further distinguished from their "iso-counter parts" by applying comparing the carbon classifications. The common names for three and four carbon branches are summarized below. Notice that the "iso" prefix is joined directly to the alkyl name. When alphabetizing branches, the "i" is considered. For "sec" and "tert", the prefix is separated from the alkyl name and is NOT considered when alphabetizing branches.



For some compounds, the common names bring a simple a simple elegance to the experience.



Common: 4-sec-butylheptane
IUPAC: 3-methyl-4-propylheptane

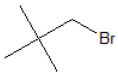


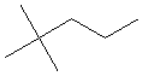
Common: 4-t-butyl-3-isopropylheptane
IUPAC: 4-*tert*-butyl-3-ethyl-2-methylheptane

Neo-alkanes

A five carbon alkane and the corresponding five carbon branch can form a structural pattern commonly known as neopentane and neopentyl respectively. The prefix neo- can also be applied to larger alkanes as shown below.



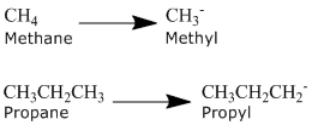




IUPAC:	2,2-dimethylpropane	1-bromo-2,2-dimethylpropane	2,2-dimethylpentane
Common:	neopentane	neopentylbromide	neoheptane

Alkyl Groups

An alkyl group is formed by removing one hydrogen from the alkane chain and is described by the formula C_nH_{2n+1}. The removal of this hydrogen results in a stem change from **-ane** to **-yl**. Take a look at the following examples.



The same approach can be used with any of the alkanes in the table above and with common names.

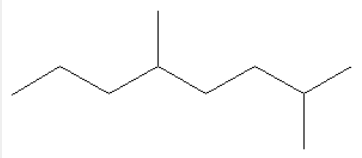
Alkyl Group Common Names that sound like Alkenes

In long hydrocarbon chains there can be many $-CH_2-$ groups in a series. These internal $-(CH_2)_n-$ groups are names using the homologous series stem with the suffice "ene" even though there are NO carbon-carbon double bonds present. For example, the common name for dichloromethane, CH_2Cl_2, is methylene chloride; and the common names for the major ingredients in antifreeze are ethylene glycol ($CH_2(OH)CH_2OH$) and propylene glycol ($CH_2(OH)CH_2(OH)CH_3$), in spite of the fact that there are no carbon-carbon double bonds in any of these three compounds.

Three Basic Principles of Naming

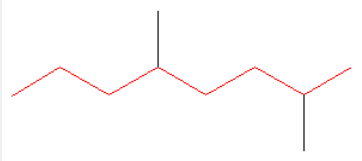
1. Choose the longest, most substituted carbon chain containing a functional group.
2. A carbon bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number.
3. Take the alphabetical order into consideration; that is, after applying the first two rules given above, make sure that your substitutes and/or functional groups are written in alphabetical order.

Example

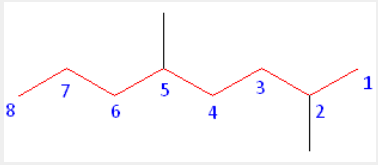


Solution

Rule #1 Choose the longest, most substituted carbon chain containing a functional group. This example does not contain any functional groups, so we only need to be concerned with choosing the longest, most substituted carbon chain. The longest carbon chain has been highlighted in red and consists of eight carbons.

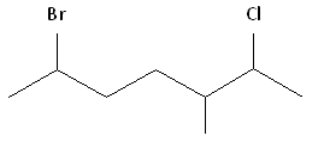


Rule #2 Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number. Because this example does not contain any functional groups, we only need to be concerned with the two substitutes present, that is, the two methyl groups. If we begin numbering the chain from the left, the methyls would be assigned the numbers 4 and 7, respectively. If we begin numbering the chain from the right, the methyls would be assigned the numbers 2 and 5. Therefore, to satisfy the second rule, numbering begins on the right side of the carbon chain as shown below. This gives the methyl groups the lowest possible numbering.



In this example, there is no need to utilize the third rule. Because the two substitutes are identical, neither takes alphabetical precedence with respect to numbering the carbons. This concept will become clearer in the next example.

Example



Solution

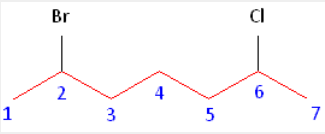
Rule #1 Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine. The longest carbon chain has been highlighted in red and consists of seven carbons.



Rule #2 Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number. In this example, numbering the chain from the left or the right would satisfy this rule. If we number the chain from the left, bromine and chlorine would be assigned the second and sixth carbon positions, respectively. If we number the chain from the right, chlorine would be assigned the second position and bromine would be assigned the sixth position. In other words, whether we choose to number from the left or right, the functional groups occupy the second and sixth positions in the chain. To select the correct numbering scheme, we need to utilize the third rule.

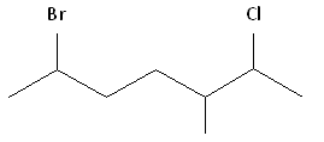


Rule #3 After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.



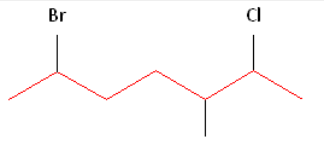
Example

https://chem.libretexts.org/@go/page/396871

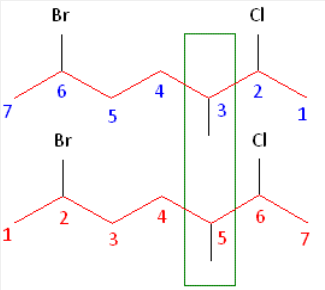


Solution

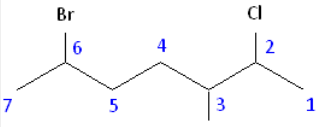
Rule #1 Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine, and one substitute, the methyl group. The longest carbon chain has been highlighted in red and consists of seven carbons.



Rule #2 Carbons bonded to a functional group must have the lowest possible carbon number. After taking functional groups into consideration, any substitutes present must have the lowest possible carbon number. This particular example illustrates the **point of difference principle**. If we number the chain from the left, bromine, the methyl group and chlorine would occupy the second, fifth and sixth positions, respectively. This concept is illustrated in the second drawing below. If we number the chain from the right, chlorine, the methyl group and bromine would occupy the second, third and sixth positions, respectively, which is illustrated in the first drawing below. The position of the methyl, therefore, becomes a **point of difference**. In the first drawing, the methyl occupies the third position. In the second drawing, the methyl occupies the fifth position. To satisfy the second rule, we want to choose the numbering scheme that provides the lowest possible numbering of this substitute. Therefore, the first of the two carbon chains shown below is correct.



Therefore, the first numbering scheme is the appropriate one to use.



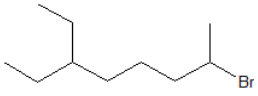
Once you have determined the correct numbering of the carbons, it is often useful to make a list, including the functional groups, substitutes, and the name of the parent chain.

Parent chain: heptane 2-Chloro 3-Methyl 6-Bromo

6-bromo-2-chloro-3-methylheptane

Exercises

Write the IUPAC (systematic) name for each of the compounds below. The parent chains have numbered for the first two compounds to help you begin.

a)	
b)	
c)	

Solutions

a) 9-chloro-7-ethyl-2,2,4-tromethyldecane

b) 3-chloro-5-ethyl-4,4-dimethylheptane

c) 2-bromo-6-ethyloctane

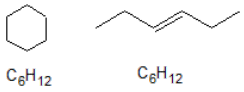
4.4: Alkanes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

4.5: Alkenes

learning objectives

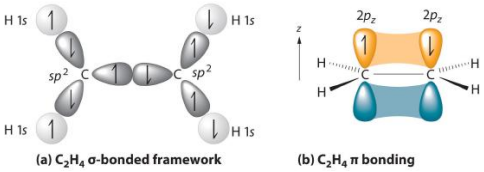
- name alkenes using IUPAC (systematic) and selected common name nomenclature
- draw the structure of alkenes from IUPAC (systematic) and selected common names

Alkenes contain carbon-carbon double bonds and are unsaturated hydrocarbons with the molecular formula is C_nH_{2n}. Be aware - this is also the same molecular formula ratio as cycloalkanes as shown in the example below.



Introduction

The parent structure is the longest chain containing both carbon atoms of the double bond. The two carbon atoms of a double bond and the four atoms attached to them lie in a plane, with bond angles of approximately 120° A double bond consists of one sigma bond formed by overlap of sp^2 hybrid orbitals and one pi bond formed by overlap of parallel 2 p orbitals.



(a) C_2H_4 σ-bonded framework (b) C_2H_4 π bonding

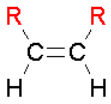
The carbon atoms sharing the double bond can be referred to as the "vinyl carbons". This common name arose because alkenes the source for vinyl polymers.

Pi Bond Rigidity & Geometric Isomers

The rigidity of the pi bond in alkenes creates the possibility of stereoisomers called geometric isomers. To name alkenes, it may be neccessary to communicate the stereochemistry of the structure using the cis/trans or E/Z systems.

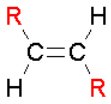
cis Isomers

The two largest groups are on the same side of the double bond.



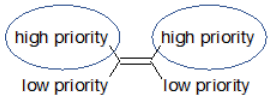
trans Isomers

The two largest groups are on opposite sides of the double bond.

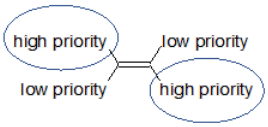


E/Z nomenclature

When the cis/trans system is ambiguous, the E/Z system can be used where E = entgegan ("trans") and Z = zusamen ("cis"). The E/Z system is used to prioritize when there are 3 or 4 different non-hydrogen atoms are attached to the vinyl carbons (carbons sharing the double bond). This system bases priority on the atomic number (Z) and/or atomic mass (A) of the atoms bonded to the vinyl carbons. An atom attached by a multiple bond is counted once for each bond. If there is a tie in priority, then move to the next atom along each chain until a difference occurs. Atomic number has higher priority than atomic mass. Atomic mass is used to establish priority for isotopes, therefore deuterium (D) has higher priority than hydrogen (H).

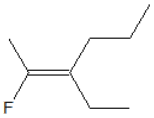


Z stereoisomer
"on the zee zame zide"



E stereoisomer

For example, when comparing atoms bonded to the vinylic carbons in the the compound below,



we would rank the priority as

fluorine atom > propyl group > ethyl group > methyl

Z = 9 > 3 x C chain > 2 x C chain > 1 x C chain

and name the compound ((2E)-3-ethyl-2-fluorohex-2-ene.

The double bond of the allylic group creates higher priority over a simple propyl grup such that $-CH_2-CH=CH_2$ > $-CH_2CH_2CH_3$.

For straight chain alkenes, it is the same basic rules as nomenclature of alkanes except change the suffix to "-ene."

1. Find the Longest Carbon Chain that Contains the Carbon Carbon double bond. If you have two ties for longest Carbon chain, and both chains contain a Carbon Carbon double bond, then identify the most substituted chain.

2. Give the lowest possible number to the Carbon Carbon double bond.

    a) Do not need to number cycloalkenes because it is understood that the double bond is in the one position.

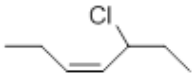
    b) Alkenes that have the same molecular formula but the location of the double bonds are different means they are constitutional isomers.

    c) Functional Groups with higher priority determine the suffix

3. Add substituents and their position to the alkene as prefixes. Of course remember to give the lowest numbers possible. And remember to name them in alphabetical order when writting them.

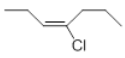
4. Next is identifying stereoisomers - cis/trans. when there are only two non hydrogen attachments to the alkene then use cis and trans to name the molecule.

    For example, the compound below is a cis isomer. It has both the substituents going upward. This molecule would be called (cis) 5-chloro-3-heptene.



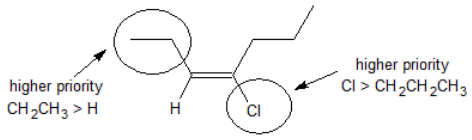
5. Next is identifying stereoisomers - E/Z if cis/trans is ambiguous or skip 4 above and jump straight to E/Z.

    For example, if we look at the "trans" alternative lo the previous compound, the cis/trans system cannot be applied.



cis or trans?

This molecule would be called (3E)-4-chlorohept-3-ene. It is E because the ethyl group ($-CH_2CH_3$) has the higher priority for the vicinal carbon on the left and the chlorine atom has the higher priority for the vicinal carbon on the right and these two groups are on opposite sides of the double bond.



(3*E*)-4-chlorohept-3-ene

6. An example of functional group priorities in nomenclature is that the hydroxyl group gets precedence (has higher priority) over the double bond.

Therefore, alkenes containing alcohol groups are called alkenols with the sufffix --enol.

7. Lastly remember that alkene substituents are called alkenyl. Suffix --enyl.

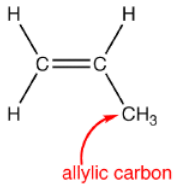
Here is a chart containing the systemic name for the first twenty straight chain alkenes.

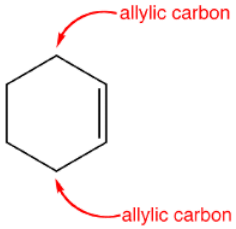
Name	Molecular formula
Ethene	C_2H_4
Propene	C_3H_6
Butene	C_4H_8
Pentene	C_5H_{10}
Hexene	C_6H_{12}
Heptene	C_7H_{14}
Octene	C_8H_{16}
Nonene	C_9H_{18}
Decene	$C_{10}H_{20}$
Undecene	$C_{11}H_{22}$
Dodecene	$C_{12}H_{24}$
Tridecene	$C_{13}H_{26}$
Tetradecene	$C_{14}H_{28}$
Pentadecene	$C_{15}H_{30}$
Hexadecene	$C_{16}H_{32}$
Heptadecene	$C_{17}H_{34}$
Octadecene	$C_{18}H_{36}$
Nonadecene	$C_{19}H_{38}$
Eicosene	$C_{20}H_{40}$

Did you notice how there is no methene? Because it is impossible for a carbon to have a double bond with nothing.

Common names

The carbon atoms sharing the double bond can be referred to as the "vinyl carbons". The carbon atoms adjacent to the vinyl carbon atoms are called "allylic carbons". These carbon atoms have unique reactivity because of the potential for interaction with the pi bond.

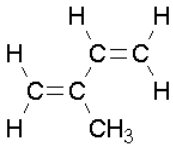




Overall, remove the -ane suffix and add -ylene.

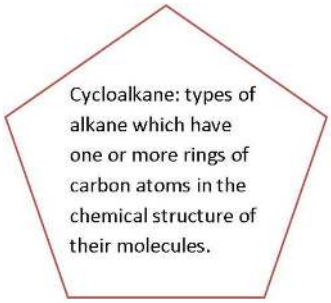
There are a couple of unique ones like ethenyl's common name is vinyl and 2-propenyl's common name is allyl, that you should know are...

- vinyl substituent $H_2C=CH-$
- allyl substituent $H_2C=CH-CH_2-$
- allene molecule $H_2C=C=CH_2$
- isoprene is shown below



Endocyclic & Exocyclic Alkenes

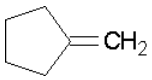
Endocyclic double bonds have both carbons in the ring and exocyclic double bonds have only one carbon as part of the ring.



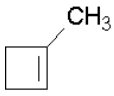
Cyclopentene is an example of an endocyclic double bond.



Methylenecylopentane is an example of an exocyclic double bond.

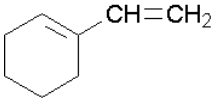


For example, when naming the compound below, the methyl group is considered when numbering the double bond.

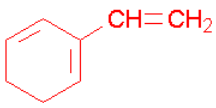


The compound can be named 1-methylcyclobutene or 1-methylcyclobut-1-ene.

When naming this next compound, the ethenyl group is considered when numbering the double bond.

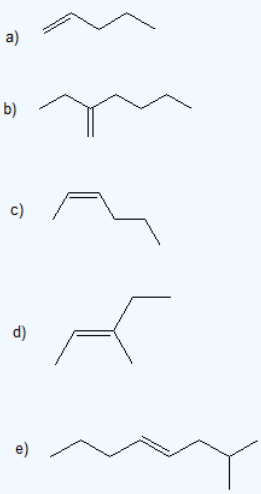


The IUPAC name for the compound can be 1-ethenylcyclohexene or 1-ethenylcyclohex-1-ene. The common name would be 1-vinylcyclohexene. For the compound below, the name is 2-vinyl-1,3-cyclohexadiene.



Exercise

1. Give the IUPAC name for the following compounds. When stereochemistry is included, write the name using both the cis/trans and E/Z names if possible.



2. Draw the bond-line structures for the following compounds.

a) trans-2-pentene

b) (Z)-3-heptene

c) 4-methyl-2-pentene

d) (Z)-5-Chloro-3-ethly-4-hexen-2-ol.

Answer

1. a) 1-pentene or pent-1-ene

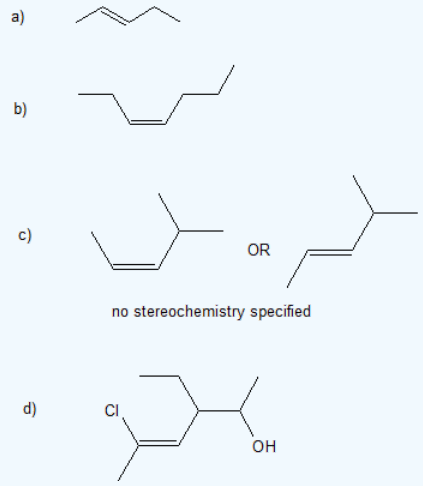
b) 2-ethyl-1-hexene or 2-ethylhex-1-ene (parent chain must include the double bond)

c) cis-2-hexene or (Z)-2-hexene or (2Z)-hex-2-ene

d) (2E)-3-methylpent-2-ene or (E)-3-methyl-2-pentene (cis/trans cannnt be applied)

e) trans-2-methyl-4-octene or (4E)-2-methyloct-4-ene or (E)-2-methyl-4-octene (branch breaks the tie in numbering the parent chain since both directions begin the double bond at carbon 4.

2.



Outside links

- http://www.vanderbilt.edu/AnS/Chemis...0a/alkenes.pdf

References

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

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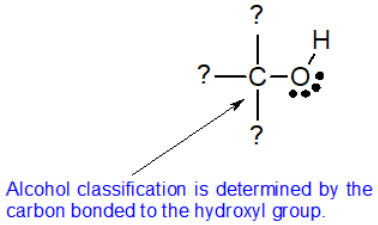
4.6: Alcohols - Classification and Nomenclature

learning objectives

- classify alcohols as primary, secondary, or tertiary
- name alkanes using IUPAC (systematic) and selected common name nomenclature
- draw the structure of alkanes from IUPAC (systematic) and selected common namesAlcohol Classification

Alcohol Classification

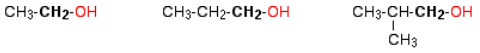
Alcohols may can be classified as primary, **1°**, secondary, **2°** & tertiary, **3°**, in the same manner as alkyl halides. This terminology refers to alkyl substitution of the carbon atom bearing the hydroxyl group (colored blue in the illustration). This classification system is based on the neutral bonding pattern for oxygen. The structure of alcohols requires one of the oxygen bonds to form with hydrogen and the other oxygen bond to form with carbon. All oxygen atoms of alcohols look the same. To distinguish between alcohol classifications, we must look at the carbon atom bonded to the hydroxyl group. The bonding pattern of this carbon atom determines the classification of the alcohol.



Alcohol classification is determined by the carbon bonded to the hydroxyl group.

Primary alcohols

In a primary (1°) alcohol, the carbon which carries the -OH group is only attached to one alkyl group. Some examples of primary alcohols include:

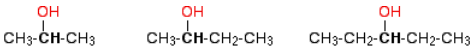


ethanol propan-1-ol 2-methylpropan-1-ol

Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH_2 group holding the -OH group. There is an exception to this. Methanol, CH_3OH, is counted as a primary alcohol even though there are no alkyl groups attached to the carbon with the -OH group on it.

Secondary alcohols

In a secondary (2°) alcohol, the carbon with the -OH group attached is joined directly to two alkyl groups, which may be the same or different. Examples:



propan-2-ol butan-2-ol pentan-3-ol

Tertiary alcohols

In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



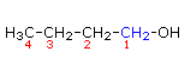
2-methylpropan-2-ol 2-methylbutan-2-ol

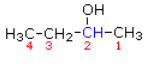
Nomenclature - IUPAC Introduction & Common Names

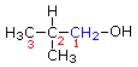
Alcohols are designated by an **ol** suffix if they are the highest priority functinal group. For example, ethanol contains a hydroxyl group to form an alcohol as shown in the follwowing condensed formula: CH_3CH_2OH. Note that a locator number is not needed on

a two-carbon chain, but on longer chains the location of the hydroxyl group determines chain numbering and must be specified in the name. For example: $CH_3CH(OH)CH_2CH_2CH_3$ is 2-pentanol or pentan-2-ol.

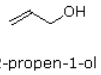
Other examples of IUPAC nomenclature are shown below, together with the common names often used for some of the simpler compounds. For the mono-functional alcohols, this common system consists of naming the **alkyl group** followed by the word **alcohol**.


1-butanol
(butyl alcohol)
a 1°-alcohol


2-butanol
(*sec*-butyl alcohol)
a 2°-alcohol

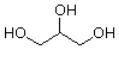

2-methyl-1-propanol
(isobutyl alcohol)
a 1°-alcohol


2-methyl-2-propanol
(*tert*-butyl alcohol)
a 3°-alcohol


2-propen-1-ol
(allyl alcohol)

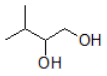

3-cyclohexen-1-ol


1,2-ethanediol
(ethylene glycol)


1,2,3-propanetriol
(glycerol)

Many functional groups have a characteristic suffix designator, and only one such suffix (other than "ene" and "yne") may be used in a name. When the hydroxyl functional group is present together with a function of higher nomenclature priority, it must be cited and located by the prefix hydroxy and an appropriate number. For example, lactic acid has the IUPAC name 2-hydroxypropanoic acid.

The terms "vicinal" and "geminal" can be applied to any two functional groups that are part of the same compound. Typically, these terms are first encountered with alcohols. Vicinal is used to describe the structure of a compound in which the two groups are bonded to neighboring carbons. Geminal is used when both functional groups are bonded to the same carbon. In Latin, "gemini" means twins. In the same way that twins are connected to the same mother, geminal groups are bonded to the same carbon. Similarly, the vicinal groups are in vicinity of each other.


a vicinal diol
3-methylbutane-1,2-diol


a geminal diol
butane-2,2-diol

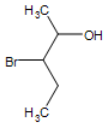
Naming Alcohols

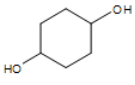
1. Find the longest chain containing the hydroxy group (OH). If there is a chain with more carbons than the one containing the OH group it will be named as a subsitutent.
2. Place the OH on the lowest possible number for the chain. With the exception of carbonyl groups such as ketones and aldehydes, the alcohol or hydroxy groups have first priority for naming.
3. When naming a cyclic structure, the -OH is assumed to be on the first carbon unless the carbonyl group is present, in which case the later will get priority at the first carbon.
4. When multiple -OH groups are on the cyclic structure, number the carbons on which the -OH groups reside.
5. Remove the final **e** from the parent alkane chain and add **-ol**. When multiple alcohols are present use **di, tri,** et.c before the **ol,** after the parent name. ex. 2,3-hexan**diol.** If a carbonyl group is present, the -OH group is named with the prefix "hydroxy," with the carbonyl group attached to the parent chain name so that it ends with **-al** or **-one.**

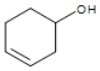
Examples

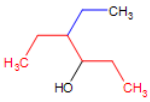
Ethan**e**: CH_3CH_3 ----->Ethan**ol**:  (the alcohol found in beer, wine and other consumed sprits)

Secondary alcohol:  2-propanol

Other functional groups on an alcohol:  3-bromo-2-pentanol

Cyclic alcohol (two -OH groups):  cyclohexan-1,4-diol

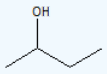
Other functional group on the cyclic structure:  3-hex**ene**ol (the alkene is in **bold** and indicated by numbering the carbon closest to the alcohol)

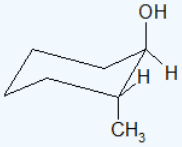
A complex alcohol:  4-ethyl-3hexanol (the parent chain is in red and the substituent is in blue)

Exercise

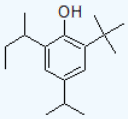
1. Give the IUPAC (Systematic) name for each compound. For parts (a)-(c), classify the alcohols as primary, secondary, or tertiary.

Part (d) is a challenge question and sneak preview of coming attractions.

a) 

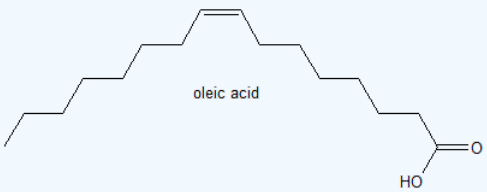
b) 

c) 

d) 

2. Draw the bond line structures, condensed strucutre, and name all the alcohols with the molecular formula C_3H_9O.

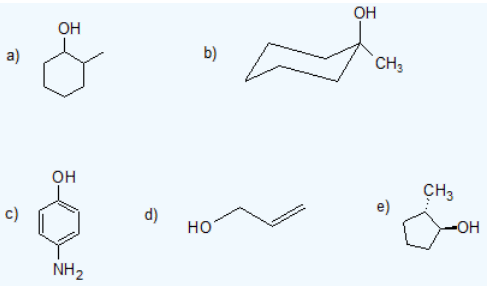
3. Oleic acid, a commonly occurring fatty acid in vegetable oils has the structure below.



a) Describe the stereochemistry of oleic acid - cis or trans?

b) Write the condensed formula for oleic acid.

4. Give the IUPAC name for each compound. For parts (a), (b), (d), and (e) classify the alcohol as primary, secondary, tertiary, or allylic. Part (c) is also a challenge question.



Answer

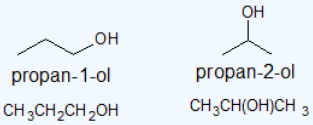
1. a) 2-butanol or butan-2-ol; secondary

   b) 2-methylcyclohexan-1-ol or 2-methyl-1-cyclohexanol; secondary

   c) cyclopentylmethanol (alcohol is higher priority over carbon chain or ring size); primary

   d) 2-(butan2-yl)-6-tert-butyl-4-(propan-2-yl)phenol or 2-sec-butyl-6-t-butyl-4-isopropylphenol (some common names are recognized by IUPAC)

2.



3. a) cis alkene

   b) $CH_3(CH_2)_6CHCH(CH_2)_6CO_2H$

4. a) 2-methyl-1-cyclohexanol or 2-methyl-cyclohexan-1-ol (no stereochemistry communicated even though it is possible); secondary

   b) 1-methyl-1-cyclohexanol or 1-methyl-cyclohexan-1-ol (no steereochemicstry because both groups are bonded to the same carbon); tertiary

   c) 4-nitrophenol

   d) 2-propen-1-ol (alcohols have higher priority than alkenes so determine numbering and suffix); allylic

   e) (1S, 2S)-2-methylcyclopentan-1-ol (For students who have learned about chirality); secondary

      There are two equivalent answers for students who have not yet learned about chirlatiy:

      trans-1-methyl-2-cyclpentanol or trans-1-methylcyclopentan-1-ol

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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4.7: Ethers, Epoxides and Sulfides

learning objectives

- name ethers, epoxides, and sulfides using IUPAC (systematic) and selected common name nomenclature
- draw the structure of ethers, epoxides, and sulfides from IUPAC (systematic) and selected common names

Note: Heterocyclic oxygen compounds are included for the sake of completion. Their nomenclature may or may not be required by the professor are requires additional instruction. Make sure to ask.

Ethers

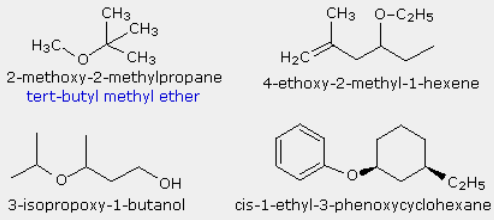
Ethers are compounds having two alkyl or aryl groups bonded to an oxygen atom, as in the formula $R^1–O–R^2$. The ether functional group does not have a characteristic IUPAC nomenclature suffix, so it is necessary to designate it as a substituent. To do so the common alkoxy substituents are given names derived from their alkyl component (below):

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

The smaller, shorter alkyl group becomes the alkoxy substituent. The larger, longer alkyl group side becomes the alkane base name. Each alkyl group on each side of the oxygen is numbered separately. The numbering priority is given to the carbon closest to the oxgen. The alkoxy side (shorter side) has an "-oxy" ending with its corresponding alkyl group. For example, $CH_3CH_2CH_2CH_2CH_2$-O-$CH_2CH_2CH_3$ is 1-propoxypentane. If there is cis or trans stereochemistry, the same rule still applies.

Example

Examples are: $CH_3CH_2OCH_2CH_3$, diethyl ether (sometimes referred to as ether), and $CH_3OCH_2CH_2OCH_3$, ethylene glycol dimethyl ether (glyme).



Common names

Simple ethers are given common names in which the alkyl groups bonded to the oxygen are named in alphabetical order followed by the word "ether". The top left example shows the common name in blue under the IUPAC name. Many simple ethers are symmetrical, in that the two alkyl substituents are the same. These are named as "dialkyl ethers". If we read the word "ether", the author is most likely communicating the compound $CH_3CH_2OCH_2CH_3$, ethoxyethane (diethyl ether), but we do not know with certainty - another example of the importance of accurate nomenclature.

Epoxides

An **epoxide** is a cyclic ether with three ring atoms. These rings approximately define an equilateral triangle, which makes it highly strained. The strained ring makes epoxides more reactive than other ethers. Simple epoxides are named from the parent compound ethylene oxide or oxirane, such as in *chloromethyloxirane*. As a functional group, epoxides feature the *epoxy* prefix, such as in the compound *1,2-epoxycycloheptane*, which can also be called *cycloheptene epoxide*, or simply *cycloheptene oxide*.



A generic epoxide.



The chemical structure of the epoxide glycidol, a common chemical intermediate

A polymer formed by reacting epoxide units is called a *polyepoxide* or an *epoxy*. Epoxy resins are used as adhesives and structural materials. Polymerization of an epoxide gives a polyether, for example ethylene oxide polymerizes to give polyethylene glycol, also known as polyethylene oxide.

Sulfides (Thioethers)

A thioether is a functional group in organosulfur chemistry with the connectivity C-S-C as shown below. Like many other sulfur-containing compounds, volatile thioethers have foul odors.[1] A thioether is similar to an ether except that it contains a sulfur atom in place of the oxygen. The grouping of oxygen and sulfur in the periodic table suggests that the chemical properties of ethers and thioethers are somewhat similar.



General structure of a thioether with the blue marked functional group.

Nomenclature

Thioethers are sometimes called sulfides, especially in the older literature and this term remains in use for the names of specific thioethers. The two organic substituents are indicated by the prefixes. $(CH_3)_2S$ is called dimethylsulfide. Some thioethers are named by modifying the common name for the corresponding ether. For example, $C_6H_5SCH_3$ is methyl phenyl sulfide, but is more commonly called thioanisole, since its structure is related to that for anisole, $C_6H_5OCH_3$.

Structure and properties

Thioether is an angular functional group, the C-S-C angle approaching 90°. The C-S bonds are about 180 pm.

Thioethers are characterized by their strong odors, which are similar to thiol odor. This odor limits the applications of volatile thioethers. In terms of their physical properties they resemble ethers but are less volatile, higher melting, and less hydrophilic. These properties follow from the polarizability of the divalent sulfur center, which is greater than that for oxygen in ethers.

Heterocycles with Oxygen

In cyclic ethers (heterocycles), one or more carbons are replaced with oxygen. Often, it's called heteroatoms, when carbon is replaced by an oxygen or any atom other than carbon or hydrogen. In this case, the stem is called the oxacycloalkane, where the prefix "oxa-" is an indicator of the replacement of the carbon by an oxygen in the ring. These compounds are numbered starting at the oxygen and continues around the ring. For example,



1,4-dioxacyclohexane



1-oxacyclopentane

If a substituent is an alcohol, the alcohol has higher priority. However, if a substituent is a halide, ether has higher priority. If there is both an alcohol group and a halide, alcohol has higher priority. The numbering begins with the end that is closest to the higher priority substituent. There are ethers that are contain multiple ether groups that are called **cyclic polyethers** or **crown ethers**. These are also named using the IUPAC system.

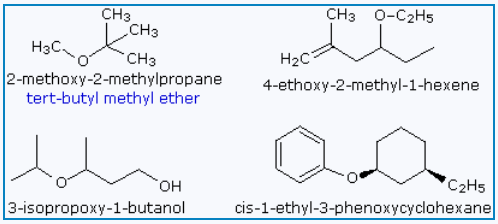
Thiophenes

Thiophenes are a special class of thioether-containing heterocyclic compounds. Because of their aromatic character, they are non-nucleophilic. The nonbonding electrons on sulfur are delocalized into the π-system. As a consequence, thiophene exhibits few

properties expected for a thioether - thiophene is non-nucleophilic at sulfur and, in fact, is sweet-smelling. Upon hydrogenation, thiophene gives tetrahydrothiophene, C_4H_8S, which indeed does behave as a typical thioether.

Example

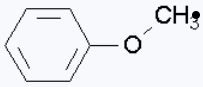
Examples of ethers include $CH_3CH_2OCH_2CH_3$, diethyl ether (sometimes referred to as ether), and $CH_3OCH_2CH_2OCH_3$, ethylene glycol dimethyl ether (glyme).



Common names

Simple ethers are given common names in which the alkyl groups bonded to the oxygen are named in alphabetical order followed by the word "ether". The top left example shows the common name in blue under the IUPAC name. Many simple ethers are symmetrical, in that the two alkyl substituents are the same. These are named as "dialkyl ethers".

- **anisole** (try naming anisole by the other two conventions.



oxirane or 1,2-epoxyethane, ethylene oxide, dimethylene oxide, oxacyclopropane,



furan (this compound is aromatic)

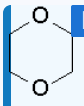


tetrahydrofuran



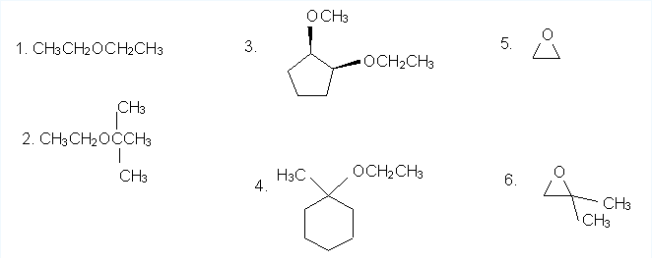
oxacyclopentane, 1,4-epoxybutane, tetramethylene oxide,

dioxane or 1,4-dioxacyclohexane



Exercise

Give the IUPAC and common name (if possible) for each compound respectively.



Answer

1. ethoxyethane; diethyl ether
2. 2-ethoxy-2-methyl-propane; etheyl t-butyl ether (ethyl tert-butyl ether)
3. cis-1-ethoxy-2-methoxycyclopentane; no common name possible
4. 1-ethoxy-1-methylcyclohexane; no common name possible
5. 1,2-epoxyethane; ethylene oxide or dimethylene oxide or oxacyclopropane or oxirane
6. 2,2-dimethyloxirane

Contributors and Attributions

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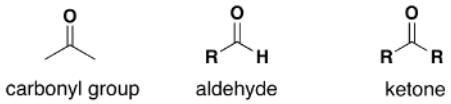
4.8: Aldehydes and Ketones

learning objectives

- name aldehydes and ketones using IUPAC (systematic) and selected common name nomenclature
- draw the structure of aldehydes and ketones from IUPAC (systematic) and selected common names

Aldehydes and ketones contain the carbonyl 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.

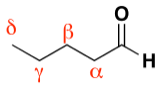
Aldehydes and ketones are organic compounds which incorporate a **carbonyl functional group**, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an **aldehyde**. If neither is hydrogen, the compound is a **ketone**. When writing the condensed formulas for aldehydes and ketones, it is important to note that the carbonyl bond is not drawn. It must be recognized. The generic condensed formula for aldehydes is RCHO (CHO is our aldehyde CHUM) and RCOR' for ketones (no cute memorization aid - if you have one please share it.)



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 moiety 

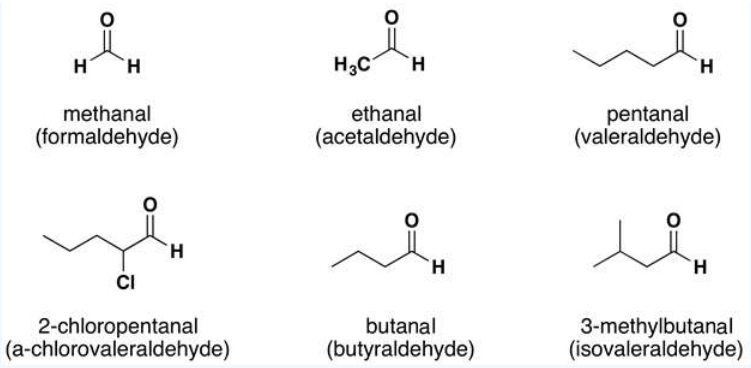
(-CHO) is attached to a ring the suffix ***–carbaldehyde*** is added to the name of the ring. The carbon attached to this moiety will get the #1 location number in naming the ring.

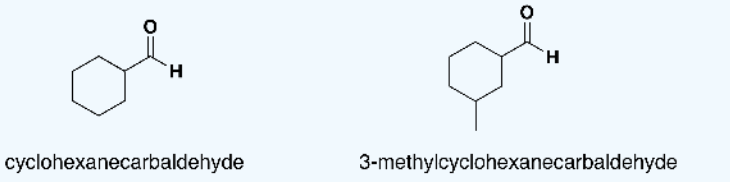
Summary of Aldehyde Nomenclature rules

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 1

The IUPAC system names are given on top while the common name is given on the bottom in parentheses.

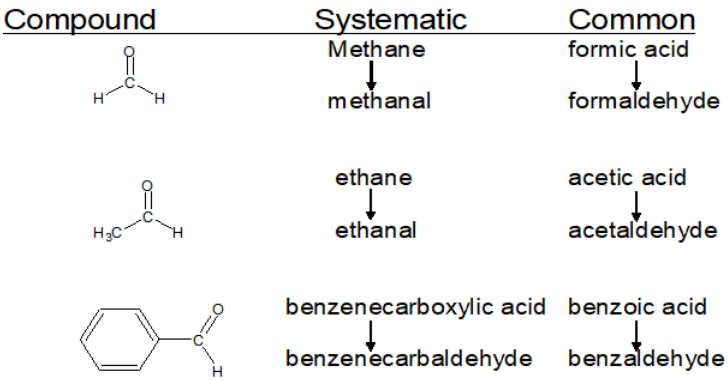






Aldehyde Common Names to Memorize

Aldehydes often called the formyl groups. There are some common names that are still used and need to be memorized. Recognizing the patterns can be helpful.



NOTE: When the aldehyde is the highest priority, there's no need to indicate its position. It has to be on carbon #1.

Naming Ketones

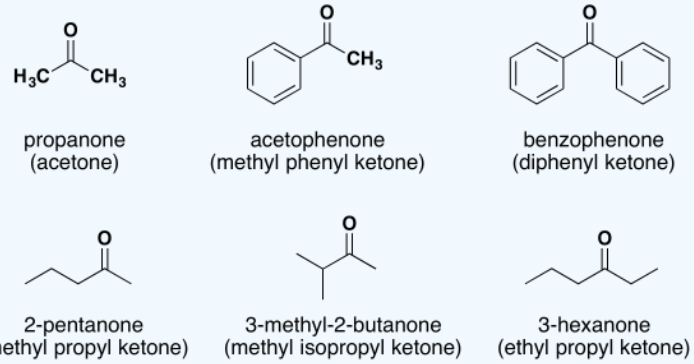
The IUPAC system of nomenclature assigns a characteristic suffix of **-one** to ketones. A ketone carbonyl function may be located anywhere within a chain or ring, and its position is usually given by a location number. Chain numbering normally starts from the end nearest the carbonyl group. Very simple 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 common ketones are known by their generic names. Such as the fact that *propanone* is commonly referred to as *acetone*.

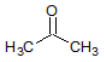
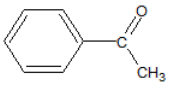
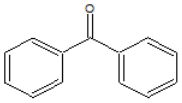
Example 2

The IUPAC system names are given on top while the common name is given on the bottom in parentheses.



Ketone Common Names to Memorize

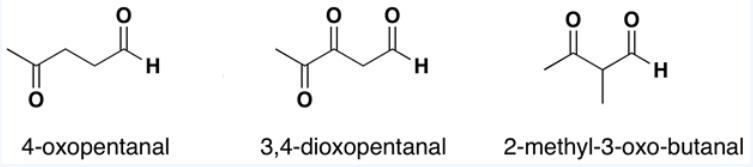
There are some common names that are still used and need to be memorized. Recognizing the patterns can be helpful.

Compound	Systematic	Common
	propane ↓ propanone	acetone or dimethyl ketone
	1-phenylethane ↓ 1-phenylethanone	acetophenone or methyl phenyl ketone
	benzophenone	diphenyl 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.

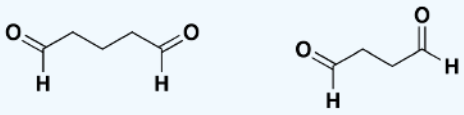
Example 3



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 4



pentanedial butanedial

For diketones both carbonyls require a location number. The ending **-dione** or **-dial** is added to the end of the parent chain.

Example 5



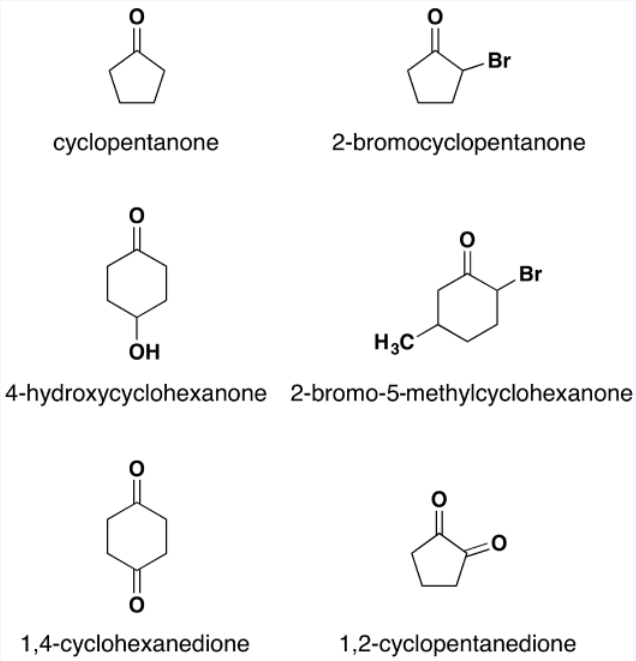
2,4-pentanedione 2,3-hexanedione

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 6



cyclopentanone 2-bromocyclopentanone

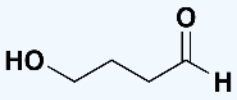
4-hydroxycyclohexanone 2-bromo-5-methylcyclohexanone

1,4-cyclohexanedione 1,2-cyclopentanedione

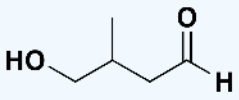
Naming Carbonyls and Hydroxyls in the Same Molecule

When and 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.

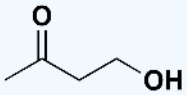
Example 7



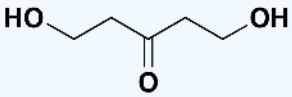
4-hydroxybutanal



4-hydroxy-3-methylbutanal



4-hydroxy-2-butanone



1,5-dihydroxy-3-pentanone

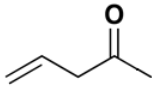
Naming Carbonyls and Alkenes in the Same Molecule

When and aldehyde or ketone is present in a molecule which also contains analkene 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:

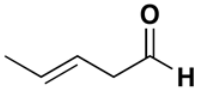
*(Location number of the alkene)-(Prefix name for the longest carbon chain minus the -**ane** ending)-(an -**en** ending to indicate the presence of an alkene)-(the location number of the carbonyl if a ketone is present)-(either an –**one** or and -**anal** ending).*

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.

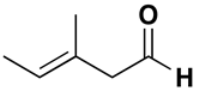
Example 8



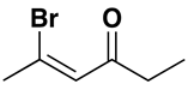
4-penten-2-one



trans-3-pentanal



(E)-3-methyl-3-pentenal

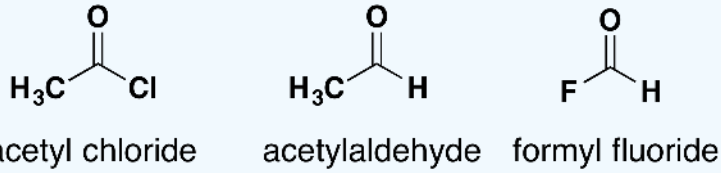


(Z)-5-bromo-4-hexen-3-one

Aldehydes and Ketones as Fragments

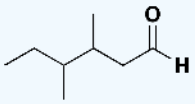
- *Alkanoyl* is the common name of the alt fragment, though the older naming, *acyl*, is still widely used.
- *Formyl* is the common name of the alt fragment.
- *Acety* is the common name of the CH_3-C=O- fragment.

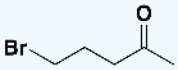
Example 9

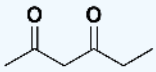


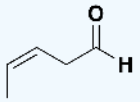
Exercise

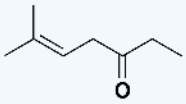
1. Give the IUPAC name for each compound and write the condensed formulas for parts (a), (b), (c), (d), (e), (f), (h), (i), and (l).

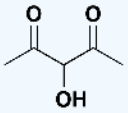
A) 

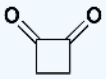
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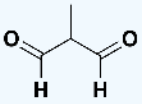
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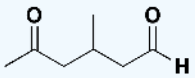
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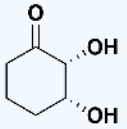
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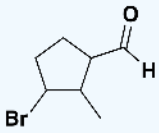
F) 

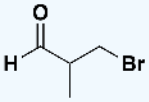
G) 

H) 

I) 

J) 

K) 

L) 

2) Draw the bond-line structure and write the condensed formula {except for (b), (d) and (h)} corresponding to each name:

A) butanal

B) 2-hydroxycyclopentanone

C) 2,3-pentanedione

D) 1,3-cyclohexanedione

E) 4-hydoxy-3-methyl-2-butanone

F) (E) 3-methyl-2-hepten-4-one

G) 3-oxobutanal

H) *cis*-3-bromocyclohexanecarboaldehyde

I) butanedial

J) *trans*-2-methyl-3-hexenal

Answer

Solutions

1.

a) 3,4-dimethylhexanal; $CH_3CH_2CH(CH_3)CH(CH_3)CH_2CHO$

b) 5-bromo-2-pentanone; $CH_2BrCH_2CH_2COCH_3$

c) 2,4-hexanedione; $CH_3COCH_2COCH_2CH_3$

d) cis-3-Penenal; cis-CH_3CHHCH_2CHO

e) 6-methyl-5-hepten-3-one; $CH_3C(CH_3)CHCH_2COCH_2CH_3$ or $(CH_3)_2CCHCH_2COCH_2CH_3$

f) 3-hydroxy-2,4-pentanedione; $CH_3OCH(OH)COCH_3$

g) 1,2-cyclobutanedione

h) 2-methyl-propanedial; $CHOCH(CH_3)CHO$

i) 3-methyl-5-oxo-hexanal; $CH_3OCH_2CH(CH_3)CH_2CHO$

j) cis-2,3-dihydroxycyclohexanone

k) 3-Bromo-2-methylcyclopentanecarboaldehyde

l) 3-bromo-2-methylpropanal; $CHOCH(CH_3)CH_2Br$

2. condensed formulas below and bond-line structures to the right

a) $CH_3CH_2CH_2CHO$

c) $CH_3COCOCH_2CH_3$

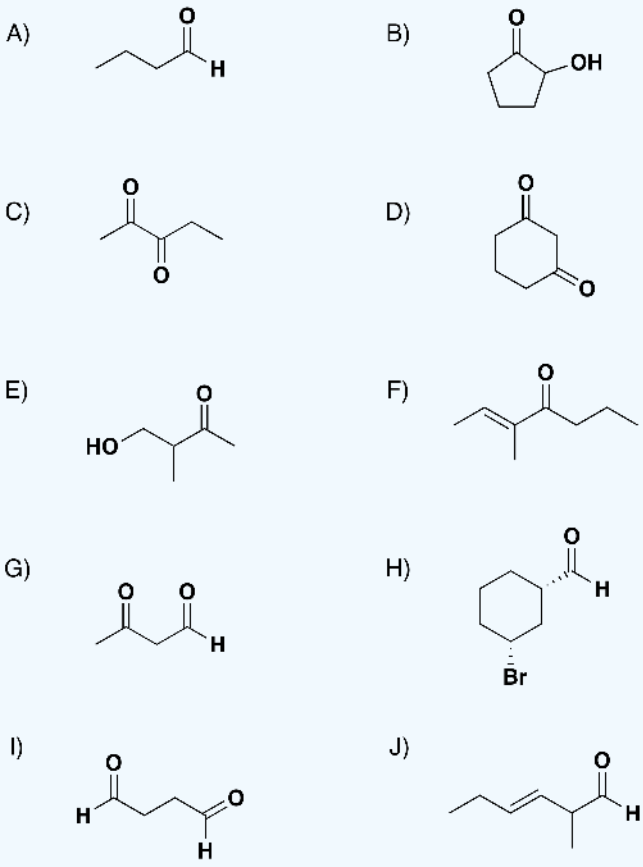
e) $CH_2(OH)CH(CH_3)COCH_3$

f) $CH_3CHC(CH_3)COCH_2CH_2CH_3$

g) CH_3COCH_2CHO

i) $CHOCH_2CH_2CHO$

j) $CH_3CH_2CHCHCH(CH_3)CHO$



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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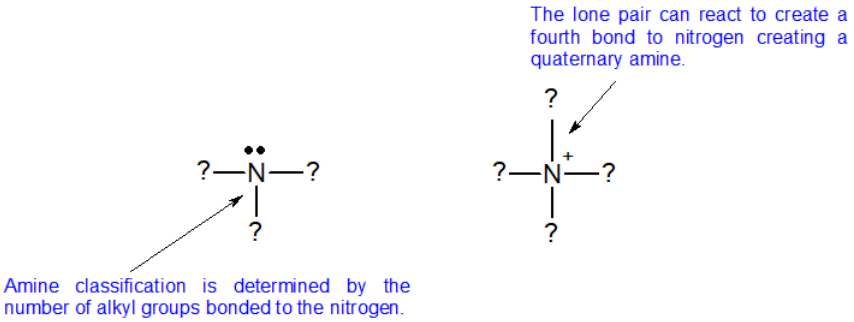
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4.9: Amines - Classification and Nomenclature

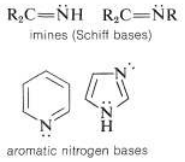
learning objectives

- classify amines as primary, secondary, tertiary, quaternary, or heterocyclic
- name amines using IUPAC (systematic) and selected common name nomenclature
- draw the structure of amines from IUPAC (systematic) and selected common names

Amine bases are classified according to the number of alkyl or aryl groups attached to nitrogen. Amines are classified differently from alkyl halides and alcohols because nitrogen has a neutral bonding pattern of three bonds with a single lone pair. To classify amines, we look at the nitrogen atom of the amine and count the number of alkyl groups bonded to it. This number is the classification of the amine.



There are two additional classifications of amines. When the nitrogen is double bonded to carbon, then it is call am imine. When nitrogen is part of a ring that includes double bonds, then it is classified as heterocyclic, as seen in the aromatic nitrogen bases shown below.

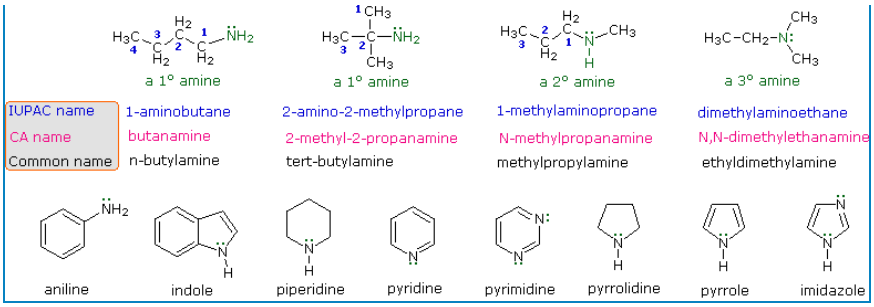


Nomenclature

Amines are derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group. Amino compounds can be named either as derivatives of ammonia or as amino-substituted compounds:

$HOCH_2CH_2NH_2$	2-hydroxyethan*amine* (2-hydroxyethyl*amine*) or 2-amino*ethanol* (preferred because —OH takes precedence over $—NH_2$; Section 7-1A)

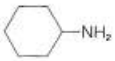
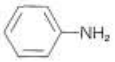
The nomenclature of amines is further complicated by the fact that several different nomenclature systems exist, and there is no clear preference for one over the others. The four compounds shown in the top row of the following diagram are all $C_4H_{11}N$ isomers. The first two are classified as 1°-amines, since only one alkyl group is bonded to the nitrogen; however, the alkyl group is primary in the first example and tertiary in the second. The third and fourth compounds in the row are 2° and 3°-amines respectively. The bottom row shows the structures for some common amines that need to be memorized.



- The Chemical Abstract Service has adopted a nomenclature system in which the suffix **-amine** is attached to the root alkyl name. For 1º-amines such as butanamine (first example) this is analogous to IUPAC alcohol nomenclature (-ol suffix). The additional nitrogen substituents in 2º and 3º-amines are designated by the prefix **N-** before the group name. These CA names are colored magenta in the diagram.
- Finally, a common system for simple amines names each alkyl substituent on nitrogen in alphabetical order, followed by the suffix **-amine**. These are the names given in the last row (colored black).

To be consistent and logical in naming amines as substituted ammonias, they strictly should be called *alkanamines* and *arenamines*, according to the nature of the hydrocarbon grouping. Unfortunately, the term *alkylamine* is used very commonly in place of alkanamine, while a host of trivial names are used for arenamines. We shall try to indicate both the trivial and the systematic names where possible. Some typical amines, their names, and their physical properties are listed in he Table below. The completely systematic names give in the Table illustrate the difficulty one gets into by using completely systematic names, and why simpler but less systematic names continue to be used for common compounds. A good example is N,N-dibutylbutamine versus tributylamine. The special ways of naming heterocyclic amines can be referenced in the appendix of this chapter.

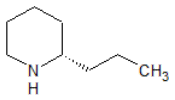
Common Amines and Their Properties

Amine	Name	Bp, °C	Mp, °C	Water solubility, g/100 ml	K_b in water[a]	pK_a[b]
NH_3	ammonia	−33	−77.7	90[a]	1.8×10^{-5}	9.26
CH_3NH_2	methanamine (methylamine)	−6.5	−92.5	1156	4.4×10^{-4}	10.64
$CH_3CH_2NH_2$	ethanamine (ethylamine)	16.6	−80.6	∞	5.6×10^{-4}	10.75
$(CH_3)_3CNH_2$	1,1-dimethylethanamine (*tert*-butylamine)	46	−67.5	∞	2.8×10^{-4}	10.45
$(CH_3CH_2)_2NH$	*N*-ethylethanamine (diethylamine)	55.5	−50	v. sol.	9.6×10^{-4}	10.98
$(CH_3CH_2)_3N$	*N*,*N*-diethylethanamine (triethylamine)	89.5	−115	1.5^{20}	4.4×10^{-4}	10.64
$(CH_3CH_2CH_2CH_2)_3N$	*N*,*N*-dibutylbutanamine (tributylamine)	214		sl. sol.		
	azacyclohexane (piperidine)	106	−9	∞	1.6×10^{-3}	11.20
	azabenzene (pyridine)	115	−42	∞	1.7×10^{-9}	5.23
	cyclohexanamine	134	−18	sl. sol.	4.4×10^{-4}	10.64
	benzenamine (aniline)	184.4	−6.2	3.4^{20}	3.8×10^{-10}	4.58
$H_2NCH_2CH_2NH_2$	1,2-ethanediamine (ethylenediamine)	116	8.5	sol.	8.5×10^{-5}	9.93

[a]Usually at 20–25°. [b]The pK_a values refer to the dissociation of the conjugate acid $RNH_3^{\oplus}$ $+ H_2O \overset{K_a}{\rightleftharpoons} RNH_2 + H_3O^{\oplus}$, where $pK_a = -\log K_a = 14 + \log K_b$ (see Sections 8-1 and 23-7).

Alkaloids

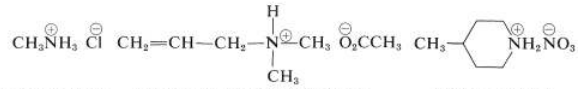
Many biologically important compounds are amines. Alkaloids are amines synthesized by plants to protect them from being eaten. Humans primarily use alkaloids medicinally as pain killers. All alkaloids are toxic and addictive. The Greeks killed Socrates with (S)-coniine. Mild cases of alkaloid poisoning produce psychological effects resembling peacefulness, euphoria or hallucinations.



(S)-coniine

Ammonium Salts

A nitrogen bonded to four alkyl groups will necessarily be positively charged, and is called a 4°-ammonium cation. For example, $(CH_3)_4N^{(+)}$ $Br^{(-)}$ is tetramethylammonium bromide. Salts of amines with inorganic or organic acids are named as *substituted ammonium* salts, except when the nitrogen is part of a ring system. Examples are



[1] Note the use of *azonia* to denote the cationic nitrogen in the ring, whereas *aza* is used for neutral nitrogen.

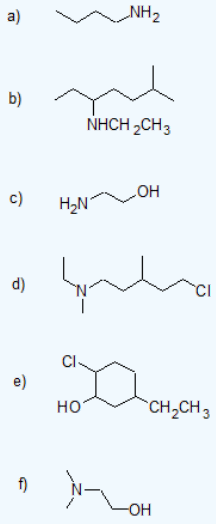
Perhaps the most noteworthy aspect of ammonium salts is that they have low odor and are water soluble. These qualities are explored more fully in the amine chapter

Heterocyclic Amine Nomenclature

Heterocyclic amines are amines in which the nitrogen is part of a ring that contains at least one double bond. Many aromatic and heterocyclic amines are known by unique common names, the origins of which are often unknown to the chemists that use them frequently. Since these names are not based on a rational system, it is necessary to memorize them. There is a systematic nomenclature of heterocyclic compounds, but it will not be discussed here. For further details, refer to the appendix of this chapter for the full IUPAC rules of organic compound nomenclature.

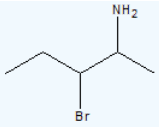
Exercise

1. Draw the bond-line structure for each compound and write the condensed structural formula for parts (a) & (d) - (g).
    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
2. Give the IUPAC name and condensed structural formula for each compound.



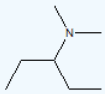
Answer

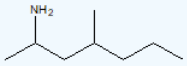
1.

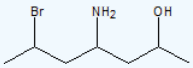
a)  $CH_3CH_2CHBrCH(NH_2)CH_3$

b) 

c) 

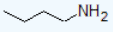
d)  $CH_3CH_2CH(N(CH_3)_2)CH_2CH_3$

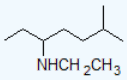
e)  $CH_3CH(NH_2)CH_2CH(CH_3)CH_2CH_2CH_3$

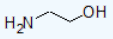
f)  $CH_3CHBrCH_2CH(NH_2)CH_2CH(OH)CH_3$

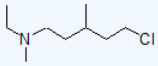
2.

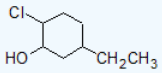
Condensed Structural Formulas

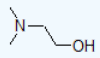
a) 
butan-1-amine $CH_3CH_2CH_2CH_2NH_2$

b) 
N-ethyl-6-methylheptan-3-amine $CH_3CH_2CH(NH_2)CH_2CH_2CH(CH_3)_2$

c) 
2-aminoethan-1-ol $NH_2CH_2CH_2OH$

d) 
5-chloro-*N*-ethyl-*N*,3-dimethylpentan-1-amine $CH_3CH_2N(CH_3)CH_2CH_2CH(CH_3)CH_2CH_2Cl$

e) 
2-chloro-5-ethylcyclohexan-1-ol not applicable

f) 
$(CH_3)_2NCH_2CH_2OH$

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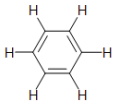
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4.10: Benzene and its Derivatives

learning objectives

- name benzene and its derivatives using IUPAC (systematic) and selected common name nomenclature
- draw the structures of benzene and its derivatives from IUPAC (systematic) and selected common names



Benzene, as shown on the left, is an organic aromatic compound with many interesting properties. Unlike aliphatic (straight chain carbons) or other cyclic organic compounds, the structure of benzene (3 conjugated π bonds) allows benzene and its derived products to be useful in fields such as health, laboratory synthesis, and other applications such as rubber synthesis. Benzene is unique because we can write a condensed formula for its ringed structure, C_6H_6.

Introduction

Benzene derived products are well known to be **pleasantly fragrant**. For this reason, organic compounds containing benzene rings were classified as being "**aromatic**" **(sweet smelling)** amongst scientists in the early 19th century when a relation was established between benzene derived compounds and sweet/spicy fragrances. There is a misconception amongst the scientific community, however, that all aromatics are sweet smelling and that all sweet smelling compounds would have a benzene ring in its structure. This is false, since non-aromatic compounds, such as camphor, extracted from the camphor laurel tree, release a strong, minty aroma, yet it lacks the benzene ring in its structure (See figure 1). On the other hand, benzene itself gives off a rather strong and unpleasant smell that would otherwise invalidate the definition of an aromatic (sweet-smelling) compound. Despite this inconsistency, however, the term **aromatic** continues to be used today in order to designate molecules with benzene-like rings in their structures. For a modern, chemical definition of **aromaticity**, refer to sections Aromaticity and Hückel's Rule.

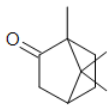


Figure 1. Top-view of camphor, along with its **monoterpene** unit. Notice how camphor lacks the benzene ring to be "aromatic".

Many **aromatic** compounds are however, **sweet/pleasant smelling**. **Eugenol**, for example, is extracted from essential oils of cloves and it releases a spicy, clove-like aroma used in perfumes. In addition, it is also used in dentistry as an analgesic.

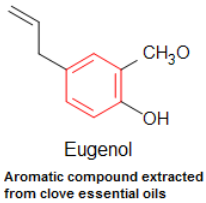


Figure 2. Eugenol, an aromatic compound extracted from clove essential oils. Used in perfumes and as an analgesic. The benzene ring is labeled in red in the eugenol molecule.

Is it cyclohexane or is it benzene?

Due to the similarity between **benzene** and **cyclohexane**, the two is often confused with each other in beginning organic chemistry students.

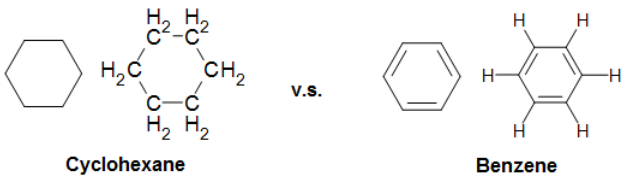


Figure 3. Structure comparison between cyclohexane and benzene

If you were to count the number of carbons and hydrogens in **cyclohexane**, you will notice that its molecular formula is $\mathbf{C_6H_{12}}$. Since the carbons in the **cyclohexane** ring is **fully** saturated with hydrogens (carbon is bound to 2 hydrogens and 2 adjacent carbons), no double bonds are formed in the cyclic ring. In contrast, **benzene** is only saturated with one hydrogen per carbon, leading to its molecular formula of $\mathbf{C_6H_6}$. In order to stabilize this structure, 3 conjugated π (double) bonds are formed in the benzene ring in order for carbon to have four adjacent bonds.

In other words, cyclohexane is not the same as benzene! These two compounds have different molecular formulas and their chemical and physical properties are not the same. The **hydrogenation** technique can be used by chemists to convert from benzene to cyclohexane by saturating the benzene ring with missing hydrogens.

IMPORTANT NOTE: A special catalyst is required to hydrogenate benzene rings due to its unusual stability and configuration. Normal catalytic hydrogenation techniques will not hydrogenate benzene and yield any meaningful products.

What about Resonance?

Benzene can be drawn a number of different ways. This is because benzene's conjugated pi electrons freely resonate within the cyclic ring, thus resulting in its two resonance forms.

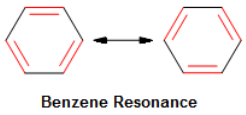


Figure 4. The figure to the left shows the two resonance forms of benzene. The **delocalized electrons** are moved from one carbon to the next, thus providing **stabilization** energy. Ring structures stabilized by the movement of delocalized electrons are sometimes referred to as **arenes**.



As the electrons in the benzene ring can resonate within the ring at a fairly high rate, a simplified notation is often used to designate the two different resonance forms. This notation is shown above, with the initial three pi bonds (#1, #2) replaced with an inner ring circle (#3). Alternatively, the circle within the benzene ring can also be dashed to show the same resonance forms (#4).

The Phenyl Group (The Foundation of Benzene Derivatives)

The **phenyl group** is formed by removing one hydrogen from benzene to create the fragment is $\mathbf{C_6H_5}$. **NOTE:** Although the molecular formula of the phenyl group is C_6H_5, the phenyl group would always have something attached to where the hydrogen was removed. Thus, the formula is often written as **Ph-R**, where Ph refers to the phenyl group and R refers to the R group attached where the hydrogen was removed.

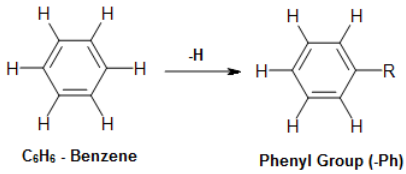
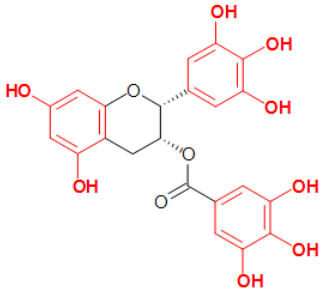


Figure 5. Figure demonstrating the removal of hydrogen to form the phenyl group.

Different R groups on the phenyl group allows different benzene derivatives to be formed. **Phenol**, **Ph-OH**, or $\mathbf{C_6H_5OH}$, for example, is formed when an alcohol (-OH) group displaces a hydrogen atom on the benzene ring. **Benzene**, for this very same reason, can be formed from the phenyl group by reattaching the hydrogen back its place of removal. Thus benzene, similar to phenol, can be abbreviated **Ph-H**, or $\mathbf{C_6H_6}$.



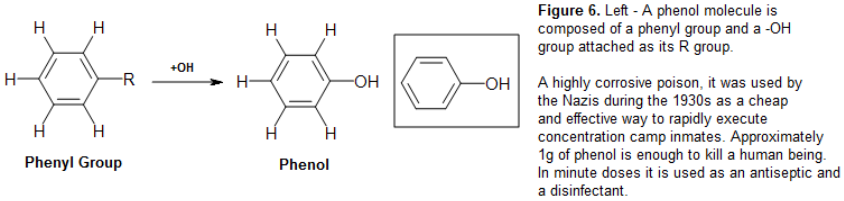


Figure 6. **Epigallocatechin gallate (EGCG)**, an antioxidant found in green teas and its extracts, is famous for its potential health benefits. The molecule is a type of catechin, which is composed of multiple **phenol (labeled in red)** units (**polyphenols** - see polycyclic aromatics). Since catechins are usually found in plant extracts, they are often referred as plant polyphenolic antioxidants.

As you can see above, these are only some of the many possibilities of the benzene derived products that have special uses in human health and other industrial fields.

Nomenclature of Benzene Derived Compounds

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. In these sections, we will analyze some of the ways these compounds can be named.

Simple Benzene Naming

Some common substituents, like NO_2, Br, and Cl, can be named this way when it is attached to a phenyl group. Long chain carbons attached can also be named this way. The general format for this kind of naming is:

(positions of substituents (if >1)- + # (di, tri, ...) + substituent)$_n$ + benzene.

For example, chlorine (Cl) attached to a phenyl group would be named **chlorobenzene (chloro + benzene)**. Since there is only one substituent on the benzene ring, we do not have to indicate its position on the benzene ring (as it can freely rotate around and you would end up getting the same compound.)

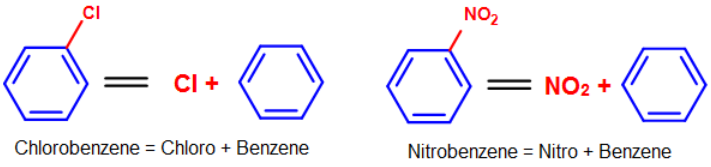


Figure 7. Example of simple benzene naming with chlorine and NO_2 as substituents.

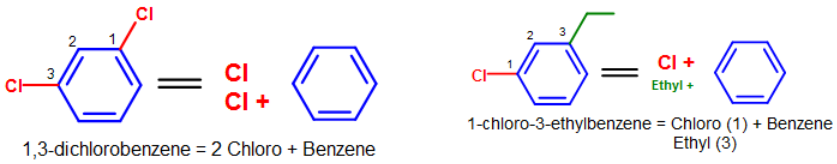


Figure 8. More complicated simple benzene naming examples - Note that standard nomenclature priority rules are applied here, causing the numbering of carbons to switch.

Ortho-, Meta-, Para- (OMP) Nomenclature for Disubstituted Benzenes

Instead of using numbers to indicate substituents on a benzene ring, ***ortho- (o-), meta- (m-), or para (p-)*** can be used in place of positional markers when there are **two** substituents on the benzene ring (disubstituted benzenes). 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)

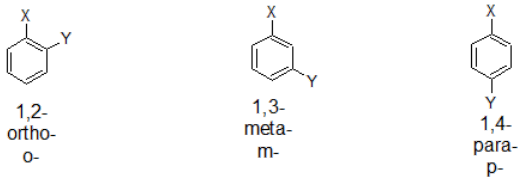


Figure 9. Prefixes to indicate the position of branches for disubstituted benzene derivatives.

Continuing with the example above in figure 8 (1,3-dichlorobenzene), we can use the ortho-, meta-, para- nomenclature to transform the chemical name into m-dichlorobenzene, as shown in the figure below.

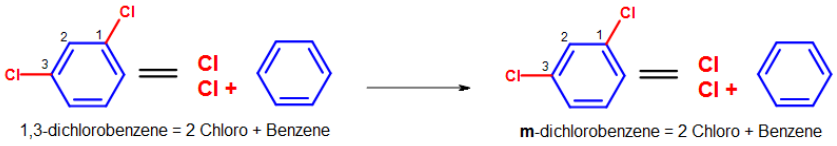


Figure 10 . Transformation of 1,3-dichlorobenzene into m-dichlorobenzene.

Here are some other examples of ortho-, meta-, para- nomenclature used in context:

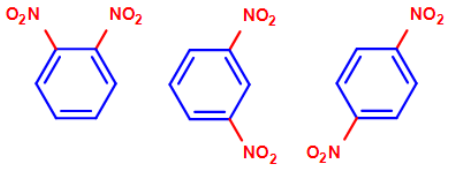


Figure 11. Example of o-, m-, p- nomenclature.
Listed in order:
1) o-dinitrobenzene
2) m-dinitrobenzene
3) p-dinitrobenzene

However, the substituents used in ortho-, meta-, para- nomenclature do not have to be the same. For example, we can use chlorine and a nitro group as substituents in the benzene ring.

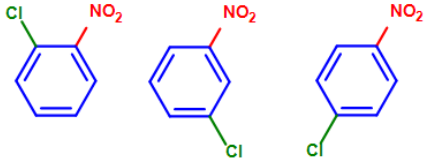


Figure 12. Example of o-, m-, p- nomenclature.
Listed in order:
1) o-nitrochlorobenzene
2) m-nitrochlorobenzene
3) p-nitrochlorobenzene
Note that the two substituents do not have to be the same.

In conclusion, these can be pieced together into a summary diagram, as shown below:

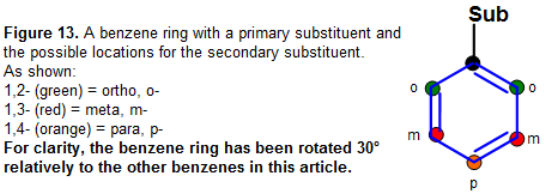


Figure 13. A benzene ring with a primary substituent and the possible locations for the secondary substituent.
As shown:
1,2- (green) = ortho, o-
1,3- (red) = meta, m-
1,4- (orange) = para, p-
For clarity, the benzene ring has been rotated 30° relatively to the other benzenes in this article.

Derivatives as Parent Names

In addition to simple benzene naming and OMP nomenclature, benzene derivtives are also sometimes used as the "parent" in the name of a larger compound. name.

For example, phenol (C_6H_5OH) is the parent name of the compound below because hydroxyl groups have higher nomenclature priority than halides. The chlorine atom is considered a branch at the ortho- position to the hydroxyl group. Accordingly, the compound is named 2-chlorophenol or o-chlorophenol.

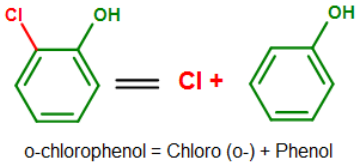


Figure 14. An example showing phenol as a base in its chemical name. Note how benzene no longer serves as a base when an OH group is added to the benzene ring.

Alternatively, we can use the numbering system to indicate this compound. When the numbering system is used, the carbon where the substituent is attached on the base will be given the first priority and named as carbon #1 (C_1). The normal priority rules then apply in the nomenclature process (give the rest of the substituents the lowest numbering as you could).

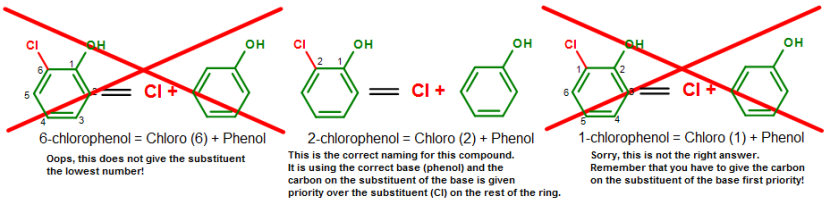


Figure 15. The naming process for 2-chlorophenol (o-chlorophenol). Note that 2-chlorophenol = o-chlorophenol.

Below is a list of commonly seen benzene-derived compounds. Some of these mono-substituted compounds (labeled in red and green), such as phenol or toluene, can be used in place of benzene for the chemical's base name.

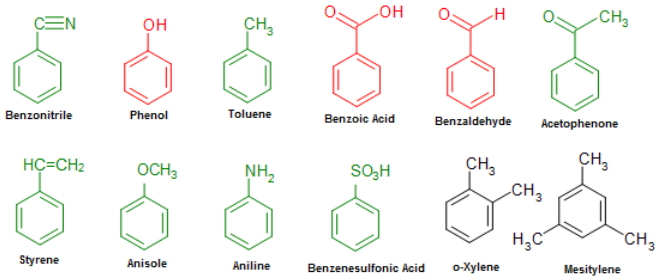


Figure 16. Common benzene derived compounds with various substituents.

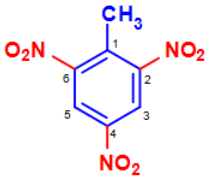
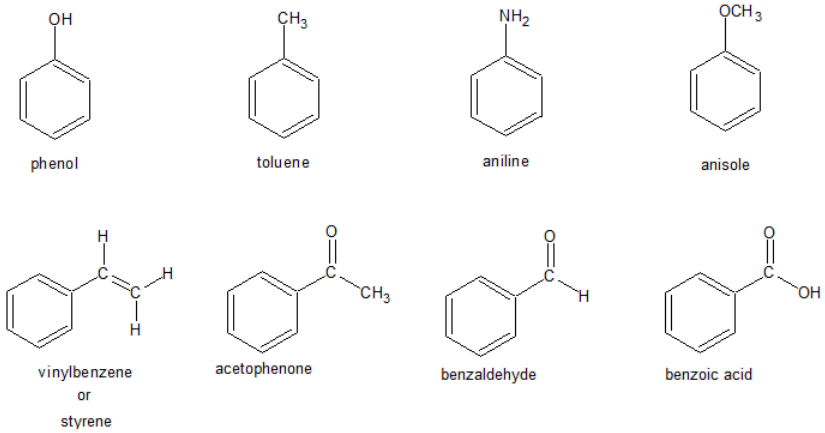


Figure 17. 2,4,6-Trinitrotoluene, or **TNT**, a common explosive used for both industrial and military purposes, is consisted of a **toluene** base (labeled in blue), along with three **nitro** groups attached as substituents (labeled in red). The explosive is characteristic for its resistance to external shock and friction, making it useful in many applications where other highly sensitive explosives would simultaneously detonate.

Common vs. Systematic (IUPAC) Nomenclature

According to the indexing preferences of the *Chemical Abstracts*, **phenol, benzaldehyde, and benzoic acid (labeled in red in Figure 16)** are some of the common names that are retained in the IUPAC (systematic) nomenclature. Other names such as toluene, styrene, naphthalene, or phenanthrene can also be seen in the IUPAC system in the same way. While the use of other common names are usually acceptable in IUPAC, their use are discouraged in the nomenclature of compounds.



Nomenclature for compounds which has such discouraged names will be named by the simple benzene naming system. An example of this would include **toluene derivatives like TNT.** (Note that toluene by itself is retained by the IUPAC nomenclature, but its derivatives, which contains additional substituents on the benzene ring, might be excluded from the convention). For this reason, the **common chemical name** 2,4,6-trinitrotoluene, or TNT, as shown in figure 17, would not be advisable under the IUPAC (**systematic**) nomenclature.

In order to correctly name TNT under the IUPAC system, the simple benzene naming system should be used:

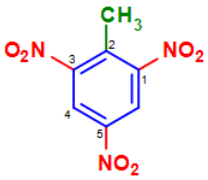


Figure 18. TNT, as named under the IUPAC nomenclature. Note that since the IUPAC nomenclature does not recognize toluene as the primary base of this compound, substituent priorities are reverted to normal defaults. As a result, TNT in IUPAC is named (systematic name): **2-methyl-1,3,5-trinitrobenzene**

Figure 18. Systematic (IUPAC) name of 2,4,6-trinitrotoluene (common name), or TNT.
Note that the methyl group is individually named due to the exclusion of toluene from the IUPAC nomenclature.

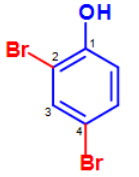


Figure 19. 2,4-dibromophenol, as shown in this diagram, is valid in both the common nomenclature as well as the IUPAC nomenclature. As mentioned previously, **phenol, benzoic acid, and benzaldehyde** substituents are allowed to be used in the IUPAC naming conventions and the base naming priority rules are applied in the nomenclature process.

Figure 19. The common name 2,4-dibromophenol, is shared by the IUPAC systematic nomenclature.
Only substituents **phenol, benzoic acid, and benzaldehyde** share this commonality.

Since the IUPAC nomenclature primarily rely on the simple benzene naming system for the nomenclature of different benzene derived compounds, the OMP (ortho-, meta-, para-) system is not accepted in the IUPAC nomenclature. For this reason, the OMP

system will yield common names that can be converted to systematic names by using the same method as above. For example, o-Xylene from the OMP system can be named 1,2-dimethylbenzene by using simple benzene naming (IUPAC standard).

The Phenyl and Benzyl Groups

The Phenyl Group

As mentioned previously, the phenyl group (Ph-R, C_6H_5-R) can be formed by removing a hydrogen from benzene and attaching a substituent to where the hydrogen was removed. To this phenomenon, we can name compounds formed this way by applying this rule: **(phenyl + substituent)**. For example, a chlorine attached in this manner would be named **phenyl chloride**, and a bromine attached in this manner would be named **phenyl bromide**. (See below diagram)

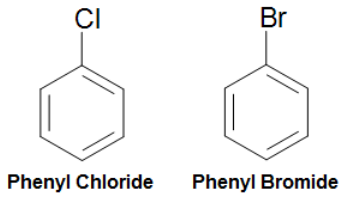


Figure 20. Naming of Phenyl Chloride and Phenyl Bromide

While compounds like these are usually named by simple benzene type naming (chlorobenzene and bromobenzene), the phenyl group naming is usually applied to benzene rings where a substituent with six or more carbons is attached, such as in the diagram below.

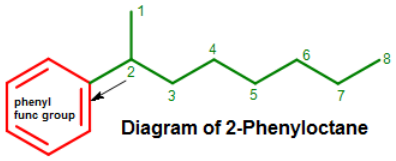


Figure 21. Diagram of 2-phenyloctane.

Although the diagram above might be a little daunting to understand at first, it is not as difficult as it seems after careful analysis of the structure is made. By looking for the longest chain in the compound, it should be clear that the longest chain is eight (8) carbons long (octane, as shown in green) and that a benzene ring is attached to the second position of this longest chain (labeled in red). As this rule suggests that the benzene ring will act as a function group (a substituent) whenever a substituent of more than six (6) carbons is attached to it, the name "benzene" is changed to **phenyl** and is used the same way as any other substituents, such as **methyl, ethyl, or bromo.** Putting it all together, the name can be derived as: **2-phenyloctane** (phenyl is attached at the second position of the longest carbon chain, octane).

The Benzyl Group

The benzyl group (abbv. Bn), similar to the phenyl group, is formed by manipulating the benzene ring. In the case of the benzyl group, it is formed by taking the phenyl group and adding a CH_2 group to where the hydrogen was removed. Its molecular fragment 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.

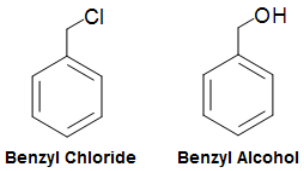


Figure 22. Benzyl Group Nomenclature

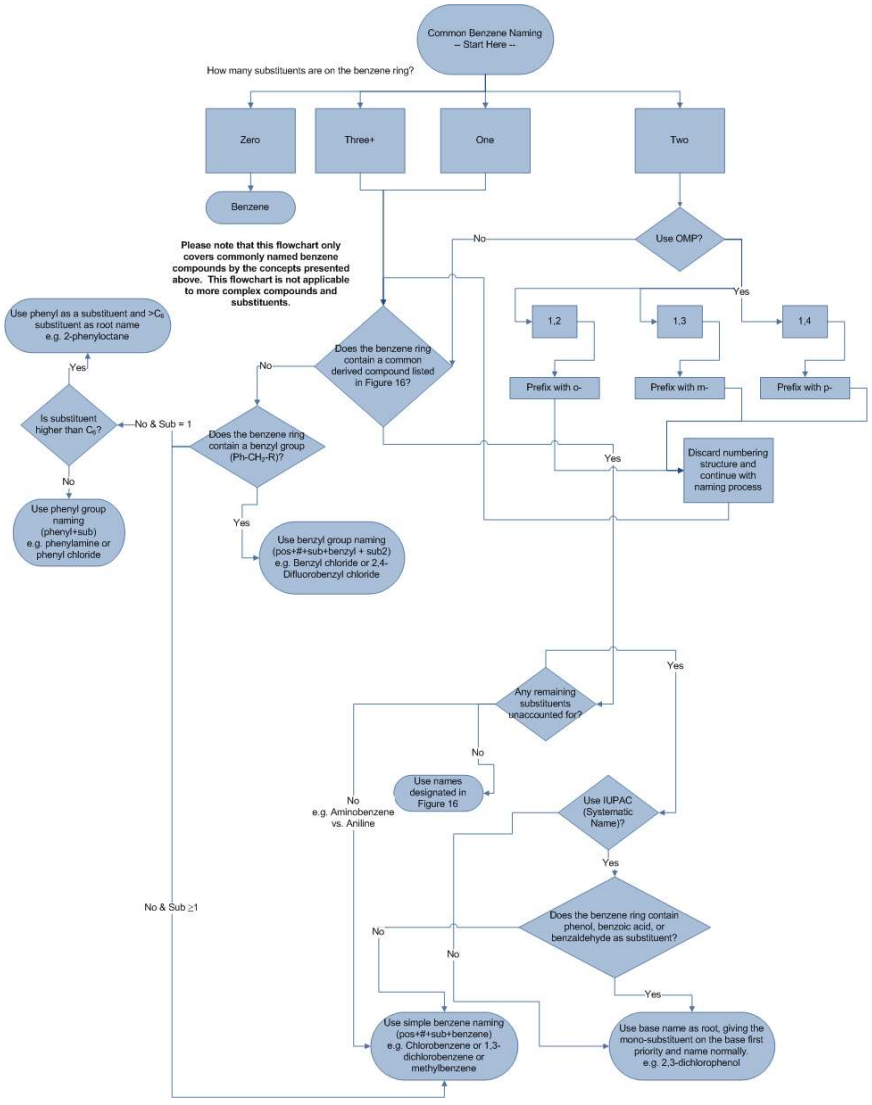
Additionally, other substituents can attach on the benzene ring in the presence of the benzyl group. An example of this can be seen in the figure below:



Figure 23. Nomenclature of 2,4-difluorobenzyl chloride. Similar to the base name nomenclature system, the carbon in which the base substituent is attached on the benzene ring is given the first priority and the rest of the substituents are given the lowest number order possible.

Similar to the base name nomenclature system, the carbon in which the base substituent is attached on the benzene ring is given the first priority and the rest of the substituents are given the lowest number order possible. Under this consideration, the above compound can be named: **2,4-difluorobenzyl chloride.**

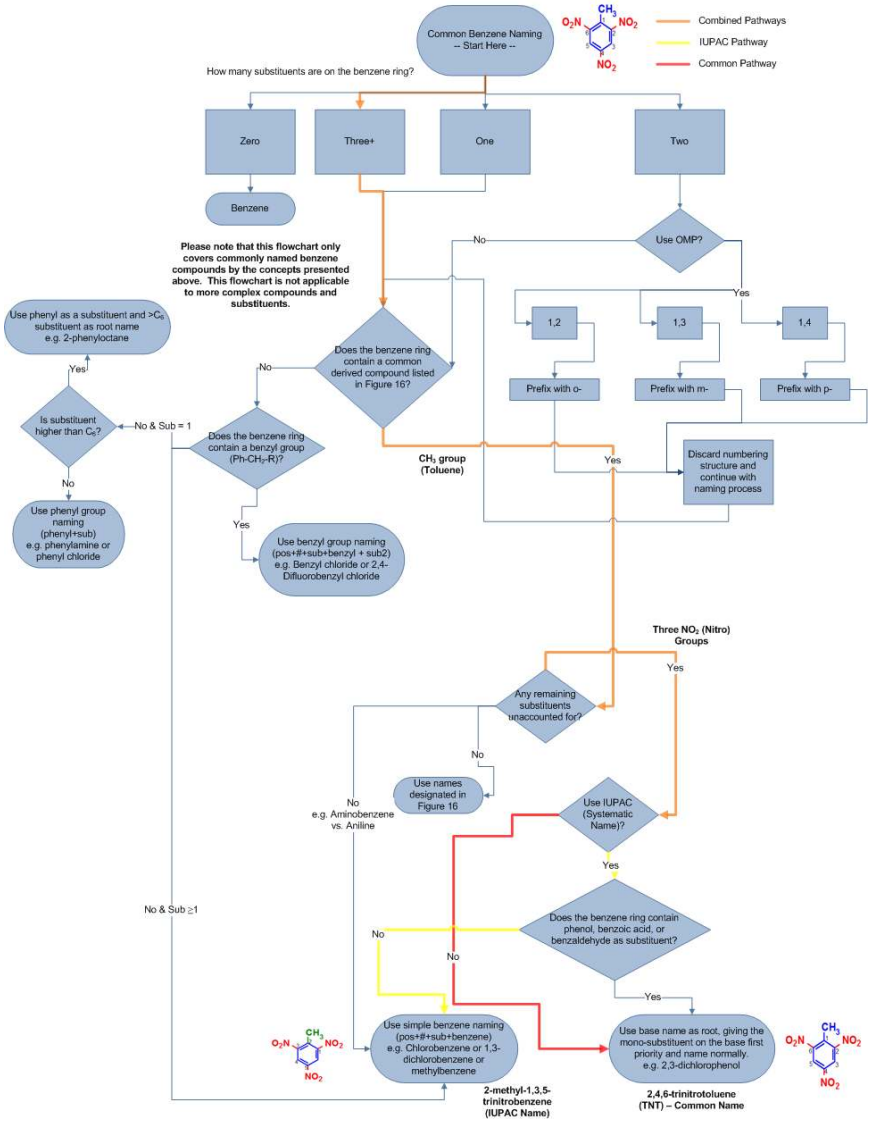
Commonly Named Benzene Compounds Nomenclature Summary Flowchart



Summary Flowchart (Figure 24). Summary of nomenclature rules used in commonly benzene derived compounds. As benzene derived compounds can be extremely complex, only compounds covered in this article and other commonly named compounds can be named using this flowchart.

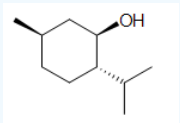
Determination of Common and Systematic Names using Flowchart

To demonstrate how this flowchart can be used to name TNT in its common and systematic (IUPAC) name, a replica of the flowchart with the appropriate flow paths are shown below:



Exercise

1. **True or False?** The compound below contains a benzene ring and thus is aromatic.

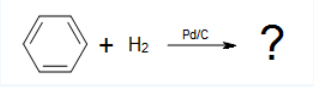


2. Benzene unusual stability is caused by a combination of the _____ conjugated pi bonds in its cyclic ring.

specify the number

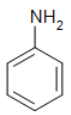
3. Menthol, a topical analgesic used in many ointments for the relief of pain, releases a peppermint aroma upon exposure to the air. Based on this conclusion, can you imply that a benzene ring is present in its chemical structure? Why or why not?

4. Predict the product of the reaction below or explain why no reaction occurs.



5. At normal conditions, benzene has ___ resonance structures.

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

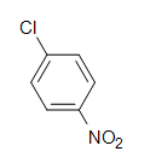


a) nitrohydride benzene
b) phenylamine
c) phenylamide
d) aniline
e) nitrogenhydrogen benzene
f) All of the above is correct

7. Convert 1,4-dimethylbenzene into its common name.

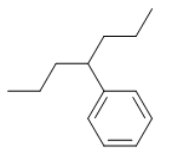
8. TNT's common name is: _____

9. Name the following compound using OMP nomenclature:

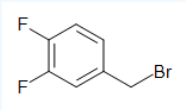


10. Draw the structure of 2,4-dinitrotoluene.

11. Give the IUPAC name the following compound:



12. 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

13. a) **True or False?** Benzyl chloride can be abbreviated Bz-Cl.

b) What is the condensed formula for benzyl chloride?

c) What is the condensed formula for phenyl chloride?

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

15. **True or False?** A single aromatic compound can have multiple names indicating its structure.

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

17. 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

18. 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

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

2. 3

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

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

5. 2

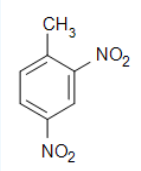
6. b, d

7. p-xylene

8. 2,4,6-trinitrotoluene

9. p-chloronitrobenzene

10.



11. 4-phenylheptane

12. a) 3,4-difluorobenzyl bromide

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

b) $C_6H_5CH_2Cl$.

c) C_6H_5Cl.

14. COOH or CO_2H

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

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

17. 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. The chemical formula would allow a determination.

18. d

Outside links

- Naming Aromatic Compounds - A good review of the concepts presented above
- Naming Aromatic Compounds - Functional groups and compounds formed by different functional groups
- Naming Aromatic Compounds - Additional practice problems are available here
- Aromatherapy and Aromatic Compounds
- Michael Faraday - Discovery of Benzene and History
- Wikipedia - Camphor
- Medicinal Uses of Camphor
- More on Terpenes
- Properties of Eugenol
- Benzene Aromaticity and Stability
- Killing with Syringes: Phenol Injections - Reminisce of the Nazi's "euthanasia" project in Auschwitz
- Green Tea Health Benefits - Antioxidant effects of EGCG
- Green Tea Nutrient EGCG Blocks Diabetes - Promoting Effects of High Fructose Corn Syrup
- Catechins in Green Tea - Why Catechins is Important to Your Health
- Phytochemicals - Catechins
- Wikipedia - Trinitrotoluene (TNT)
- IUPAC Nomenclature System and Recommendations
- Wikipedia - Phenyl Group
- Wikipedia - Benzyl Group

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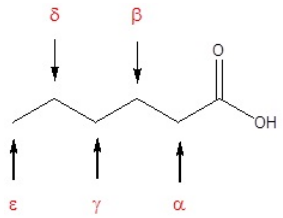
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4.11: Carboxylic Acids

learning objectives

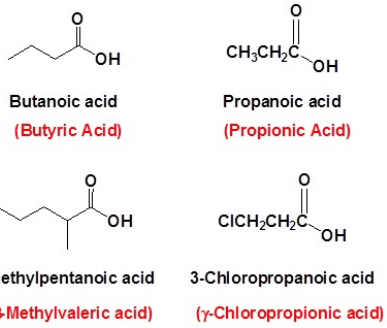
- name carboxylic acids using IUPAC (systematic) and selected common name nomenclature
- draw the structure of carboxylic acids from IUPAC (systematic) and selected common names

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 **-anoic 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 that were chosen by chemists to usually describe the origin of the compound. In common names of aldehydes, 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.



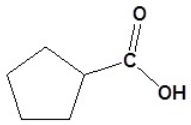
Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	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

Examples (Common Names Are in Red)

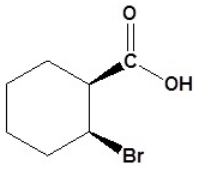


Naming carboxyl groups added to a ring

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.



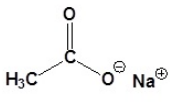
Cyclopentanecarboxylic acid



Cis-2-Bromocyclohexanecarboylic acid

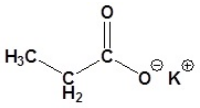
Naming carboxylates

Salts of carboxylic acids are named by writing the name of the cation followed by the name of the 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)

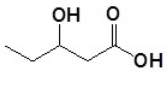


Potassium Propanoate

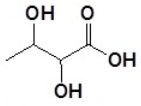
(Potassium propionate)

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.

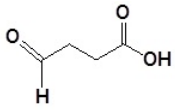


3-Hydroxypentanoic acid

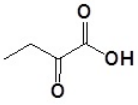


2,3-Dihydroxybutanoic acid

In the case of molecules containing a carboxylic acid and aldehydes and/or ketones functional groups the carbonyl is named as a "Oxo" substituent.

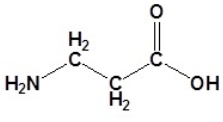


4-Oxobutanoic acid

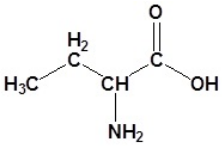


2-Oxobutanoic acid

In the case of molecules containing a carboxylic acid an amine functional group the amine is named as an "amino" substituent.



3-Aminopropanoic acid

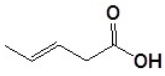


2-Aminobutanoic acid

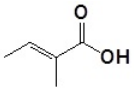
When carboxylic acids are included with an alkene the following order is followed:

(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.



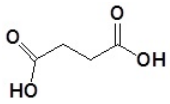
Trans-3-pentenoic acid



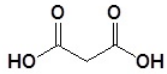
(E)-2-Methyl-2-butenoic acid

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.



Butanedioic acid



Propanedioic acid

Common Names for selected dicarboxylic acids

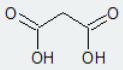
The following common names for these selected dicarboxylic acids are important to memorize; they are prevalent in biochemistry or industrial applications.



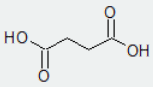
carbonic acid



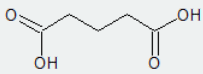
oxalic acid



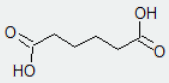
malonic acid



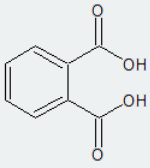
succinic acid



glutaric acid



adipic acid



phthalic acid

The saying, "Oh my, such good apple pie!", can help us remember these common names by correlating the first letters of each word with the common names:

oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, and phthalic.

Exercise

1. Draw the bond-line structure and write the condensed structural formula for each compound.

    a) octanoic acid

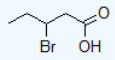
    b) 4-hydroxypentanoic acid

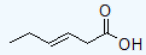
    c) cis-4-hexenoioc acid or cis-hex-4-enoic acid

    d) (E)-5-bromo-3-heptenoic acid or (E)-5-bromohept-3-enoic acid.

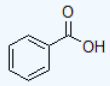
    e) 2-aminopropanoic acid

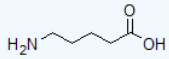
2. Give the IUPAC name and condensed structural formula for each compound.

a) 

b) 

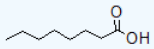
c) 

d) 

e) 

Answer

1.

a) 

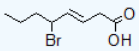
$CH_3(CH_2)_6CO_2H$

b) 

$CH_3CH(OH)CH_2CH_2CO_2H$

c) 

$CH_3CHCHCH_2CH_2CO_2H$

d) 

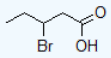
$CH_3CH_2CH_2CHBCHCHCH_2CO_2H$

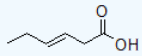
e) 

$CH_3CH(NH_2)CO_2H$

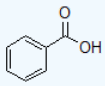
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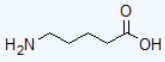
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a)  3-bromopentanoic acid $CH_3CHBrCH_2CO_2H$

b)  (3*E*)-hex-3-enoic acid $CH_3CH_2CHCHCH_2CO_2H$

c)  2-hydroxypropanoic acid $CH_2CH(OH)CO_2H$

d)  benzoic acid $C_6H_5CO_2$

e)  5-aminopentanoic acid $NH_2CH_2CH_2CH_2CH_2CO_2H$ or $NH_2(CH_2)_4CO_2H$

Contributors and Attributions

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CHAPTER OVERVIEW

5: An Overview of Organic Reactions

This chapter is designed to provide a gentle introduction to the subject of reaction mechanisms. Two types of reactions are introduced—polar reactions and radical reactions. The chapter briefly reviews a number of topics you should be familiar with, including rates and equilibria, elementary thermodynamics and bond dissociation energies. You must have a working knowledge of these topics to obtain a thorough understanding of organic reaction mechanisms. Reaction energy diagrams are used to illustrate the energy changes that take place during chemical reactions, and to emphasize the difference between a reaction intermediate and a transition state.

5.1: Kinds of Organic Reactions
5.2: How Organic Reactions Occur - Mechanisms
5.3: Radical Reactions
5.4: Polar Reactions
5.5: An Example of a Polar Reaction - Addition of HBr to Ethylene
5.6: Using Curved Arrows in Polar Reaction Mechanisms
5.7: Describing a Reaction - Equilibria, Rates, and Energy Changes
5.8: Describing a Reaction - Bond Dissociation Energies
5.9: Describing a Reaction - Energy Diagrams and Transition States
5.10: Describing a Reaction- Intermediates
5.11: A Comparison between Biological Reactions and Laboratory Reactions
5.12: Chapter Objectives
5.S: An Overview of Organic Reactions (Summary)

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5.1: Kinds of Organic Reactions

Objective

After completing this section, you should be able to list and describe the four important “kinds” of reactions that occur in organic chemistry.

Key Terms

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

- addition reaction
- elimination reaction
- rearrangement reaction
- substitution reaction

Study Notes

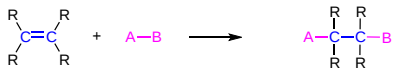
It is sufficient that you know the general form of each kind of reaction. However, given a chemical equation, you should be able to recognize which kind of reaction it involves.

If you scan any organic textbook you will encounter what appears to be a very large, often intimidating, number of reactions. These are the "tools" of a chemist, and to use these tools effectively, we must organize them in a sensible manner and look for patterns of reactivity that permit us make plausible predictions. Most of these reactions occur at special sites of reactivity known as functional groups, and these constitute one organizational scheme that helps us catalog and remember reactions.

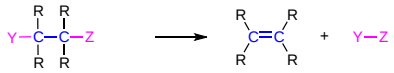
> *Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course.*

First, we identify four broad classes of reactions based solely on the **structural change** occurring in the reactant molecules. This classification does not require knowledge or speculation concerning reaction paths or mechanisms. The four main reaction classes are additions, eliminations, substitutions, and rearrangements.

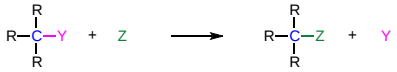
Addition Reaction



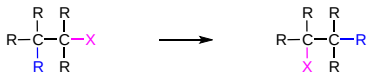
Elimination Reaction



Substitution Reaction



Rearrangement Reaction

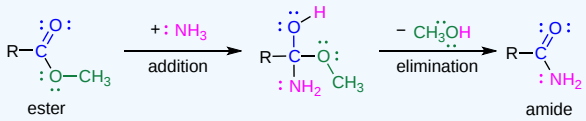


In an **addition** reaction the number of σ-bonds in the substrate molecule increases, usually at the expense of one or more π-bonds. The reverse is true of **elimination** reactions, *i.e.*the number of σ-bonds in the substrate decreases, and new π-bonds are often formed. **Substitution** reactions, as the name implies, are characterized by replacement of an atom or group (Y) by another atom or group (Z). Aside from these groups, the number of bonds does not change. A **rearrangement** reaction generates an isomer, and again the number of bonds normally does not change.

The examples illustrated above involve simple alkyl and alkene systems, but these reaction types are general for most functional groups, including those incorporating carbon-oxygen double bonds and carbon-nitrogen double and triple bonds. Some common reactions may actually be a combination of reaction types.

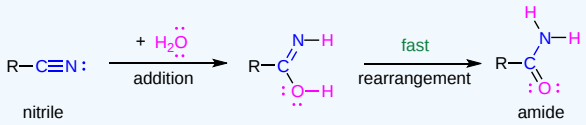
Example 5.1.1: Reaction of an Ester with Ammonia

The reaction of an ester with ammonia to give an amide, as shown below, appears to be a substitution reaction (Y = CH_3O & Z = NH_2); however, it is actually two reactions, an addition followed by an elimination.



Example 5.1.2: The Addition of water to a Nitrile

The addition of water to a nitrile does not seem to fit any of the above reaction types, but it is simply a slow addition reaction followed by a rapid rearrangement, as shown in the following equation. Rapid rearrangements of this kind are called **tautomerizations**.



Exercise 5.1.3

Classify each reaction as addition, elimination, substitution, or rearrangement.

A) $CH_3CH_2Br + LiOH \longrightarrow CH_3CH_2OH + LiBr$

B) $CH_3CH_2CH_2Cl \longrightarrow CH_3CH{=}CH_2 + HCl$

C) $CH_3CH{=}CH_2 + H_2 \longrightarrow CH_3CH_2CH_3$

Answer

A = Substitution; B = Elimination; C = Addition

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5.2: How Organic Reactions Occur - Mechanisms

Objectives

After completing this section, you should be able to

- explain the difference between heterolytic and homolytic bond breakage, and between heterogenic and homogenic bond formation.
- state the two reaction types involved in symmetrical and unsymmetrical processes.

Key Terms

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

- heterogenic
- heterolytic
- homogenic
- homolytic
- polar reaction
- radical reaction
- reaction mechanism

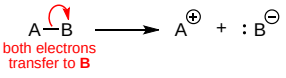
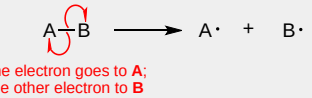
Study Notes

Upon first reading first four key terms, it is easy to be puzzled. The ending of the word tells you whether a bond is being formed (-genic) or broken (-lytic), while the root of the word describes the nature of that formation or decomposition. So hetero (meaning different) reactions involve asymmetrical bond making (or breaking) and homo (meaning same) involve symmetrical processes.

Because one pair of electrons constitutes a single bond, the unsymmetrical making or breaking of that bond in a hetero processes are described as polar reactions. Similarly, symmetrical homo processes of bond making and breaking are called radical reactions. Radicals (sometimes referred to as free radicals) are highly reactive neutral chemical species with one unpaired electron. In later sections we discuss radical and polar reactions in more detail.

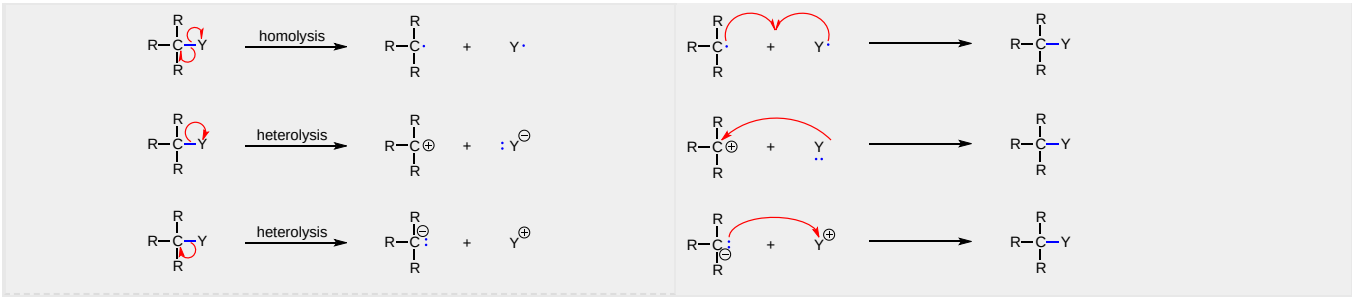
The Arrow Notation in Mechanisms

Since chemical reactions involve the breaking and making of bonds, a consideration of the movement of bonding (and non-bonding) valence shell electrons is essential to this understanding. It is now common practice to show the movement of electrons with curved arrows, and a sequence of equations depicting the consequences of such electron shifts is termed a **mechanism**. In general, two kinds of curved arrows are used in drawing mechanisms:

A full head on the arrow indicates the movement or shift of an electron pair:		
A partial head (fishhook) on the arrow indicates the shift of a single electron:		

The use of these symbols in bond-breaking and bond-making reactions is illustrated below. If a covalent single bond is broken so that one electron of the shared pair remains with each fragment, as in the first example, this bond-breaking is called **homolysis**. If the bond breaks with both electrons of the shared pair remaining with one fragment, as in the second and third examples, this is called **heterolysis**.

Bond-Breaking	Bond-Making

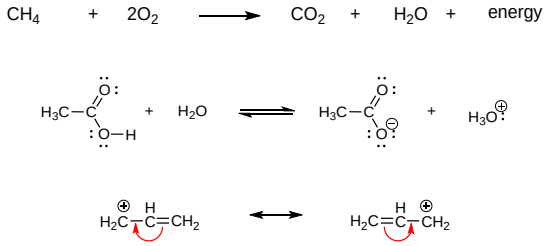


Other Arrow Symbols

Chemists also use arrow symbols for other purposes, and it is essential to use them correctly.

The Reaction Arrow	The Equilibrium Arrow	The Resonance Arrow
		

The following equations illustrate the proper use of these symbols:



Reactive Intermediates

The products of bond breaking, shown above, are not stable in the usual sense, and cannot be isolated for prolonged study. Such species are referred to as **reactive intermediates**, and are believed to be transient intermediates in many reactions. The general structures and names of four such intermediates are given below.

Charged Intermediates	Uncharged Intermediates
 a carbocation	 a radical
 a carbanion	 a carbene

A pair of widely used terms, related to the Lewis acid-base notation, should also be introduced here.

- Electrophile: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.
- Nucleophile: An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

Using these definitions, it is clear that carbocations (called carbonium ions in the older literature) are electrophiles and carbanions are nucleophiles. Carbenes have only a valence shell sextet of electrons and are therefore electron deficient. In this sense they are electrophiles, but the non-bonding electron pair also gives carbenes nucleophilic character. As a rule, the electrophilic character dominates carbene reactivity. Carbon radicals have only seven valence electrons, and may be considered electron deficient;

however, they do not in general bond to nucleophilic electron pairs, so their chemistry exhibits unique differences from that of conventional electrophiles. Radical intermediates are often called **free radicals**.

The importance of electrophile / nucleophile terminology comes from the fact that many organic reactions involve at some stage the bonding of a nucleophile to an electrophile, a process that generally leads to a stable intermediate or product. Reactions of this kind are sometimes called **ionic reactions**, since ionic reactants or products are often involved. Some common examples of ionic reactions and their mechanisms may be examined below.

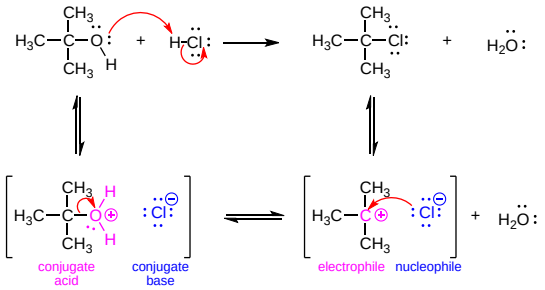
The shapes ideally assumed by these intermediates becomes important when considering the stereochemistry of reactions in which they play a role. A simple tetravalent compound like methane, CH_4, has a tetrahedral configuration. Carbocations have only three bonds to the charge bearing carbon, so it adopts a planar trigonal configuration. Carbanions are pyramidal in shape (tetrahedral if the electron pair is viewed as a substituent), but these species invert rapidly at room temperature, passing through a higher energy planar form in which the electron pair occupies a p-orbital. Radicals are intermediate in configuration, the energy difference between pyramidal and planar forms being very small. Since three points determine a plane, the shape of carbenes must be planar; however, the valence electron distribution varies.

Ionic Reactions

The principles and terms introduced in the previous sections can now be summarized and illustrated by the following three examples. Reactions such as these are called **ionic** or **polar** reactions, because they often involve charged species and the bonding together of **electrophiles and nucleophiles**. Ionic reactions normally take place in liquid solutions, where solvent molecules assist the formation of charged intermediates.

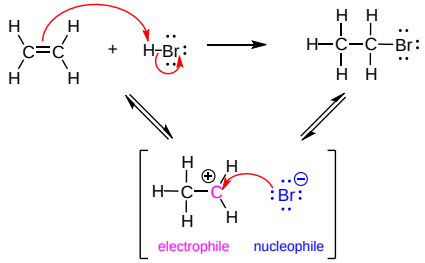
Substitution Reaction

The substitution reaction shown below can be viewed as taking place in three steps. The first is an acid-base equilibrium, in which HCl protonates the oxygen atom of the alcohol. The resulting conjugate acid then loses water in a second step to give a carbocation intermediate. Finally, this electrophile combines with the chloride anion nucleophile to give the final product.



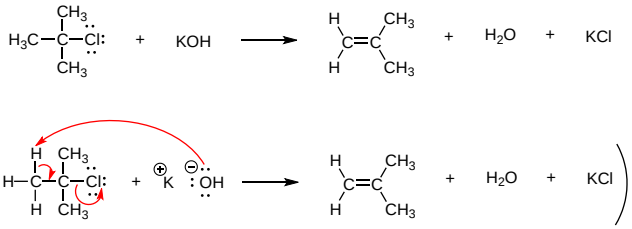
Addition Reaction

The addition reaction shown below can be viewed as taking place in two steps. The first step can again be considered an acid-base equilibrium, with the pi-electrons of the carbon-carbon double bond functioning as a base. The resulting conjugate acid is a carbocation, and this electrophile combines with the nucleophilic bromide anion.



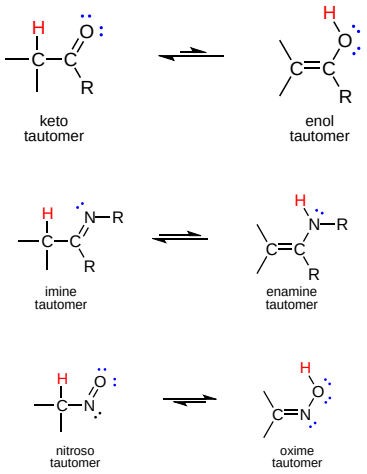
Elemination Reaction

The elimination reaction shown below takes place in one step. The bond breaking and making operations that take place in this step are described by the curved arrows. The initial stage may also be viewed as an acid-base interaction, with hydroxide ion serving as the base and a hydrogen atom component of the alkyl chloride as an acid. **rearrangement** (tautomerism)



Tautomerization Reaction

There are many kinds of molecular rearrangements. The examples shown below are from an important class called **tautomerization** or, more specifically, keto-enol tautomerization. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom (colored red here) and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.



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5.3: Radical Reactions

Objectives

After completing this section, you should be able to

- give an example of a radical substitution reaction.
- identify the three steps (initiation, propagation and termination) that occur in a typical radical substitution reaction.
- write out the steps involved in a simple radical substitution reaction, such as the chlorination of methane.
- explain why the halogenation of an alkane is not a particularly useful method of preparing specific alkyl halides.

Key Terms

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

- chain reaction
- initiation step
- propagation step
- radical substitution
- termination step

Study Notes

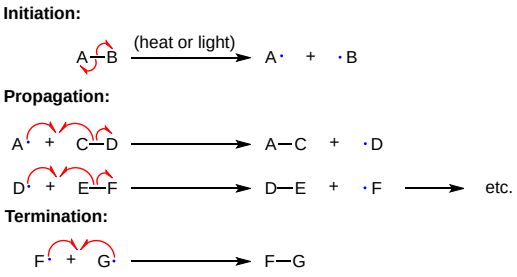
A *radical substitution reaction* is a reaction which occurs by a free radical mechanism and results in the substitution of one or more of the atoms or groups present in the substrate by different atoms or groups.

The *initiation step* in a radical chain reaction is the step in which a free radical is first produced. A *termination step* of a radical chain reaction is one in which two radicals react together in some way so that the chain can no longer be propagated.

While radical halogenation of very simple alkanes can be an effective synthetic strategy, it cannot be employed for larger more complex alkanes to yield specific alkyl halides, since the reactive nature of radicals always leads to mixtures of single- and multiple-halogenated products.

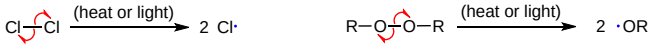
The Three Phases of Radical Chain Reactions

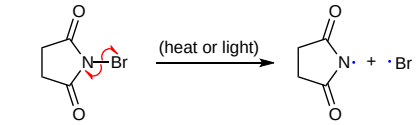
Because of their high reactivity, free radicals have the potential to be both extremely powerful chemical tools and extremely harmful contaminants. Much of the power of free radical species stems from the natural tendency of radical processes to occur in a chain reaction fashion. **Radical chain reactions** have three distinct phases: initiation, propagation, and termination.



The **initiation phase** describes the step that initially creates a radical species. In most cases, this is a homolytic cleavage event, and takes place very rarely due to the high energy barriers involved. Often the influence of heat, UV radiation, or a metal-containing catalyst is necessary to overcome the energy barrier.

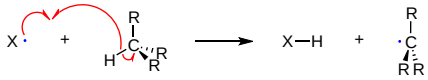
Molecular chlorine and bromine will both undergo homolytic cleavage to form radicals when subjected to heat or light. Other functional groups which also tend to form radicals when exposed to heat or light are chlorofluorocarbons, peroxides, and the halogenated amide N-bromosuccinimide (NBS).

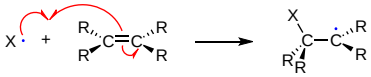




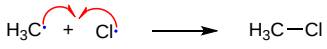
N-bromosuccinimide (NBS)

The **propagation phase** describes the 'chain' part of chain reactions. Once a reactive free radical is generated, it can react with stable molecules to form new free radicals. These new free radicals go on to generate yet more free radicals, and so on. Propagation steps often involve hydrogen abstraction or addition of the radical to double bonds.





Chain termination occurs when two free radical species react with each other to form a stable, non-radical adduct. Although this is a very thermodynamically downhill event, it is also very rare due to the low concentration of radical species and the small likelihood of two radicals colliding with one another. In other words, the Gibbs free energy barrier is very high for this reaction, mostly due to entropic rather than enthalpic considerations. The active sites of enzymes, of course, can evolve to overcome this entropic barrier by positioning two radical intermediates adjacent to one another.



Exercise 5.3.1

Radical chlorination of alkanes are not useful due to uncontrolled substitution. Draw the mono-substituted products of Cl_2 reacting with 2-methylbutane.

Answer

Exercise 5.3.2

Propose a radical mechanism for the following reaction:

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Answer



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5.4: Polar Reactions

Objectives

After completing this section, you should be able to

- identify the positive and negative ends of the bonds present in the common functional groups.
- explain how bond polarity can be enhanced by the interaction of a functional group with a solvent, metal cation or acid.
- explain how the polarizability of an atom can be an important factor in determining the reactivity of a bond.
- describe the heterolytic bond-breaking process.
- use curved (curly) arrows to indicate the movement of electron pairs during bond breakage and bond formation.
- predict whether a given species (compound or ion) is likely to behave as a nucleophile or as an electrophile.

Key Terms

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

- electrophile
- nucleophile
- polar reaction
- polarizability

Study Notes

You may wish to review Section 2.1 before you begin this section. The relative electronegativities of the elements shown in the periodic table should already be familiar. Remember that it is the relative electronegativities that are important, not the actual numerical values.

Make sure that you understand the polarity patterns of the common functional groups. Do not try to memorize these polarities; rather, concentrate on why they arise. You will encounter these group polarities so frequently that they will soon become "second nature" to you.

Halogens and the Character of the Carbon-Halogen Bond

With respect to electronegativity, most halogens are more electronegative than carbon. This results in a carbon-halogen bond that is polarized. As shown in the image below, the carbon atom has a partial positive charge, while the halogen has a partial negative charge.



The following table shows the relationship between the halogens and electronegativity. Notice, as we move up the periodic table from iodine to fluorine, electronegativity increases.

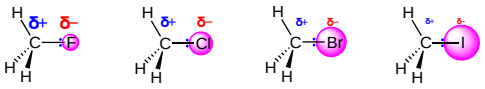
Electronegativity	I < Br < Cl < F

The following table shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases and we get longer bonds, the strength of those bonds decreases.

Bond length	C–F < C–Cl < C–Br < C–I
Bond strength	C–I < C–Br < C–Cl < C–F
Molecular size	F < Cl < Br < I

The influence of bond polarity

Of the four halogens, fluorine is the most electronegative and iodine the least. That means that the electron pair in the carbon-fluorine bond will be dragged most towards the halogen end. Looking at the methyl halides as simple examples:



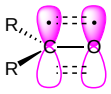
The electronegativities of carbon and iodine are not very different, and so there will be little separation of charge on the bond. One of the important set of reactions of alkyl halides involves replacing the halogen by something else - substitution reactions. These reactions can involve the carbon-halogen bond breaking to give positive and negative ions. The ion with the positively charged carbon atom then reacts with something either fully or slightly negatively charged. Alternatively, something either fully or negatively charged is attracted to the slightly positive carbon atom and pushes off the halogen atom.

You might have thought that either of these would be more effective in the case of the carbon-fluorine bond with the quite large amounts of positive and negative charge already present. But that's not so - quite the opposite is true! The thing that governs the reactivity is the strength of the bonds which have to be broken. It is difficult to break a carbon-fluorine bond, but easy to break a carbon-iodine one.

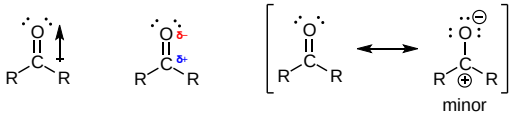
The Carbonyl Group

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.

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 overlaps with orbitals on the oxygen and on the two carbon or hydrogen atoms. These three bonds adopt trigonal planar geometry. The remaining unhybridized 2p orbital on the central carbonyl carbon is perpendicular to this plane, and forms a ‘side-by-side’ pi bond with a 2p orbital on the oxygen.



The carbon-oxygen double bond is polar: 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, or by showing the oxygen as holding a partial negative charge and the carbonyl carbon a partial positive charge.



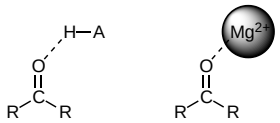
A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pbond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty 2p orbital and a full positive charge.

Some Carbonyl Compounds

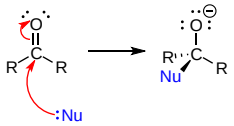
Compound	aldehyde	ketone	formaldehyde	carboxylic acid	ester	amide	enone	acyl halide	acid anhydride
Structure									
General Formula	RCHO	RCOR'	CH_2O	RCOOH	RCOOR'	RCONR'R''	RC(O)C(R'')CR'''R''''	RCOX	RCO_2COR'

Nucleophilic Addition to Aldehydes and Ketones

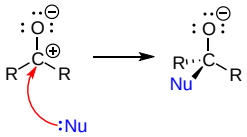
The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative 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.



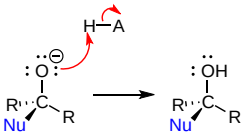
The same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen. Unlike the situation in a nucleophilic substitution reaction, when a nucleophile attacks an aldehyde or ketone carbon there is no leaving group – the incoming nucleophile simply 'pushes' the electrons in the pi bond up to the oxygen.



Alternatively, if you start with the minor resonance contributor, you can picture this as an attack by a nucleophile on a carbocation.



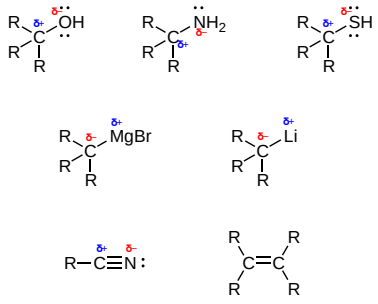
After the carbonyl is attacked by the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. However, most commonly the oxygen acts instead as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site.



This very common type of reaction is called a **nucleophilic addition**. In many biologically relevant examples of nucleophilic addition to carbonyls, the nucleophile is an alcohol oxygen or an amine nitrogen, or occasionally a thiol sulfur. In one very important reaction type known as an aldol reaction, the nucleophile attacking the carbonyl is a resonance-stabilized carbanion. In this chapter, we will concentrate on reactions where the nucleophile is an oxygen or nitrogen.

1. Nucleophilic Addition to Aldehydes and Ketones
2. Nucleophilic Substitution of RCOZ (Z = Leaving Group)
3. General reaction
4. General mechanism

Polarity Patterns in Other Common Functional Groups



Nucleophile?

Nucleophilic functional groups are those which have electron-rich atoms able to donate a pair of electrons to form a new covalent bond. In both laboratory and biological organic chemistry, the most relevant nucleophilic atoms are oxygen, nitrogen, and sulfur, and the most common nucleophilic functional groups are water, alcohols, phenols, amines, thiols, and occasionally carboxylates.

More specifically in laboratory reactions, halide and azide (N_3^-) anions are commonly seen acting as nucleophiles.

Of course, carbons can also be nucleophiles - otherwise how could new carbon-carbon bonds be formed in the synthesis of large organic molecules like DNA or fatty acids? Enolate ions (section 7.5) are the most common carbon nucleophiles in biochemical reactions, while the cyanide ion (CN^-) is just one example of a carbon nucleophile commonly used in the laboratory. Reactions with carbon nucleophiles will be dealt with in chapters 13 and 14, however - in this chapter and the next, we will concentrate on non-carbon nucleophiles.

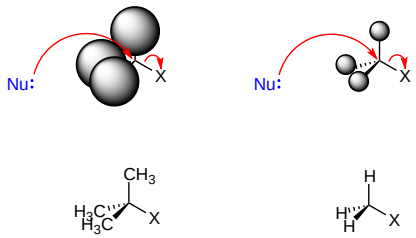
When thinking about nucleophiles, the first thing to recognize is that, for the most part, the same quality of 'electron-richness' that makes a something nucleophilic also makes it basic: *nucleophiles can be bases, and bases can be nucleophiles*. It should not be surprising, then, that most of the trends in basicity that we have already discussed also apply to nucleophilicity.

Neutral Nucleophiles	Charged Nucleophiles
H_2O, NH_3, RNH_2, R_2NH, R_3N, ROH, RCOOH, RSH, and PR_3	$^{\ominus}OH$, $^{\ominus}OR$, $^{\ominus}NH_2$, $^{\ominus}NHR$, $^{\ominus}NR_2$, $^{\ominus}SH$, $^{\ominus}SR$, $^{\ominus}SeR$, $^{\ominus}Cl$, $^{\ominus}Br$, $^{\ominus}I$, $^{\ominus}F$, $^{\ominus}CN$, $RCOO^{\ominus}$

Electrophiles

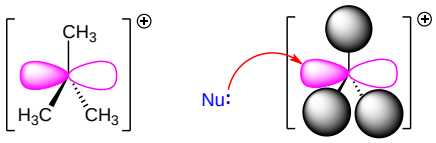
In the vast majority of the nucleophilic substitution reactions you will see in this and other organic chemistry texts, the electrophilic atom is a carbon which is bonded to an electronegative atom, usually oxygen, nitrogen, sulfur, or a halogen. The concept of electrophilicity is relatively simple: an electron-poor atom is an attractive target for something that is electron-rich, *i.e.* a nucleophile. However, we must also consider the effect of steric hindrance on electrophilicity. In addition, we must discuss how the nature of the electrophilic carbon, and more specifically the stability of a potential carbocationic intermediate, influences the S_N1 vs. S_N2 character of a nucleophilic substitution reaction.

Consider two hypothetical S_N2 reactions: one in which the electrophile is a methyl carbon and another in which it is tertiary carbon.



Because the three substituents on the methyl carbon electrophile are tiny hydrogens, the nucleophile has a relatively clear path for backside attack. However, backside attack on the tertiary carbon is blocked by the bulkier methyl groups. Once again, steric hindrance - this time caused by bulky groups attached to the electrophile rather than to the nucleophile - hinders the progress of an associative nucleophilic (S_N2) displacement.

The factors discussed in the above paragraph, however, do not prevent a sterically-hindered carbon from being a good electrophile - they only make it less likely to be attacked in a *concerted S_N2 reaction*. Nucleophilic substitution reactions in which the electrophilic carbon is sterically hindered are more likely to occur by a two-step, dissociative (S_N1) mechanism. This makes perfect sense from a geometric point of view: the limitations imposed by sterics are significant mainly in an S_N2 displacement, when the electrophile being attacked is a sp^3-hybridized tetrahedral carbon with its relatively 'tight' angles of 109.4°. Remember that in an S_N1 mechanism, the nucleophile attacks an sp^2-hybridized carbocation intermediate, which has trigonal planar geometry with 'open' 120 angles.



With this open geometry, the empty p orbital of the electrophilic carbocation is no longer significantly shielded from the approaching nucleophile by the bulky alkyl groups. A carbocation is a very potent electrophile, and the nucleophilic step occurs very rapidly compared to the first (ionization) step.

Exercise 5.4.1

Label the following either an electrophile or a nucleophile.



Answer

A = Electrophile

B = Nucleophile

C = Both (carbonyl carbon is electrophile and oxygen is nucleophile)

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5.5: An Example of a Polar Reaction - Addition of HBr to Ethylene

Objectives

After completing this section, you should be able to

- give an example of a simple polar reaction (e.g., a electrophilic addition).
- identify the electrophile and nucleophile in a simple polar reaction.

Key Terms

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

- electrophilic addition
- carbocation

Study Notes

The curved arrows introduced in this section are used throughout the course to indicate the movement of electron pairs. It takes practice for the beginning student to feel comfortable using these arrows. Remember that the head of the arrow indicates where the electron pair moves to; its tail shows where the electron pair comes from. (Chemists often refer to the use of curved arrows as “electron pushing.")

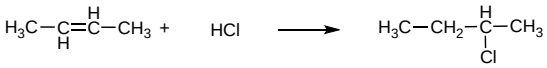
This page looks at the reaction of the carbon-carbon double bond in alkenes such as ethene with hydrogen halides such as hydrogen chloride and hydrogen bromide. Symmetrical alkenes (like ethene or but-2-ene) are dealt with first. These are alkenes where identical groups are attached to each end of the carbon-carbon double bond.

Addition to symmetrical alkenes

All alkenes undergo addition reactions with the hydrogen halides. A hydrogen atom joins to one of the carbon atoms originally in the double bond, and a halogen atom to the other. For example, with ethene and hydrogen chloride, you get chloroethane:



With but-2-ene you get 2-chlorobutane:

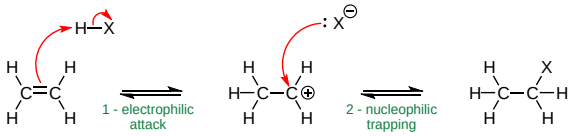


What happens if you add the hydrogen to the carbon atom at the right-hand end of the double bond, and the chlorine to the left-hand end? You would still have the same product. The chlorine would be on a carbon atom next to the end of the chain - you would simply have drawn the molecule flipped over in space. That would be different of the alkene was unsymmetrical - that's why we have to look at them separately.

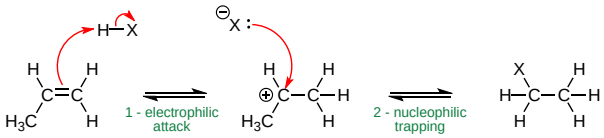
Mechanism

The addition of hydrogen halides is one of the easiest electrophilic addition reactions because it uses the simplest electrophile: the proton. Hydrogen halides provide both an electrophile (proton) and a nucleophile (halide). First, the electrophile will attack the double bond and take up a set of pi electrons, attaching it to the molecule (1). This is basically the reverse of the last step in the E1 reaction (deprotonation step). The resulting molecule will have a single carbon-carbon bond with a positive charge on one of them (carbocation). The next step is when the nucleophile (halide) bonds to the carbocation, producing a new molecule with both the original hydrogen and halide attached to the organic reactant (2). The second step will only occur if a good nucleophile is used.

Mechanism of Electrophilic Addition of Hydrogen Halide to Ethene



Mechanism of Electrophilic Addition of Hydrogen Halide to Propene

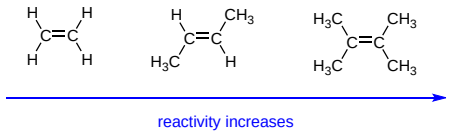


All of the halides (HBr, HCl, HI, HF) can participate in this reaction and add on in the same manner. Although different halides do have different rates of reaction, due to the H-X bond getting weaker as X gets larger (poor overlap of orbitals)s.

Reaction rates

Reaction rates increase in the order HF - HCl - HBr - HI. Hydrogen fluoride reacts much more slowly than the other three, and is normally ignored in talking about these reactions. When the hydrogen halides react with alkenes, the hydrogen-halogen bond has to be broken. The bond strength falls as you go from HF to HI, and the hydrogen-fluorine bond is particularly strong. Because it is difficult to break the bond between the hydrogen and the fluorine, the addition of HF is bound to be slow.

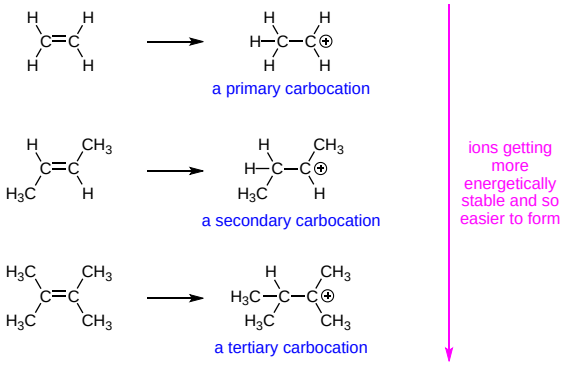
This applies to unsymmetrical alkenes as well as to symmetrical ones. For simplicity the examples given below are all symmetrical ones- but they don't have to be. Reaction rates increase as the alkene gets more complicated - in the sense of the number of alkyl groups (such as methyl groups) attached to the carbon atoms at either end of the double bond. For example:



There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

Alkenes react because the electrons in the pi bond attract things with any degree of positive charge. Anything which increases the electron density around the double bond will help this. Alkyl groups have a tendency to "push" electrons away from themselves towards the double bond. The more alkyl groups you have, the more negative the area around the double bonds becomes.

The more negatively charged that region becomes, the more it will attract molecules like hydrogen chloride. The more important reason, though, lies in the stability of the intermediate ion formed during the reaction. The three examples given above produce these carbocations (carbonium ions) at the half-way stage of the reaction:

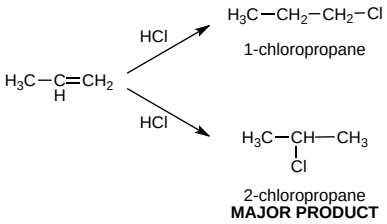


The stability of the intermediate ions governs the activation energy for the reaction. As you go towards the more complicated alkenes, the activation energy for the reaction falls. That means that the reactions become faster.

Addition to unsymmetrical alkenes

In terms of reaction conditions and the factors affecting the rates of the reaction, there is no difference whatsoever between these alkenes and the symmetrical ones described above. The problem comes with the orientation of the addition - in other words, which way around the hydrogen and the halogen add across the double bond.

If HCl adds to an unsymmetrical alkene like propene, there are two possible ways it could add. However, in practice, there is only one major product.



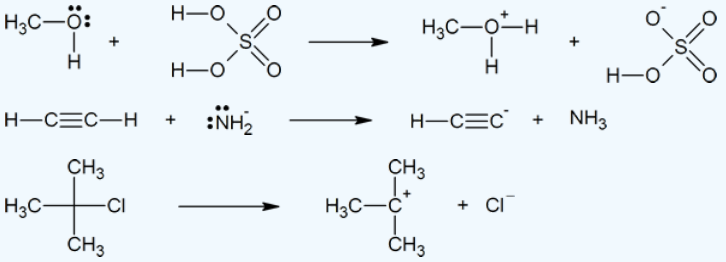
This is in line with Markovnikov's Rule which says:

> When a compound HX is added to an unsymmetrical alkene, the hydrogen becomes attached to the carbon with the most hydrogens attached to it already.

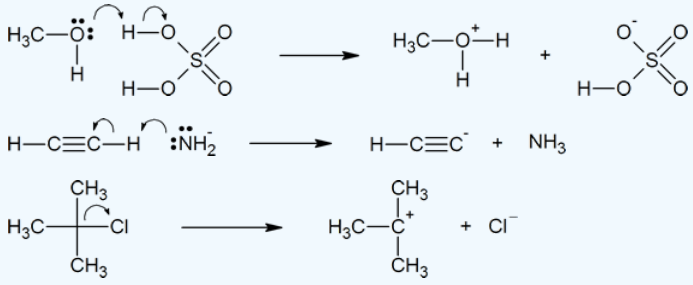
In this case, the hydrogen becomes attached to the CH_2 group, because the CH_2 group has more hydrogens than the CH group. Notice that only the hydrogens directly attached to the carbon atoms at either end of the double bond count. The ones in the CH_3 group are totally irrelevant.

Exercise 5.5.1

Supply the missing curved arrows in the equations given below.

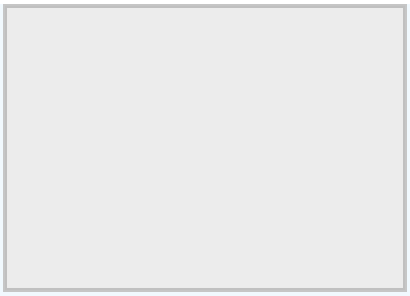


Answer



Exercise 5.5.2

Predict the product of the following reactions:



Answer



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5.6: Using Curved Arrows in Polar Reaction Mechanisms

Objective

After completing this section, you should be able to use curved (curly) arrows, in conjunction with a chemical equation, to show the movement of electron pairs in a simple polar reaction, such as electrophilic addition.

Key Terms

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

- electrophlic
- nucleophlic

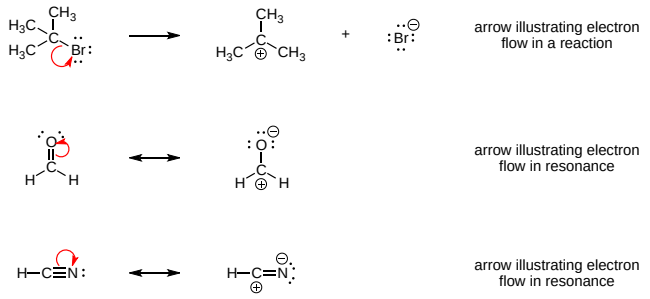
Pushing Electrons and Curved Arrows

Understanding the location of electrons and being able to draw the curved arrows that depict the mechanisms by which the reactions occur is one of the most critical tools for learning organic chemistry since they allow you to understand what controls reactions, and how reactions proceed.

Before you can do this you need to understand that a **bond** is due to a pair of electrons shared between atoms. When asked to draw a mechanism, curved arrows should be used to show all the bonding changes that occur. A few simple lessons that illustrate these concepts can be found below.

Lesson 1

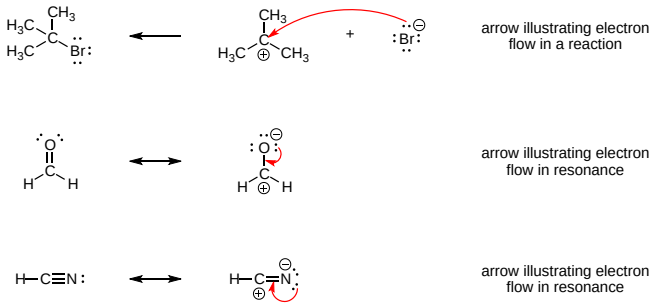
If we remove the pair of electrons in a bond, then we BREAK that bond. This is true for single and multiple bonds as shown below:



Notice that since the starting materials were *neutral*, the products are also *neutral*. In general terms, the *sum of the charges* on the starting materials MUST equal the *sum of the charges* on the products since we have the **same number of electrons**.

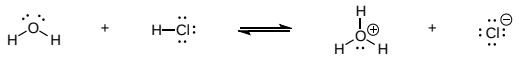
The first example is a REACTION since we broke a sigma bond. In the second two examples, we moved pi electrons into long pairs. This is RESONANCE.

If we move electrons between two atoms, then we MAKE a new bond:

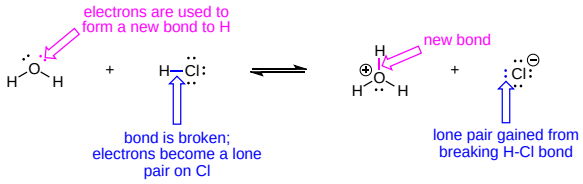


We always show electrons moving from **electron rich** to **electron poor**.

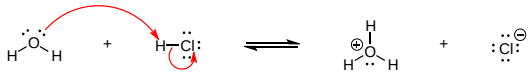
Lesson 2



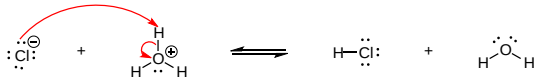
This is a simple acid/base reaction, showing the formation of the hydronium ion produced when hydrochloric acid is dissolved in water. It is useful to analyze the bond changes that are occurring. Water is functioning as a **base** and hydrochloric acid as an **acid**. Consider the differences in bonding between the starting materials and the products:



One of the lone pairs on the oxygen atom of water was used to form a bond to a hydrogen atom, creating the hydronium ion (H_3O^+) seen in the products. The hydrogen-chlorine bond of HCl was broken, and the electrons in this bond became a lone pair on the chlorine atom, thus generating a chloride ion. We can illustrate these changes in bonding using the curved arrows shown below.



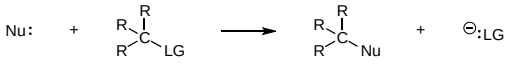
Note that in this diagram, the overall charge of the reactants is the same as the overall charge of the products. We can also show the curved arrows for the reverse reaction:



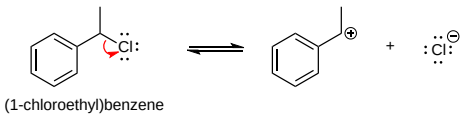
This shows the formation of the new H-Cl bond by using a lone pair of electrons from the electron-rich chloride ion to form a bond to an electron poor hydrogen atom of the hydronium ion. Because hydrogen can only form one bond, the oxygen-hydrogen bond is broken and its electrons become a lone pair on the electron-poor oxygen atom. Notice that the charges balance!

Lesson 3

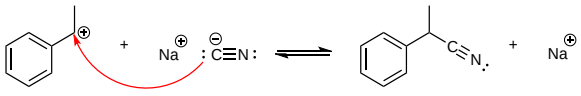
In this section, we will look at the curved arrows for some nucleophilic substitution reactions. Overall, the processes involved are similar to those for the acid/base reactions described above. In a nucleophilic substitution reaction, an electron-rich nucleophile (Nu) becomes bonded to an electron-poor carbon atom, and a leaving group (LG) is displaced. In bonding terms, we must *make* a Nu-C bond and *break* a C-LG bond.



Let's consider the stepwise S_N1 reaction between (1-chloroethyl)benzene and sodium cyanide. The first step of this process is breaking the C-Cl bond, where the electrons in that bond become a lone pair on the chlorine atom. The carbon atom has lost electrons and therefore becomes positive, generating a secondary carbocation. Because the chlorine atom gained an additional lone pair of electrons, it becomes a negatively charged chloride ion.

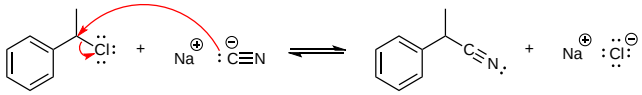


In the second step, the electron-rich nucleophile donates electrons to form a new C-C bond with the electron-poor secondary carbocation.



In an S_N2 reaction, the bond forming and breaking processes occur simultaneously. The scheme below shows the Nu donating electrons to form a new C-C bond at the same time that the C-Cl bond is breaking. The electrons in the C-Cl bond become a long

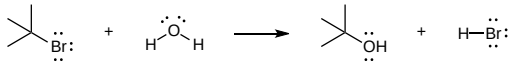
pair on the chlorine atom, generating a chloride ion. Forming and breaking the bonds simultaneously allows carbon to obey the octet rule throughout this process.



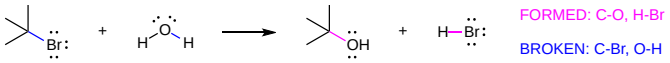
Notice that in all steps for the processes above, the overall charges of the starting materials match those of the products.

Lesson 4

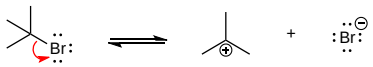
This section will dissect another substitution reaction, although it is more involved. Let's consider the S_N1 reaction of *tert*-butyl bromide with water.



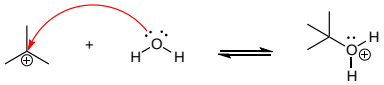
It can be helpful to take inventory of which bonds have been formed, and which bonds have been broken.



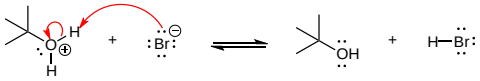
The curved arrows we draw must account for ALL of these bonding changes. Since we are dealing with an S_N1 reaction process, the first step will be cleavage of the C-Br bond to give a carbocation and and a bromide anion.



Water then acts as a nucleophile, using one of its lone pairs to form a bond to the electron-poor *t*-butyl cation. This generates an oxonium ion, where oxygen has three bonds and a positive formal charge.

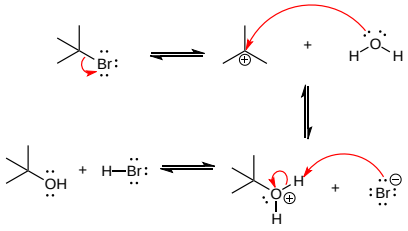


The final step is an acid/base reaction between the bromide anion generated in step 1 and the oxonium product of step 2. The bromide anion acts as a base, using a lone pair to form a bond to one of the hydrogen atoms. The O-H bond then breaks, and its electrons become a lone pair on oxygen. This gives the final products of HBr and *t*-butyl alcohol.

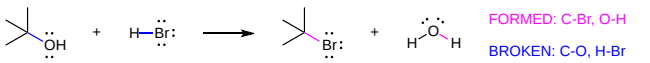


Notice that in each of the mechanistic steps above, the overall charge of the reactant side balances with the overall charge of the product side.

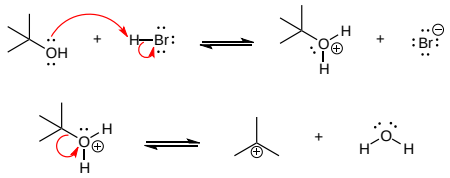
While the above process was broken down into distinct steps, however it is important to note that mechanisms are almost always shown as a continuous process. The overall mechanism for this processes can be found below:



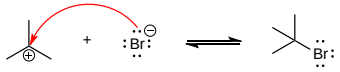
Now consider the reverse reaction, i.e. the reaction of *t*-butyl alcohol with hydrobromic acid to generate *t*-butyl bromide and water. The scheme is shown below, along with an analysis of the bonds formed and broken in this process:



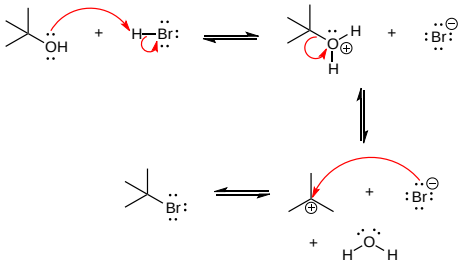
The mechanism must occur via the same pathway as shown above (Law of Macroscopic Reversibility), however this mechanism can still be deduced without knowing that. First, it is known that HBr is a strong acid and can donate a proton to a base. The most basic sites in the whole system are the lone pairs on the oxygen atom of *t*-butanol. Since the lone pairs are the electron-rich area of the molecule, the arrow starts at a lone pair and ends at the proton of HBr. The H-Br bond breaks, pushing its electrons onto the bromine atom and generating a bromide ion.



The bromide ion generated in the first step can then react with the *t*-butyl cation to generate *t*-butyl bromide.



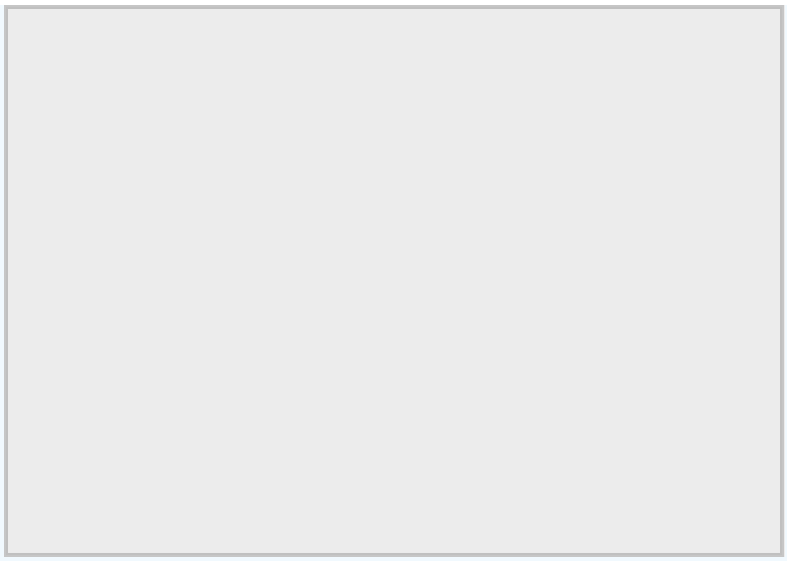
Once again, the above the overall process is broken down into individual steps, however it is more common to illustrate this as one overall process:



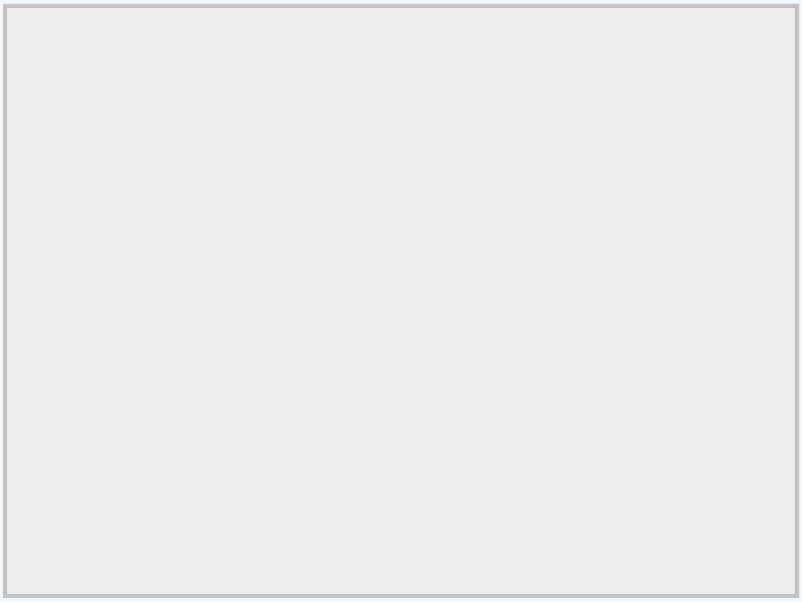
Curved Arrow Summary

- Curved arrows flow from electron rich to electron poor.
- Therefore they start from lone pairs or bonds.
- The charges in any particular step should always be balanced.
- Remember to obey the rules of valence (*eg*. octet rule for C,N,O,F *etc*.)
- If electrons are taken out of a bond, then that bond is broken.
- If electrons are placed between two atoms then it implies a bond is being made.

Exercise 5.6.1



Answer



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5.7: Describing a Reaction - Equilibria, Rates, and Energy Changes

Objectives

After completing this section, you should be able to

- write the equilibrium constant expression for a given reaction.
- assess, qualitatively, how far a reaction will proceed in a given direction, given the value of K_{eq}.
- explain the difference between rate and equilibrium.
- state the relationship between $\Delta G°$ and K_{eq}, and use this relationship to determine the value of either of the two variables, given the other.
- state the relationship between Gibbs free-energy, enthalpy and entropy, and use the relationship to calculate any one of $\Delta G°$, $\Delta H°$ and $\Delta S°$, given the other two.
- make a qualitative assessment of whether $\Delta S°$ for a given process is expected to be positive or negative.

Key Terms

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

- exergonic
- endergonic
- exothermic
- endothermic
- enthalpy change (heat of reaction), $\Delta H°$
- entropy change, $\Delta S°$
- reaction mechanism
- standard Gibbs free-energy change, $\Delta G°$

Study Notes

Throughout this course you will be paying a great deal of attention to the mechanisms of the reactions that you study. Some students see this as a laborious task of little practical use. However, you will find that a knowledge of reaction mechanisms can help reduce the number of reactions to memorize, provide a connecting link between apparently unrelated reactions, and enable someone with a basic knowledge of organic chemistry to deduce how a previously unseen reaction might proceed. The investigation of reaction mechanisms is a popular research area for organic chemists.

Equilibrium Constant

For the hypothetical chemical reaction:

$$aA + bB \rightleftharpoons cC + dD$$

the equilibrium constant is defined as:

$$K_C = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

The notation [A] signifies the molar concentration of species A. An alternative expression for the equilibrium constant involves partial pressures:

$$K_P = \frac{P_C^c P_D^d}{P_A^a P_B^b}$$

Note that the expression for the equilibrium constant includes only solutes and gases; pure solids and liquids do not appear in the expression. For example, the equilibrium expression for the reaction

$$\mathrm{CaH_2(s) + 2\,H_2O(g) \rightleftharpoons Ca(OH)_2(s) + 2\,H_2(g)}$$

is the following:

$$K_C = \frac{[H_2]^2}{[H_2O]^2}$$

Observe that the gas-phase species H_2O and H_2 appear in the expression but the solids CaH_2 and $Ca(OH)_2$ do not appear.

The equilibrium constant is most readily determined by allowing a reaction to reach equilibrium, measuring the concentrations of the various solution-phase or gas-phase reactants and products, and substituting these values into the Law of Mass Action.

Free Energy

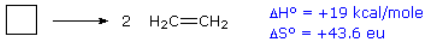
The interaction between enthalpy and entropy changes in chemical reactions is best observed by studying their influence on the equilibrium constants of reversible reactions. To this end a new thermodynamic function called Free Energy (or Gibbs Free Energy), symbol ΔG, is defined as shown in the first equation below. Two things should be apparent from this equation. First, in cases where the entropy change is small, $\Delta G \cong \Delta H$. Second, the importance of ΔS in determining ΔG increases with increasing temperature.

$$\Delta G^o = \Delta H^o - T\Delta S^o$$

where the temperature is measured in absolute temperature (K).

The free energy function provides improved insight into the thermodynamic driving forces that influence reactions. A negative ΔG^o is characteristic of an **exergonic reaction**, one which is thermodynamically favorable and often spontaneous, as is the melting of ice at 1 ºC. Likewise a positive ΔG^o is characteristic of an **endergonic reaction**, one which requires an input of energy from the surroundings.

For an example of the relationship of free energy to enthalpy consider the decomposition of cyclobutane to ethene, shown in the following equation. The standard state for all the compounds is gaseous.



This reaction is endothermic, but the increase in number of molecules from one (reactants) to two (products) results in a large positive ΔSº.

At 25 ºC (298 K):

ΔGº = 19 kcal/mol – 298(43.6) cal/mole = 19 – 13 kcal/mole = +6 kcal/mole.

Thus, the entropy change opposes the enthalpy change, but is not sufficient to change the sign of the resulting free energy change, which is endergonic. Indeed, cyclobutane is perfectly stable when kept at room temperature.

Because the entropy contribution increases with temperature, this energetically unfavorable transformation can be made favorable by raising the temperature. At 200 ºC (473 K),

$$\Delta G^o = 19\,kcal/mol - 473(43.6)\,cal/mole \tag{5.7.1}$$

$$= 19 - 20.6\,kcal/mole \tag{5.7.2}$$

$$= -1.6 kcal/mole. \tag{5.7.3}$$

This is now an **exergonic reaction**, and the thermal cracking of cyclobutane to ethene is known to occur at higher temperatures.

$$\Delta G^o = -RT\ln K = -2.303RT\log_{10} K \tag{5.7.4}$$

where R = 1.987 cal/ K mole T = temperature in K and K = equilibrium constant

Note

Equation 5.7.4 is important because it demonstrates the fundamental relationship of ΔG^o to the equilibrium constant, K. Because of the negative logarithmic relationship between these variables, a negative ΔGº generates a K>1, whereas a positive ΔGº generates a K<1. When ΔGº = 0, K = 1. Furthermore, small changes in ΔGº produce large changes in K. A change of 1.4 kcal/mole in ΔGº changes K by approximately a factor of 10. This interrelationship may be explored with the calculator on the

right. Entering free energies outside the range -8 to 8 kcal/mole or equilibrium constants outside the range 10^{-6} to 900,000 will trigger an alert, indicating the large imbalance such numbers imply.

Exercise 5.7.1

At 155°C, the equilibrium constant, K_{eq}, for the reaction

$$CH_3CO_2H + CH_3CH_2OH \rightleftharpoons CH_3CO_2CH_2CH_3 + H_2O$$

has a value of 4.0. Calculate $\Delta G°$ for this reaction at 155°C.

Exercise 5.7.2

Acetylene (C_2H_2) can be converted into benzene (C_6H_6) according to the equation:

$$3\,H{-}C{\equiv}C{-}H(g) \rightleftharpoons C_6H_6(l)$$

At 25°C, $\Delta G°$ for this reaction is −503 kJ and $\Delta H°$ is −631 kJ. Determine $\Delta S°$ and indicate whether the size of $\Delta S°$ agrees with what you would have predicted simply by looking at the chemical equation.

Answer

The entropy change is negative, as one would expect from looking at the chemical equation, since three moles of reactants yield one mole of product; that is, the system becomes much more “ordered” as it goes from reactants to products.

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5.8: Describing a Reaction - Bond Dissociation Energies

Objectives

After completing this section, you should be able to

- predict the value of $\Delta H°$ for a gas-phase reaction, given the necessary bond dissociation energy data.
- predict the dissociation energy of a particular bond, given $\Delta H°$ for a reaction involving the bond and any other necessary bond dissociation energy data.
- outline the limitations of using bond dissociation energies to predict whether or not a given reaction will occur.

Key Terms

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

- bond dissociation energy
- solvation

Study Notes

The idea of calculating the standard enthalpy of a reaction from the appropriate bond dissociation energy data should be familiar to you from your first-year chemistry course.

Solvation is the interaction between solvent molecules and the ions or molecules dissolved in that solvent.

The homolytic bond dissociation energy is the amount of energy needed to break apart one mole of covalently bonded gases into a pair of radicals. The SI units used to describe bond energy are kiloJoules per mole of bonds (kJ/Mol). It indicates how strongly the atoms are bonded to each other.

Introduction

Breaking a covalent bond between two partners, A-B, can occur either heterolytically, where the shared pair of electron goes with one partner or another

$$A-B \rightarrow A^{+} + B:^{-}$$

or

$$A-B \rightarrow A:^{-} + B^{+}$$

or homolytically, where one electron stays with each partner.

$$A-B \rightarrow A^{\bullet} + B^{\bullet}$$

The products of homolytic cleavage are radicals and the energy that is required to break the bond homolytically is called the Bond Dissociation Energy (BDE) and is a measure of the strength of the bond.

Calculation of the BDE

The BDE for a molecule A-B is calculated as the difference in the enthalpies of formation of the products and reactants for homolysis

$$BDE = \Delta_f H(A^{\bullet}) + \Delta_f H(B^{\bullet}) - \Delta_f H(A-B)$$

Officially, the IUPAC definition of bond dissociation energy refers to the energy change that occurs at 0 K, and the symbol is D_o. However, it is commonly referred to as BDE, the bond dissociation energy, and it is generally used, albeit imprecisely, interchangeably with the bond dissociation *enthalpy*, which generally refers to the enthalpy change at room temperature (298K). Although there are technically differences between BDEs at 0 K and 298 K, those difference are not large and generally do not affect interpretations of chemical processes.

Bond Breakage/Formation

Bond dissociation energy (or enthalpy) is a state function and consequently does not depend on the path by which it occurs. Therefore, the specific mechanism in how a bond breaks or is formed does not affect the BDE. Bond dissociation energies are useful in assessing the energetics of chemical processes. For chemical reactions, combining bond dissociation energies for bonds formed and bonds broken in a chemical reaction using Hess's Law can be used to estimate reaction enthalpies.

Example 6.8.1: Chlorination of Methane

Consider the chlorination of methane

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$$

the overall reaction thermochemistry can be calculated exactly by combining the BDEs for the bonds broken and bonds formed

$CH_4 \rightarrow CH_3\bullet + H\bullet$ BDE(CH_3-H)

$Cl_2 \rightarrow 2Cl\bullet$ BDE(Cl_2) \nonumber \]

$H\bullet + Cl\bullet \rightarrow HCl$ -BDE(HCl)

$CH_3\bullet + Cl\bullet \rightarrow CH_3Cl$ -BDE(CH_3-Cl)

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$$

$$\Delta H = BDE(R-H) + BDE(Cl_2) - BDE(HCl) - BDE(CH_3 - Cl)$$

Because reaction enthalpy is a state function, it does not matter what reactions are combined to make up the overall process using Hess's Law. However, BDEs are convenient to use because they are readily available.

Alternatively, BDEs can be used to assess individual steps of a mechanism. For example, an important step in free radical chlorination of alkanes is the abstraction of hydrogen from the alkane to form a free radical.

$RH + Cl\bullet \rightarrow R\bullet + HCl$

The energy change for this step is equal to the difference in the BDEs in RH and HCl

$$\Delta H = BDE(R-H) - BDE(HCl)$$

This relationship shows that the hydrogen abstraction step is more favorable when BDE(R-H) is smaller. The difference in energies accounts for the selectivity in the halogenation of hydrocarbons with different types of C-H bonds.

Table 6.8.1: Representative C-H BDEs in Organic Molecules

R-H	D_o, kJ/mol	D_{298}, kJ/mol	R-H	D_o, kJ/mol	D_{298}, kJ/mol
CH_3-H	432.7±0.1	439.3±0.4	H_2C=CH-H	456.7±2.7	463.2±2.9
CH_3CH_2-H		423.0±1.7	C_6H_5-H	465.8±1.9	472.4±2.5
$(CH_3)_2$CH-H		412.5±1.7	HCCH	551.2±0.1	557.8±0.3
$(CH_3)_3$C-H		403.8±1.7			
			H_2C=$CHCH_2$-H		371.5±1.7
HC(O)-H		368.6±0.8	$C_6H_5CH_2$-H		375.3±2.5
CH_3C(O)-H		374.0±1.2			

Trends in C-H BDEs

It is important to remember that C-H BDEs refer to the energy it takes to break the bond, and is the difference in energy between the reactants and the products. Therefore, it is not appropriate to interpret BDEs solely in terms of the "stability of the radical

products" as is often done.

Analysis of the BDEs shown in the table above shows that there are some systematic trends:

1. **BDEs vary with hybridization:** Bonds with sp^3 hybridized carbons are weakest and bonds with sp hybridized carbons are much stronger. The vinyl and phenyl C-H bonds are similar, reflecting their sp^2 hybridization. The correlation with hybridization can be viewed as a reflection of the C-H bond lengths. Longer bonds formed with sp^3 orbitals are consequently weaker. Shorter bonds formed with orbitals that have more s-character are similarly stronger.
2. **C-H BDEs vary with substitution:** Among sp^3 hybridized systems, methane has the strongest C-H bond. C-H bonds on primary carbons are stronger than those on secondary carbons, which are stronger than those on tertiary carbons.

Interpretation of C-H BDEs for sp^3 Hybridized Carbons

The interpretation of the BDEs in saturated molecules has been subject of recent controversy. As indicated above, the variation in BDEs with substitution has traditionally been interpreted as reflecting the stabilities of the alkyl radicals, with the assessment that more highly substituted radicals are more stable, as with carbocations. Although this is a popular explanation, it fails to account fo the fact the bonds to groups other than H do not show the same types of variation.

R	BDE(R-CH_3)	BDE(R-Cl)	BDE(R-Br)	BDE(R-OH)
CH_3-	377.0±0.4	350.2±0.4	301.7±1.3	385.3±0.4
CH_3CH_2-	372.4±1.7	354.8±2.1	302.9±2.5	393.3±1.7
$(CH_3)_2CH$-	370.7±1.7	356.5±2.1	309.2±2.9	399.6±1.7
$(CH_3)_3C$-	366.1±1.7	355.2±2.9	303.8±2.5	400.8±1.7

Therefore, although C-CH_3 bonds get weaker with more substitution, the effect is not nearly as large as that observed with C-H bonds. The strengths of C-Cl and C-Br bonds are not affected by substitution, despite the fact that the same radicals are formed as when breaking C-H bonds, and the C-OH bonds in alcohols actually *increase* with more substitution.

Gronert has proposed that the variation in BDEs is alternately explained as resulting from destabilization of the reactants due to steric repulsion of the substituents, which is released in the nearly planar radicals.[1] Considering that BDEs reflect the relative energies of reactants and products, either explanation can account for the trend in BDEs.

Another factor that needs to be considered is the electronegativity. The Pauling definition of electronegativity says that the bond dissociation energy between unequal partners is going to be dependent on the difference in electrongativities, according to the expression

$$D_o(A-B) = \frac{D_o(A-A)+D_o(B-B)}{2} + (X_A - X_B)^2$$

where X_A and X_B are the electronegativities and the bond energies are in eV. Therefore, the variation in BDEs can be interpreted as reflecting variation in the electronegativities of the different types of alkyl fragments.

There is likely some merit in all three interpretations. Since Gronert's original publication of his alternate explanation, there have been many desperate attempts to defend the radical stability explanation.

? Exercise 5.8.1

Given that $\Delta H°$ for the reaction

$CH_4\,(g) + 4F_2\,(g) \rightarrow CF_4\,(g) + 4HF\,(g)$

is −1936 kJ, use the following data to calculate the average bond energy of the C-F bonds in CF_4.

Bond	Average Bond Energy
C−H	413 kJ · mol^{-1}
F−F	155 kJ · mol^{-1}

H−F	567 kJ · mol^{-1}

Answer

Bonds broken:

$$4 \text{ mol C-H bonds} \times \frac{(413\,\text{kJ})}{(1\,\text{mol})} = 1652\,\text{kJ}$$

$$4 \text{ mol F-F bonds} \times \frac{(155\,\text{kJ})}{(1\,\text{mol})} = 620\,\text{kJ}$$

Bonds formed:

$$4 \text{ mol CF bonds} \times \frac{(x\,\text{kJ})}{(1\,\text{mol})} = 4x\,\text{kJ}$$

(where x = the average energy of one mole of C-F bonds in CF_4, expressed in kJ)

$$4 \text{ mol H-F bonds} \times \frac{(567\,\text{kJ})}{(1\,\text{mol})} = 2268\,\text{kJ}$$

$\Delta H° = \Delta H°(\text{bonds broken}) - \Delta H°(\text{bonds formed}) = (1652\text{ kJ} + 620\text{ kJ}) - (4x + 2268\text{ kJ}) = 1652\text{ kJ} + 620\text{ kJ} - 4x - 2268\text{ kJ} = -1936\text{ kJ}$

Thus,

$$\begin{aligned} 4x &= 1936\,\text{kJ} - 2268\,\text{kJ} + 620\,\text{kJ} + 1652\,\text{kJ} \\ &= 1940\,\text{kJ} \end{aligned}$$

and

$$\begin{aligned} x &= \frac{1940\,\text{kJ}}{4\,\text{mol}} \\ &= 385\,\text{kJ} \cdot \text{mol}^{-1} \end{aligned}$$

The average energy of a C-F bond in CF_4 is 385 kJ · mol^{-1}

Exercise 5.8.1

Calculate $\Delta H°$ for the reactions given below. [Access bond energy tables via left-hand blue column Resources > Reference Tables > Reference Tables > Thermodynamic Tables > T3: Bond Energies]

a. $CH_3CH_2OCH_3$ + HI -> CH_3CH_2OH + CH_3I
b. CH_3Cl + NH_3 -> CH_3NH_2 + HCl

Answer

$CH_3CH_2OCH_3$ + HI → CH_3CH_2OH + CH_3I

Reactant bonds broken	D	Product bonds formed	D
$CH_3CH_2O-CH_3$	339 kJ/mol	CH_3CH_2O-H	438 kJ/mol
H−I	298 kJ/mol	CH_3-I	238 kJ/mol
	637 kJ/mol		676 kJ/mol

$$\begin{aligned} \Delta H^\circ &= D_{\text{bonds broken}} + D_{\text{bonds formed}} \\ &= 637\ \text{kJ/mol} - 676\ \text{kJ/mol} \\ &= -39\ \text{kJ/mol} \end{aligned}$$

CH_3Cl + NH_3 → CH_3NH_2 + HCl

Reactant bonds broken	D	Product bonds formed	D
CH_3-Cl	356 kJ/mol	CH_3-NH_2	364 kJ/mol
NH_2-H	450 kJ/mol	$H-Cl$	432 kJ/mol
	806 kJ/mol		796 kJ/mol

$$\begin{aligned}\Delta H^\circ &= D_{\text{bonds broken}} + D_{\text{bonds formed}} \\ &= 806\ \text{kJ/mol} - 796\ \text{kJ/mol} \\ &= +10\ \text{kJ/mol}\end{aligned}$$

References

1. Gronert, S. *J. Org. Chem.* **2006**, *13*, 1209

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5.9: Describing a Reaction - Energy Diagrams and Transition States

Objectives

After completing this section, you should be able to

- sketch the reaction energy diagram for a single-step reaction, given some indication of whether the reaction is fast or slow, exothermic or endothermic.
- interpret the reaction energy diagram for a single-step process (e.g., use the diagram to decide whether the reaction is exothermic or endothermic).
- suggest possible transition-state structures for simple one-step processes.
- assess the likelihood of a reaction occurring at room temperature, given the value of the activation energy $\Delta G^{\ddagger}$.

Key Terms

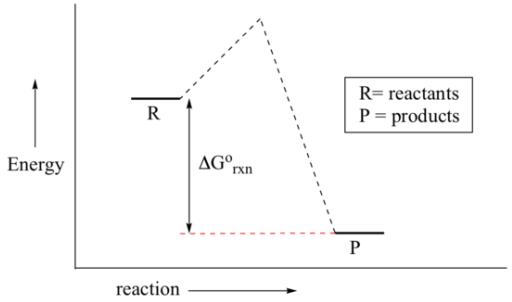
Make certain that you can define, and use in context, the key terms below.

- activation energy, $\Delta G^{\ddagger}$
- reaction energy diagram
- transition state

Study Notes

You may have been taught to use the term "activated complex" rather than "transition state," as the two are often used interchangeably. Similarly, the activation energy of a reaction is often represented by the symbol E_{act} or E_a.

You may recall from general chemistry that it is often convenient to describe chemical reactions with energy diagrams. In an energy diagram, the vertical axis represents the overall energy of the reactants, while the horizontal axis is the 'reaction coordinate', tracing from left to right the progress of the reaction from starting compounds to final products. The energy diagram for a typical one-step reaction might look like this:



Despite its apparent simplicity, this energy diagram conveys some very important ideas about the thermodynamics and kinetics of the reaction. Recall that when we talk about the **thermodynamics** of a reaction, we are concerned with the difference in energy between reactants and products, and whether a reaction is 'downhill' (exergonic, energy releasing) or 'uphill (endergonic, energy absorbing). When we talk about **kinetics**, on the other hand, we are concerned with the *rate* of the reaction, regardless of whether it is uphill or downhill thermodynamically.

First, let's review what this energy diagram tells us about the thermodynamics of the reaction illustrated by the energy diagram above. The energy level of the products is *lower* than that of the reactants. This tells us that the change in standard Gibbs Free Energy for the reaction (ΔG°_{rnx}) is negative. In other words, the reaction is exergonic, or 'downhill'. Recall that the ΔG°_{rnx} term encapsulates both ΔH°_{rnx}, the change in enthalpy (heat) and ΔS°_{rnx} , the change in entropy (disorder):

$$\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ}$$

where T is the absolute temperature in Kelvin. For chemical processes where the entropy change is small (~0), the enthalpy change is essentially the same as the change in Gibbs Free Energy. Energy diagrams for these processes will often plot the enthalpy (H)

instead of Free Energy for simplicity.

The standard Gibbs Free Energy change for a reaction can be related to the reaction's equilibrium constant (\(K_{eq}_) by a simple equation:

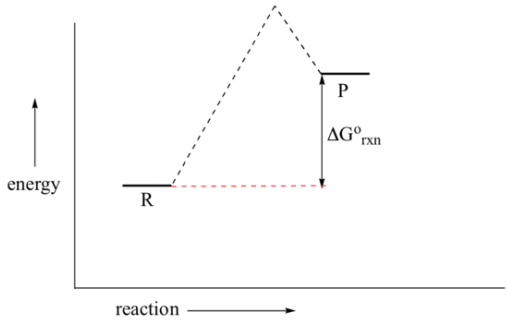
$$\Delta G^\circ = -RT \ln K_{eq}$$

where:

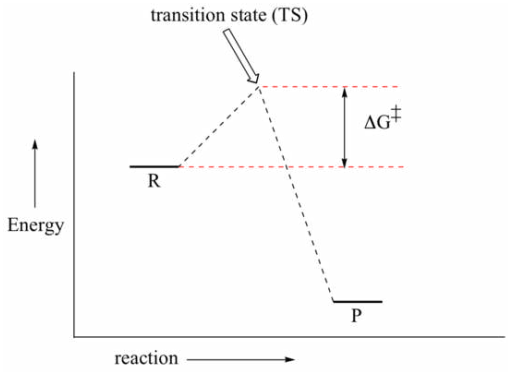
- K_{eq} = [product] / [reactant] at equilibrium
- R = 8.314 J×K^{-1}×mol^{-1} *or* 1.987 cal× K^{-1}×mol^{-1}
- T = temperature in Kelvin (K)

If you do the math, you see that a negative value for ΔG°_{rnx} (an exergonic reaction) corresponds - as it should by intuition - to K_{eq} being greater than 1, an equilibrium constant which favors product formation.

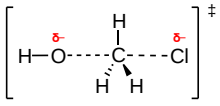
In a hypothetical endergonic (energy-absorbing) reaction the products would have a higher energy than reactants and thus ΔG°_{rnx} would be positive and K_{eq} would be less than 1, favoring reactants.



Now, let's move to kinetics. Look again at the energy diagram for exergonic reaction: although it is 'downhill' overall, it isn't a straight downhill run.



First, an 'energy barrier' must be overcome to get to the product side. The height of this energy barrier, you may recall, is called the '**activation energy'** ($\Delta G^\ddagger$). The activation energy is what determines the kinetics of a reaction: the higher the energy hill, the slower the reaction. At the very top of the energy barrier, the reaction is at its **transition state** (TS), which is the point at which the bonds are in the process of breaking and forming. The transition state is an '**activated complex'**: a transient and dynamic state that, unlike more stable species, does not have any definable lifetime. It may help to imagine a transition state as being analogous to the exact moment that a baseball is struck by a bat. Transition states are drawn with dotted lines representing bonds that are in the process of breaking or forming, and the drawing is often enclosed by brackets. Here is a picture of a likely transition state for a substitution reaction between hydroxide and chloromethane:



Note that this species is absent from the chemical equation (that is it is neither a reactant nor product)

$$CH_3Cl + HO^- \rightarrow CH_3OH + Cl^-$$

This reaction involves a collision between *two* molecules: for this reason, we say that it has **second order kinetics**. The **rate expression** for this type of reaction is:

$$\text{rate} = k[\text{reactant 1}][\text{reactant 2}]$$

... which tells us that the rate of the reaction depends on the **rate constant** k as well as on the concentration of *both* reactants. The rate constant can be determined experimentally by measuring the rate of the reaction with different starting reactant concentrations. The rate constant depends on the activation energy, of course, but also on temperature: a higher temperature means a higher *k* and a faster reaction, all else being equal. This should make intuitive sense: when there is more heat energy in the system, more of the reactant molecules are able to get over the energy barrier.

Here is one more interesting and useful expression. Consider a simple reaction where the reactants are A and B, and the product is AB (this is referred to as a **condensation reaction**, because two molecules are coming together, or condensing). If we know the rate constant k for the forward reaction and the rate constant $k_{reverse}$ for the reverse reaction (where AB splits apart into A and B), we can simply take the quotient to find our equilibrium constant K_{eq}:

$$A + B \rightleftharpoons AB$$

with

$$K_{eq} = \frac{[AB]}{[A][B]} = \frac{k_{\text{forward}}}{k_{\text{reverse}}}$$

This too should make some intuitive sense; if the forward rate constant is higher than the reverse rate constant, equilibrium should lie towards products.

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5.10: Describing a Reaction- Intermediates

Objectives

After completing this section, you should be able to

- explain the difference between a transition state and an intermediate.
- draw a reaction energy diagram for a given multistep process.
- interpret the reaction energy diagram of a multistep process (e.g., determine which of the steps is rate-determining).

Key Terms

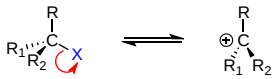
Make certain that you can define, and use in context, the key term below.

- reaction intermediate

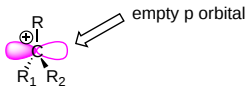
Study Notes

Each step in a multistep reaction has its own activation energy. The overall activation energy is the difference in energy between the reactants and the transition state of the slowest (rate-determining) step. The rate-determining step, that is, the one that controls the overall rate of reaction, is the step with the highest activation energy.

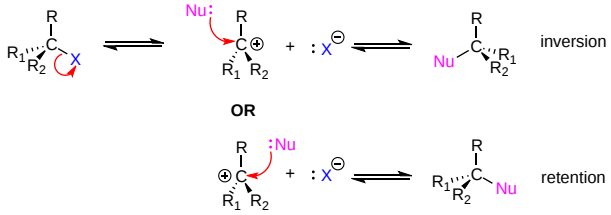
A second model for a nucleophilic substitution reaction is called the '**dissociative**', or '**S_N1**' mechanism: in this picture, the C-X bond breaks *first*, before the nucleophile approaches:



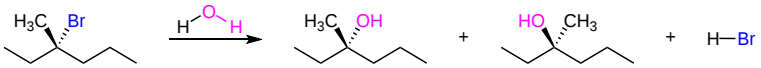
This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.



In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.



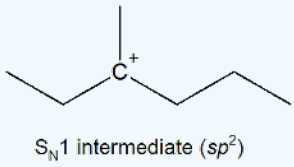
We saw that S_N2 reactions result specifically in inversion of stereochemistry at the electrophilic carbon center. What about the stereochemical outcome of S_N1 reactions? In the model S_N1 reaction shown above, the leaving group dissociates completely from the vicinity of the reaction before the nucleophile begins its attack. Because the leaving group is no longer in the picture, the nucleophile is free to attack from either side of the planar, sp^2-hybridized carbocation electrophile. This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, *racemization* has occurred at the carbon center. As an example, the tertiary alkyl bromide below would be expected to form a racemic mix of *R* and *S* alcohols after an S_N1 reaction with water as the incoming nucleophile.



Exercise 5.10.1

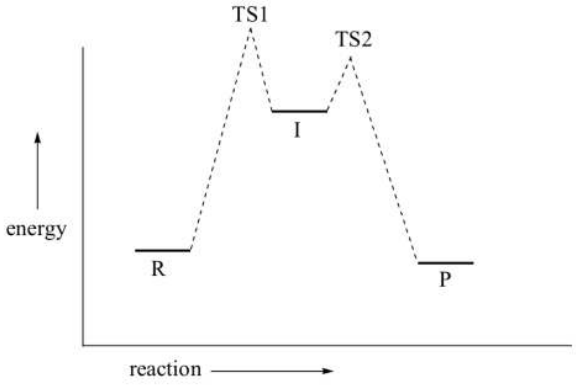
Draw the structure of the intermediate in the two-step nucleophilic substitution reaction above.

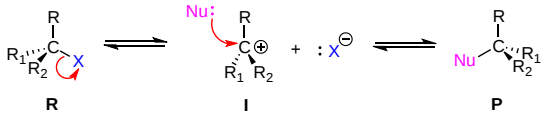
Answer



S_N1 intermediate (sp^2)

The S_N1 reaction we see an example of a **reaction intermediate**, a very important concept in the study of organic reaction mechanisms that was introduced earlier in the module on organic reactivity Recall that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discreet bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the S_N1 reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an S_N1 reaction shows that the carbocation **intermediate** can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states.

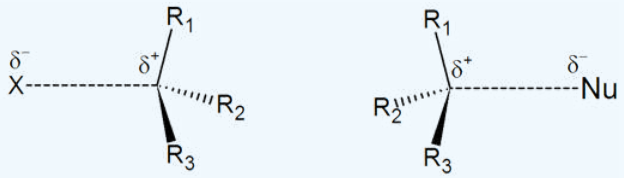




Exercise 5.10.2

Draw structures representing TS1 and TS2 in the reaction above. Use the solid/dash wedge convention to show three dimensions.

Answer

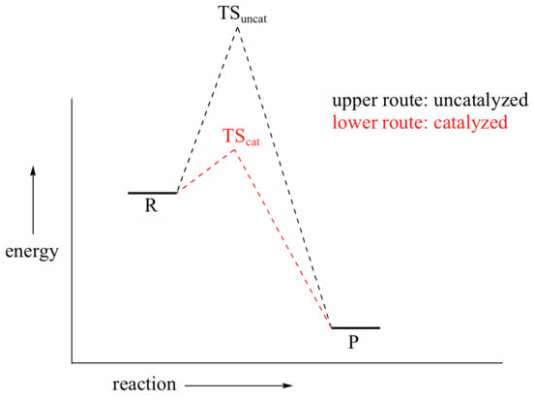


Recall that the first step of the reaction above, in which two charged species are formed from a neutral molecule, is much the slower of the two steps, and is therefore rate-determining. This is illustrated by the energy diagram, where the activation energy for

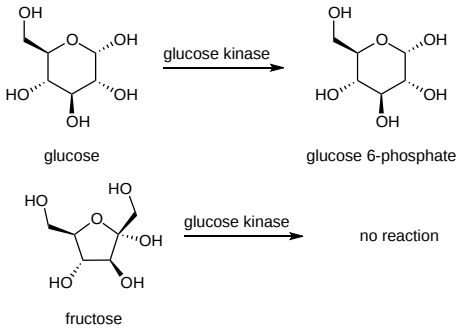
the first step is higher than that for the second step. Also recall that an S_N1 reaction has *first order* kinetics, because the rate determining step involves one molecule splitting apart, not two molecules colliding

We come now to the subject of catalysis. Our hypothetical bowl of sugar (from section 6.2) is still stubbornly refusing to turn into carbon dioxide and water, even though by doing so it would reach a much more stable energy state. There are, in fact, two ways that we could speed up the process so as to avoid waiting several millennia for the reaction to reach completion. We could supply enough energy, in the form of heat from a flame, to push some of the sugar molecules over the high energy hill. Heat would be released from the resulting exothermic reaction, and this energy would push more molecules over their energy hills, and so on - the sugar would literally burn up.

A second way to make the reaction go faster is to employ a **catalyst**. You probably already know that a catalyst is an agent that causes a chemical reaction to go faster by lowering its activation energy.



How might you catalyze the conversion of sugar to carbon dioxide and water? It's not too hard – just eat the sugar, and let your digestive enzymes go to work catalyzing the many biochemical reactions involved in breaking it down. Enzymes are proteins, and are very effective catalysts. 'Very effective' in this context means very specific, and very fast. Most enzymes are very selective with respect to reactant molecules: they have evolved over millions of years to catalyze their specific reactions. An enzyme that attaches a phosphate group to glucose, for example, will not do anything at all to fructose (the details of these reactions are discussed in section 10.2B).



Glucose kinase is able to find and recognize glucose out of all of the other molecules floating around in the 'chemical soup' of a cell. A different enzyme, fructokinase, specifically catalyzes the phosphorylation of fructose.

We have already learned (section 3.9) that enzymes are very specific in terms of the stereochemistry of the reactions that they catalyze . Enzymes are also highly **regiospecific**, acting at only one specific part of a molecule. Notice that in the glucose kinase reaction above only one of the alcohol groups is phosphorylated.

Finally, enzymes are capable of truly amazing rate acceleration. Typical enzymes will speed up a reaction by anywhere from a million to a billion times, and the most efficient enzyme currently known to scientists is believed to accelerate its reaction by a factor of about 10^{17} (see *Chemical and Engineering News*, March 13, 2000, p. 42 for an interesting discussion about this enzyme, orotidine monophosphate decarboxylase).

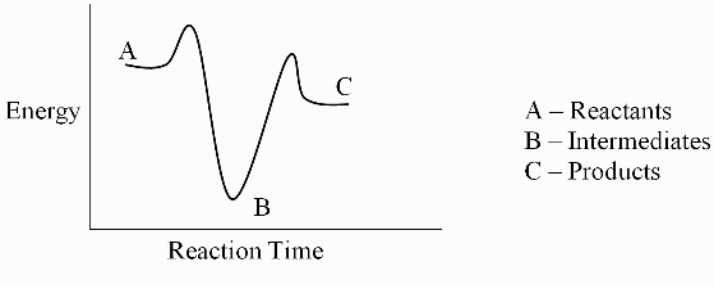
We will now begin an exploration of some of the basic ideas about how enzymes accomplish these amazing feats of catalysis, and these ideas will be revisited often throughout the rest of the text as we consider various examples of enzyme-catalyzed organic

reactions. But in order to begin to understand how enzymes work, we will first need to learn (or review, as the case may be) a little bit about protein structure.

Exercise 5.10.3

Draw an energy diagram with a exergonic first step and an endergonic second step. Label the diagram.

Answer



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5.11: A Comparison between Biological Reactions and Laboratory Reactions

Objectives

- No objectives have been identified for this section

Key Terms

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

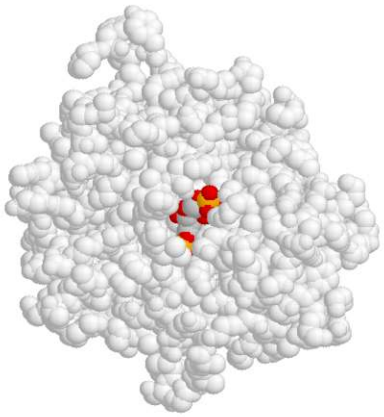
- enzyme

Study Notes

This section is a brief (but perhaps interesting) overview of some of the key differences between reactions performed in the lab and those in living systems. At this point, do not concern yourself with memorizing large biological molecules and reactions.

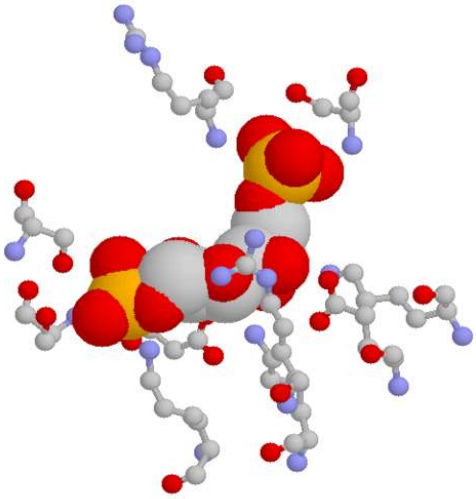
The Active Site

A critical element in the three-dimensional structure of any enzyme is the presence of an '**active site'**, which is a pocket, usually located in the interior of the protein, that serves as a docking point for the enzyme's **substrate**(s) ('substrate' is the term that biochemists use for a reactant molecule in an enzyme-catalyzed reaction). It is inside the active site pocket that enzymatic catalysis occurs. Shown below is an image of the glycolytic enzyme fructose-1,6-bisphosphate aldolase, with its substrate bound inside the active site pocket.

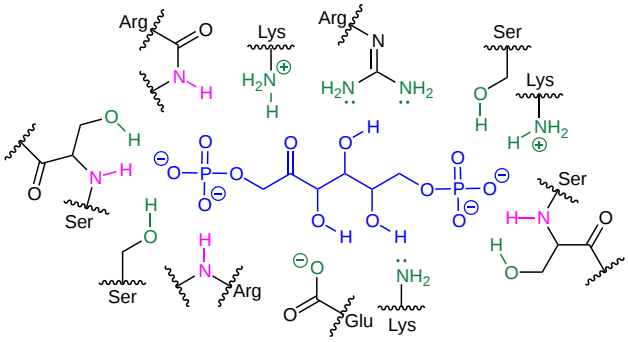


When the substrate binds to the active site, a large number of noncovalent interactions form with the amino acid residues that line the active site. The shape of the active site, and the enzyme-substrate interactions that form as a result of substrate binding, are *specific to the substrate-enzyme pair*: the active site has evolved to 'fit' one particular substrate and to catalyze one particular reaction. Other molecules do not fit in this active site nearly so well as fructose 1,6-bisphosphate.

Here are two close-up views of the same active site pocket, showing some of the specific hydrogen-bonding interactions between the substrate and active site amino acids. The first image below is a three-dimensional rendering directly from the crystal structure data. The substrate is shown in 'space-filling' style, while the active site amino acids are shown in the 'ball and stick' style. Hydrogens are not shown. The color scheme is grey for carbon, red for oxygen, blue for nitrogen, and orange for phosphorus.



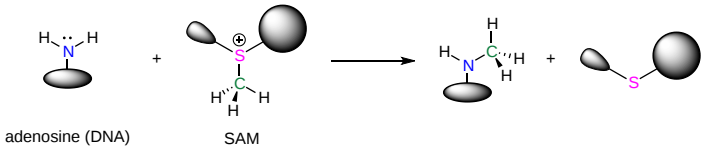
Below is a two-dimensional picture of the substrate (colored blue) surrounded by hydrogen-bonding active site amino acids. Notice that both main chain and side chain groups contribute to hydrogen bonding: in this figure, main chain H-bonding groups are colored purple, and side chain H-bonding groups are colored green.



Looking at the last three images should give you some appreciation for the specific manner in which a substrate fits inside its active site.

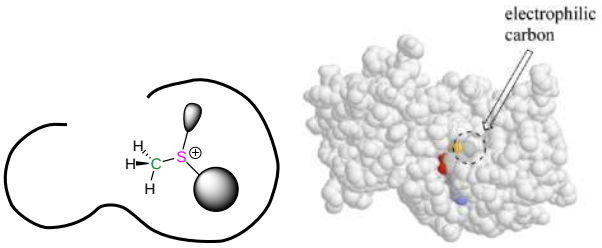
Transition State Stabilization

One of the most important ways that an enzyme catalyzes any given reaction is through entropy reduction: by bringing order to a disordered situation (remember that entropy is a component of Gibbs Free Energy, and thus a component of the activation energy). Let's turn again to our previous example (from section 6.1C) of a biochemical nucleophilic substitution reaction, the methylation of adenosine in DNA. The reaction is shown below with non-reactive sections of the molecules depicted by variously shaped 'bubbles' for the sake of simplicity.



In order for this reaction to occur, the two substrates (reactants) must come into contact in precisely the right way. If they are both floating around free in solution, the likelihood of this occurring is very small – the entropy of the system is simply too high. In other words, this reaction takes place *very* slowly without the help of a catalyst.

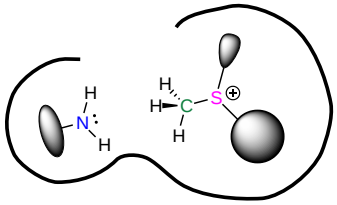
Here's where the enzyme's active site pocket comes into play. It is lined with various functional groups from the amino acid main and side chains, and has a very specific three-dimensional architecture that has evolved to bind to both of the substrates. If the SAM molecule, for example, diffuses into the active site, it can replace its (favorable) interactions with the surrounding water molecules with (even more favorable) new interactions with the functional groups lining the active site.



Depiction of SAM bound in active site of enzyme

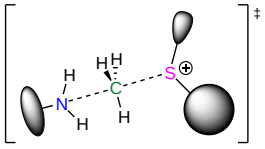
In a sense, SAM is moving from one solvent (water) to another 'solvent' (the active site), where many new energetically favorable interactions are possible. Remember: these new contacts between SAM and the active site groups are *highly specific* to SAM and SAM alone – no other molecule can 'fit' so well in this precise active site environment, and thus no other molecule will be likely to give up its contacts to water and bind to the active site.

The second substrate also has a specific spot reserved in the active site. (Because in this case the second substrate is a small segment of a long DNA molecule, the DNA-binding region of the active site is more of a 'groove' than a 'pocket').



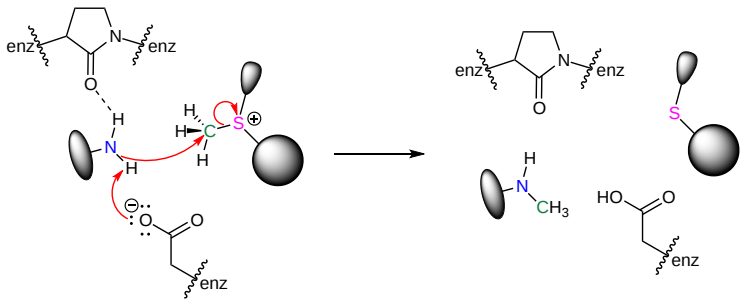
So now we have both substrates bound in the active site. But they are not just bound in any random orientation – they are specifically positioned relative to one another so that the nucleophilic nitrogen is held very close to the electrophilic carbon, with a free path of attack. What used to be a very disordered situation – two reactants diffusing freely in solution – is now a very highly ordered situation, with everything set up for the reaction to proceed. This is what is meant by entropy reduction: the entropic component of the energy barrier has been lowered.

Looking a bit deeper, though, it is not really the noncovalent interaction between enzyme and *substrate* that are responsible for catalysis. Remember: all catalysts, enzymes included, accelerate reactions by lowering the energy of the *transition state*. With this in mind, it should make sense that the primary job of an enzyme is to maximize favorable interactions with the transition state, *not* with the starting substrates. This does not imply that enzyme-substrate interactions are not strong, rather that enzyme-TS interactions are far *stronger*, often by several orders of magnitude. Think about it this way: if an enzyme were to bind to (and stabilize) its substrate(s) more tightly than it bound to (and stabilized) the transition state, it would actually *slow down* the reaction, because it would be *increasing* the energy difference between starting state and transition state. ***The enzyme has evolved to maximize favorable noncovalent interactions to the transition state***: in our example, this is the state in which the nucleophilic nitrogen is already beginning to attack the electrophilic carbon, and the carbon-sulfur bond has already begun to break.

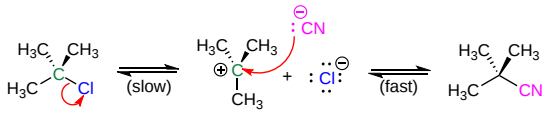


enzyme binds best to
the transition state

In many enzymatic reactions, certain active site amino acid residues contribute to catalysis by *increasing the reactivity of the substrates*. Often, the catalytic role is that of acid and/or base. In our DNA methylation example, the nucleophilic nitrogen is deprotonated by a nearby aspartate side chain as it begins its nucleophilic attack on the methyl group of SAM. We will study nucleophilicity in greater detail in chapter 8, but it should make intuitive sense that deprotonating the amine increases the electron density of the nitrogen, making it *more nucleophilic*. Notice also in the figure below that the main chain carbonyl of an active site proline forms a hydrogen bond with the amine, which also has the effect of increasing the nitrogen's electron density and thus its nucleophilicity (*Nucleic Acids Res.* **2000**, *28*, 3950).

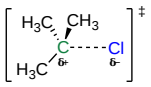


How does our picture of enzyme catalysis apply to multi-step reaction mechanisms? Although the two-step nucleophilic substitution reaction between 2-chloro-2-methylpropane and the cyanide anion is not a biologically relevant process, let's pretend just for the sake of illustration that there is a hypothetical enzyme that catalyzes this reaction.

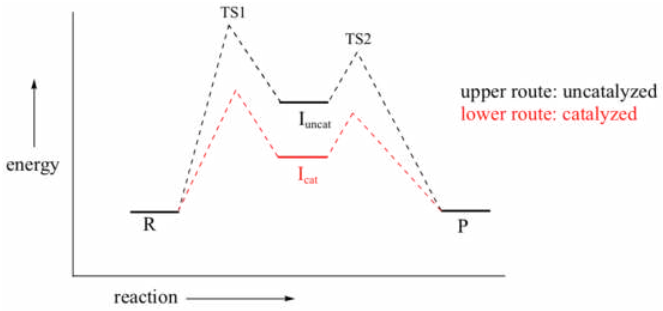


The same basic principles apply here: the enzyme binds best to the transition state. But therein lies the problem: there are two transition states! To which TS does the enzyme maximize its contacts?

Recall that the first step – the loss of the chloride leaving group to form the carbocation intermediate – is the slower, rate-limiting step. It is this step that our hypothetical enzyme needs to accelerate if it wants to accelerate the overall reaction, and it is thus the energy of TS1 that needs to be lowered.



By Hammond's postulate, we also know that the intermediate I is a close approximation of TS1. So the enzyme, by stabilizing the intermediate, will also stabilize TS1 (as well as TS2) and thereby accelerate the reaction.



If you read scientific papers about enzyme mechanisms, you will often see researchers discussing how an enzyme stabilizes a reaction intermediate. By virtue of Hammond's postulate, they are, at the same time, talking about how the enzyme lowers the energy of the transition state.

An additional note: although we have in this section been referring to SAM as a 'substrate' of the DNA methylation reaction, it is also often referred to as a **coenzyme**, or **cofactor**. These terms are used to describe small (relative to protein and DNA) biological organic molecules that bind specifically in the active site of an enzyme and help the enzyme to do its job. In the case of SAM, the job is methyl group donation. In addition to SAM, we will see many other examples of coenzymes in the coming chapters, a number of which - like ATP (adenosine triphosphate), coenzyme A, thiamine, and flavin - you have probably heard of before. The full structures of some common coenzymes are shown in table 6 in the tables section.

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5.12: Chapter Objectives

Organic reactions form the backbone of organic chemistry, defining how molecules interact and transform into new compounds. These reactions involve the breaking and formation of chemical bonds between carbon atoms and other elements, leading to the synthesis of complex molecules with diverse functionalities. Understanding organic reactions is essential for designing synthetic pathways, predicting chemical behavior, and elucidating the mechanisms underlying biological processes. An overview of some key categories of organic reactions include:

1. **Substitution Reactions**: In substitution reactions, one functional group in a molecule is replaced by another. This can occur through either nucleophilic or electrophilic substitution mechanisms. Examples include S_N1 (nucleophilic substitution, unimolecular), S_N2 (nucleophilic substitution, bimolecular), and electrophilic aromatic substitution.
2. **Addition Reactions**: Addition reactions involve the addition of atoms or groups to carbon-carbon multiple bonds (such as alkenes or alkynes). Examples include hydration (addition of water), hydrogenation (addition of hydrogen), and halogenation (addition of halogens).
3. **Elimination Reactions**: In elimination reactions, a molecule loses atoms or functional groups to form a double or triple bond. Common examples include dehydration (loss of water), dehydrohalogenation (loss of a hydrogen halide), and beta-elimination reactions.
4. **Oxidation-Reduction (Redox) Reactions**: Redox reactions involve the transfer of electrons between reactants. Oxidation involves the loss of electrons, while reduction involves the gain of electrons. Organic redox reactions often involve the conversion of functional groups, such as alcohols to ketones/aldehydes or alkenes to diols.
5. **Acid-Base Reactions**: Acid-base reactions involve the transfer of a proton (H+) from an acid to a base. In organic chemistry, this can occur between molecules containing acidic or basic functional groups, such as carboxylic acids and amines.
6. **Condensation Reactions**: Condensation reactions involve the combination of two molecules with the loss of a small molecule, often water. Examples include esterification (formation of esters from carboxylic acids and alcohols) and peptide bond formation (condensation of amino acids to form peptides and proteins).
7. **Functional Group Transformation Reactions**: These reactions involve the conversion of one functional group into another through a series of chemical steps. Examples include hydrolysis (cleavage of esters, amides, etc., by water), reduction of carbonyl compounds to alcohols, and Grignard reactions (formation of carbon-carbon bonds).

Organic reactions can be classified based on various criteria, including reaction mechanism, types of reactants and products, and the nature of the functional groups involved. Mastery of organic reactions is essential for synthetic chemists, medicinal chemists, and biochemists alike, enabling the design and manipulation of molecules for a wide range of applications in industry, medicine, and materials science.

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5.S: An Overview of Organic Reactions (Summary)

Concepts & Vocabulary

6.1: Kinds of Organic Reactions

- **Addition** reactions increase the number of sigma bonds in a molecule.
- **Elimination** reactions reduce the number of sigma bonds in a molecule.
- **Substitution** reactions incorporate replacement of an atom or group with another.
- **Rearrangement** reactions cause a molecule to be converted to a constitutional isomer without gaining or losing any atoms.

6.2: How Organic Reactions Occur: Mechanisms

- A reaction **mechanism** describes movement of electrons by using curved arrows to show bonds that are breaking and forming.
- **Homolysis** occurs when a bond breaks with each atom keeping one electron.
- **Heterolysis** occurs when a bond breaks and both electrons remain with one of the atoms.
- Some reactions occur in more than one step with a **reactive intermediate** formed briefly on the way to the new product.
- **Reactive intermediates** can be charged species such as carbocations and carbanions or uncharged species such as **radicals**.
- In organic chemistry Lewis acids are more often referred to as **electrophiles**, having an affinity for an electron pair.
- In organic chemistry Lewis bases are more often referred to as **nucleophiles**, having an electron pair that is available to bond to an **electrophile**.
- **Ionic** reactions involve charged species.
- **Polar** reactions involve bonds with unequally shared electrons.

6.3: Radical Reactions

- **Radical chain reactions** have three distinct phases: initiation, propagation and termination.
  - Initiation causes radicals to be created from non-radical species.
  - During the Propagation phase, radicals react with stable molecules to form new radicals.
  - Termination occurs when two radicals react together to form a stable molecule.

6.4: Polar Reactions

- Carbon when bonded to a halogen, oxygen, nitrogen, sulfur, or metal has a partial positive charge. This allows these carbons to react with many **nucleophiles**.
- For carbonyl groups bond polarity is reinforced by resonance making the carbon even more positive than in other molecules. This makes carbonyl groups prone to addition and substitution reactions with **nucleophiles**.
- **Nucleophiles** have electron rich atoms that are able to donate a pair of electrons.
- In nucleophilic substitution reactions, the **electrophile** is typically carbon bonded to a more electronegative atom.

6.5: An Example of a Polar Reaction: Addition of HBr to Ethylene

- Alkene addition reaction with HBr occurs through the pi bond reacting as a nucleophile and abstracting a proton from the acid. This creates a carbocation intermediate which reacts with the bromide ion to form the final product.
- Reaction rates for this alkene addition reaction increase with larger halogens and more substituted alkenes.
- Markovnikov's Rule states that addition reactions of unsymmetrical alkenes yield the more substituted product.

6.6: Using Curved Arrows in Polar Reaction Mechanisms

- Curved arrows in mechanism drawings always represent electrons moving, starting at either a bond or lone pair of electrons.
- Electrons flow from electron rich to electron poor.

6.7: Describing a Reaction: Equilibria, Rates, and Energy Changes

- **Exergonic reactions** have a negative free energy meaning they are thermodynamically favorable and give off energy.
- **Endergonic reactions** have a positive free energy and require energy from the surroundings to occur.

6.8: Describing a Reaction: Bond Dissociation Energies

- **Bond dissociation energy** for a molecule is the difference in enthalpy of formation (**homolytic**) for the products and reactants.
- **Bond dissociation energies** are independent of path of reaction, so they do not give direct information on mechanisms. However, they can be used to evaluate the results of individual steps of a mechanism.

- **Bond dissociation energies** show that sigma bonds formed with sp hybridized carbon are stronger than sp^2 which are stronger than bonds formed with sp^3 carbons.
- **Bond dissociation energies** show that carbon-hydrogen bonds on primary carbons are stronger than secondary, which are stronger than tertiary.

6.9: Describing a Reaction: Energy Diagrams and Transition States

- **Reaction coordinate** diagrams are a special type of energy diagram that has the reaction coordinate (or reaction progress) on the x-axis.
- **Thermodynamics** of a reaction is conveyed on a reaction coordinate diagram by the difference in energy between the reactants and products.
- **Activation energy** is the energy barrier to a reaction occurring.
- A **transition state** is the highest energy point during the process of bonds forming and breaking in a reaction step.
- **Kinetics** of a reaction is conveyed on a **reaction coordinate** diagram by the difference in energy between the reactants and transition state.
- A r**ate expression** relates rate to the **rate constant** and concentration of reactants.

6.10: Describing a Reaction: Intermediates

- A **reaction intermediate** is a short-lived species that goes on to react in a subsequent reaction step.
- **Reaction intermediates** appear as a local minimum (or valley) on a reaction coordinate diagram.
- **Catalysts** cause reaction rates to increase by lowing activation energy.

6.11: A Comparison between Biological Reactions and Laboratory Reactions

- An enzyme **active site** is the location where the enzyme interacts with its **substrate** and where **catalysis** occurs.
- **Substrates** are reactant molecules in enzymatic reactions.

Skills to Master

- Skill 6.1 Identify organic reactions by type (addition, elimination, substitution, rearrangement).
- Skill 6.2 Draw homolytic and heterolytic bond breaking as part of reaction mechanisms.
- Skill 6.3 Identify radical and ionic reactions.
- Skill 6.4 Identify and write out steps in a typical radical substitution reaction (initiation, propagation, termination).
- Skill 6.5 Identify polarity of bonds in organic molecules.
- Skill 6.6 Use curved arrows to indicate movement of electrons in resonance and reaction mechanisms.
- Skill 6.7 Predict whether a chemical species will act as an electrophile or nucleophile.
- Skill 6.8 Write an equilibrium expression for a reaction.
- Skill 6.9 Determine the direction of a reaction based on the equilibrium constant.
- Skill 6.10 Explain how rate and equilibrium are related to ΔG^o and K_{eq}.
- Skill 6.11 Calculate bond dissociation energy given enthalpies of formation for reactants and products.
- Skill 6.12 Describe order of bond strength based on bond dissociation energy.
- Skill 6.13 Explain activation energy, kinetics, thermodynamics and transition states based on energy diagrams (reaction coordinate diagrams).
- Skill 6.14 Predict possible transition state structures for single reaction steps.
- Skill 6.15 Differentiate between transition states and intermediates.
- Skill 6.16 Draw a reaction coordinate diagram for a given multi-step process.
- Skill 6.17 Interpret a reaction coordinate diagram for a multi-step process.
- Skill 6.18 Briefly explain how enzymes catalyze reactions.

Memorization Tasks

MT 6.1 Memorize that arrows in reaction mechanisms always define movement of electrons.

MT 6.2 Memorize the relative electronegativities of common atoms (necessary for determining polarity of bonds).

MT 6.3 Memorize the equations that relate equilibrium, free energy, enthalpy and entropy.

$\Delta G^o = -RT\ln K$

$$\Delta G^{o} = \Delta H^{o} - T\Delta S^{o}$$

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CHAPTER OVERVIEW

6: Biomolecules- Carbohydrates

This chapter is designed to provide you with an overview of the biologically important group of compounds known as carbohydrates. Many of the compounds you will encounter while studying this chapter may appear to have very complex structures, but much of their chemistry can be readily understood in terms of the concepts and reactions discussed in earlier chapters of the course.

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.

6.1: Introduction
6.2: Classification of Carbohydrates
6.3: Depicting Carbohydrate Stereochemistry - Fischer Projections
6.4: D, L Sugars
6.5: Configurations of Aldoses
6.6: Cyclic Structures of Monosaccharides- Anomers
6.7: Reactions of Monosaccharides
6.8: The Eight Essential Monosaccharides
6.9: Disaccharides
6.10: Polysaccharides and Their Synthesis
6.11: Other Important Carbohydrates
6.12: Cell-Surface Carbohydrates and Influenza Viruses
6.S: Biomolecules- Carbohydrates (Summary)

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6.1: 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.

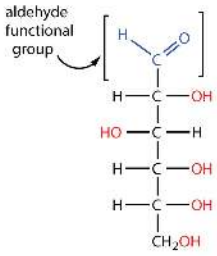
Key Terms

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

- carbohydrate

Introduction

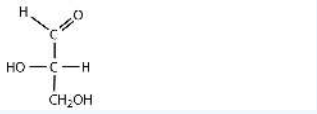
All carbohydrates consist of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes or ketones or are compounds that can be broken down to form such compounds. Examples of carbohydrates include starch, fiber, the sweet-tasting compounds called sugars, and structural materials such as cellulose. 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 $C_6 \cdot 6H_2O$.

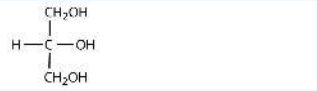
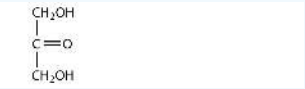
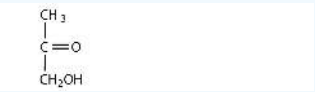


Because glucose has an aldehyde functional group and several –OH (hydroxyl) groups, it is described as a polyhydroxy aldehyde.

Example 1

Which compounds would be classified as carbohydrates?

a. 

- 
- 
- 

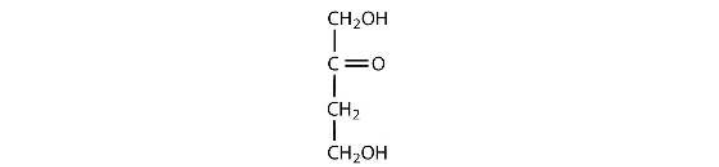
Solution

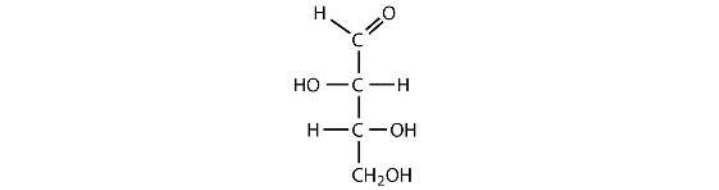
a. This is a carbohydrate because the molecule contains an aldehyde functional group with OH groups on the other two carbon atoms.
b. This is not a carbohydrate because the molecule does not contain an aldehyde or a ketone functional group.
c. This is a carbohydrate because the molecule contains a ketone functional group with OH groups on the other two carbon atoms.

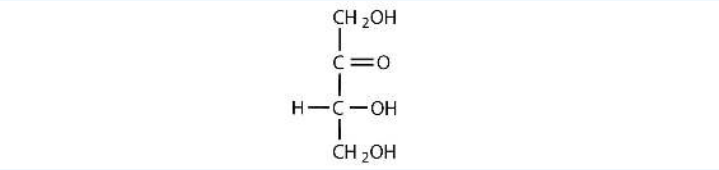
d. This is not a carbohydrate; although it has a ketone functional group, one of the other carbons atoms does not have an OH group attached.

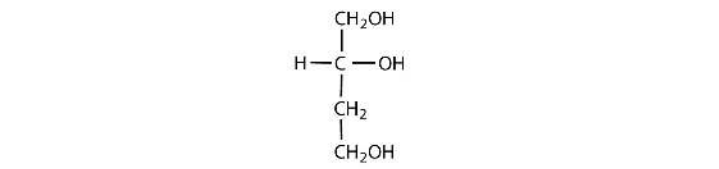
? Exercise 1

Which compounds would be classified as carbohydrates?

1. 

- 

- 

- 

Green plants are capable of synthesizing glucose ($C_6H_{12}O_6$) from carbon dioxide (CO_2) and water (H_2O) by using solar energy in the process known as photosynthesis:

$$6\,CO_2 + 6\,H_2O + 2870\,kJ \longrightarrow C_6H_{12}O_6 + 6\,O_2$$

(The 2870 kJ comes from solar energy.) Plants can use the glucose for energy or convert it to larger carbohydrates, such as starch or cellulose. Starch provides energy for later use, perhaps as nourishment for a plant's seeds, while cellulose is the structural material of plants. We can gather and eat the parts of a plant that store energy—seeds, roots, tubers, and fruits—and use some of that energy ourselves. Carbohydrates are also needed for the synthesis of nucleic acids and many proteins and lipids.

Animals, including humans, cannot synthesize carbohydrates from carbon dioxide and water and are therefore dependent on the plant kingdom to provide these vital compounds. We use carbohydrates not only for food (about 60%–65% by mass of the average diet) but also for clothing (cotton, linen, rayon), shelter (wood), fuel (wood), and paper (wood).

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6.2: 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 key terms below.

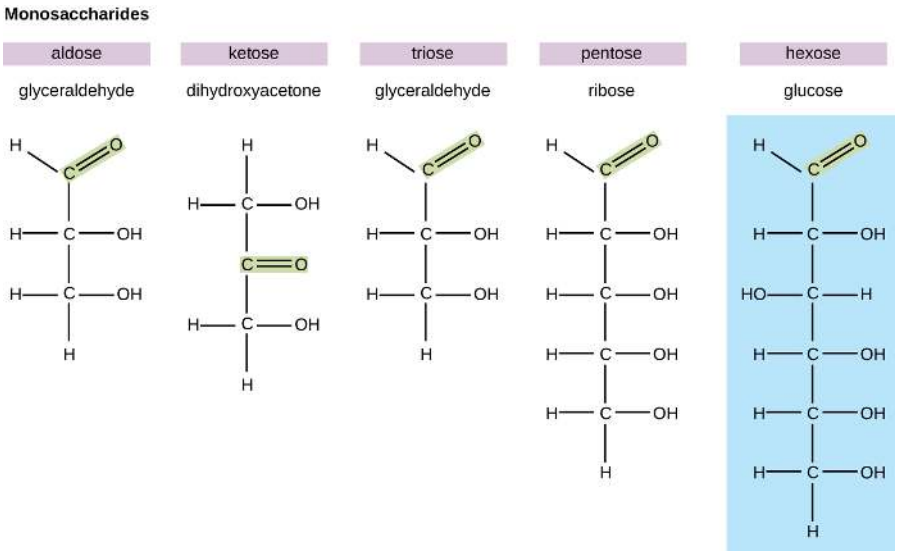
- aldose
- disaccharide
- ketose
- monosaccharide (simple sugar)
- polysaccharide

What Are Carbohydrates?

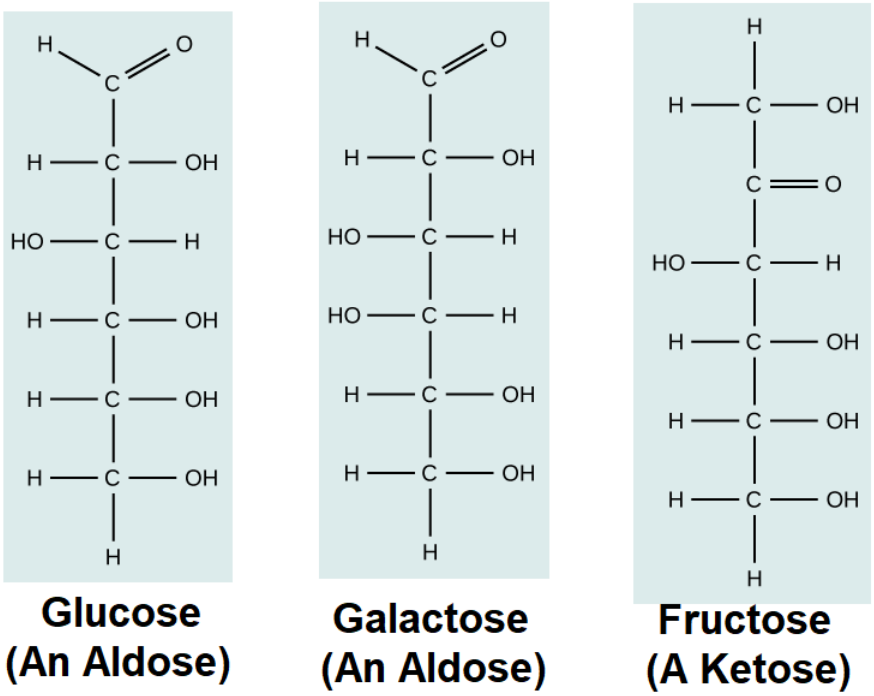
The most abundant biomolecules on earth are carbohydrates. From a chemical viewpoint, carbohydrates are primarily a combination of carbon and water, and many of them have the empirical formula $(CH_2O)_n$, where *n* is the number of repeated units. This view represents these molecules simply as "hydrated" 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: $C_6H_{12}O_6$.



Complex Carbohydrates

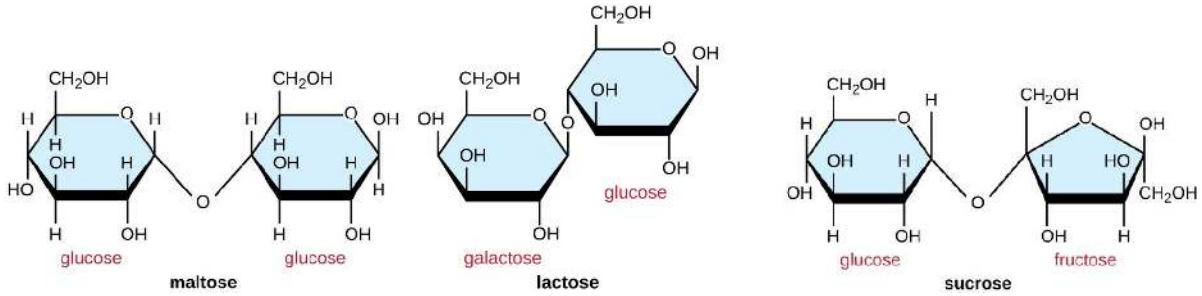
The simple sugars form the foundation of more complex carbohydrates. The cyclic forms of two sugars can be linked together by means of a condensation reaction to form a disaccharide. Multiple sugars can be linked to form polysaccharides.

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.

$$\text{monosaccharide—OH} + \text{HO—monosaccharide} \longrightarrow \underbrace{\text{monosaccharide—O—monosaccharide}}_{\text{disaccharide}}$$

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.

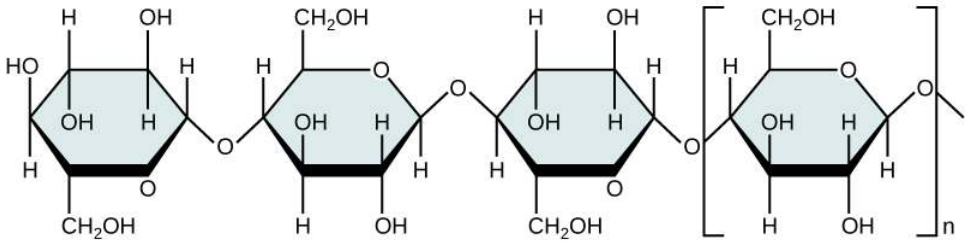


Polysaccharides

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.

Cellulose structure



Summary

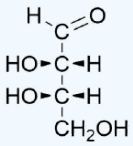
Complexity		**Simple Carbohydrates** monosaccharides		**Complex Carbohydrates** disaccharides, oligosaccharides & polysaccharides	
Size	**Tetrose** C_4 sugars	**Pentose** C_5 sugars	**Hexose** C_6 sugars	**Heptose** C_7 sugars	etc.

C=O Function	**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.

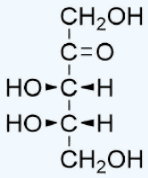
Exercise 6.2.1

1) Classify each of the following sugars.

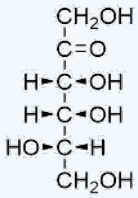
a)



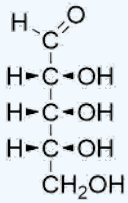
b)



c)



d)



Answer

a. Aldoterose
b. Ketopentose
c. Ketohexose
d. Aldopentose

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6.3: 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.

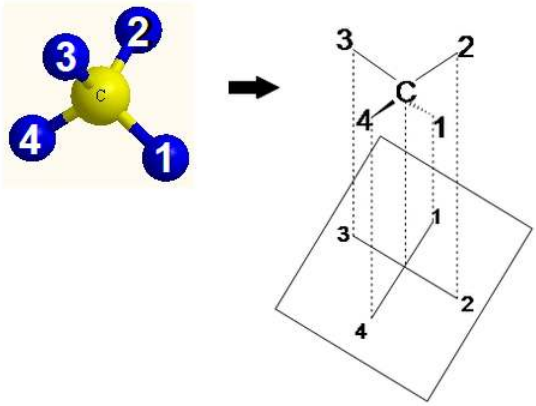
- Fischer projection

Study Notes

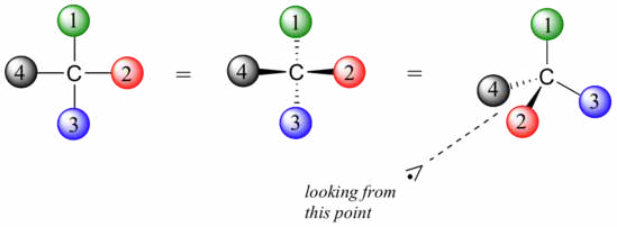
When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often 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

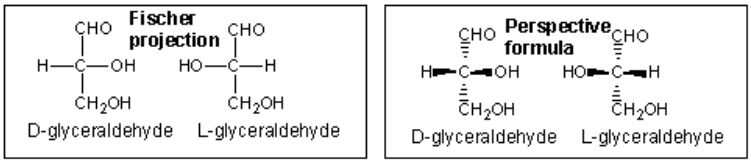
The problem of drawing three-dimensional configurations on a two-dimensional surface, such as a piece of paper, has been a long-standing concern of chemists. The wedge and dash notations we have been using are effective, but can be troublesome when applied to compounds having many chiral centers. As 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.



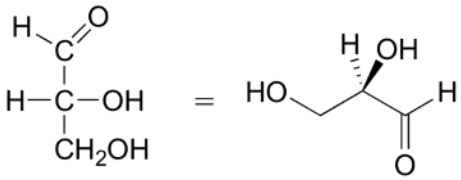
Fisher projections show sugars in their open chain form. In a Fischer projection, the carbon atoms of a sugar molecule are connected vertically by solid lines, while carbon-oxygen and carbon-hydrogen bonds are shown horizontally. Stereochemical information is conveyed by a simple rule: vertical bonds point into the plane of the page, while horizontal bonds point out of the page.



Sugars can be drawn in the straight chain form as either Fisher projections or perspective structural formulas. When drawing Fischer projections, the aldehyde group is written at the top, and the H and OH groups that are attached to each chiral carbon are written to the right or left. The arrangement of the atoms distinguishes one stereoisomer from the other.

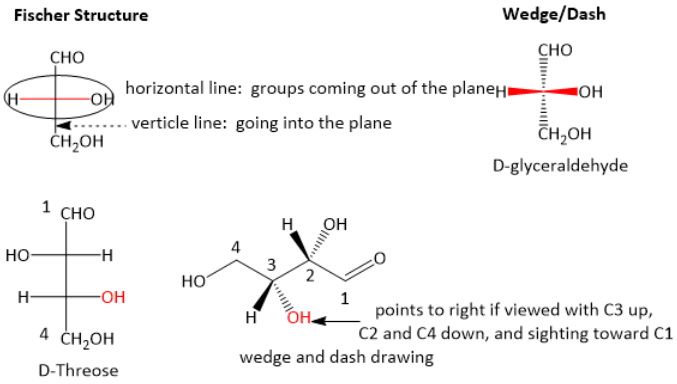


Below are two different representations of (R)-glyceraldehyde, the smallest sugar molecule (also called D-glyceraldehyde in the stereochemical nomenclature used for sugars):

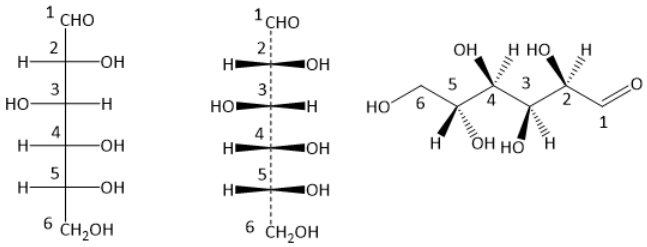


(R)-glyceraldehyde
(D-glyceraldehyde)

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 and D-glucose.

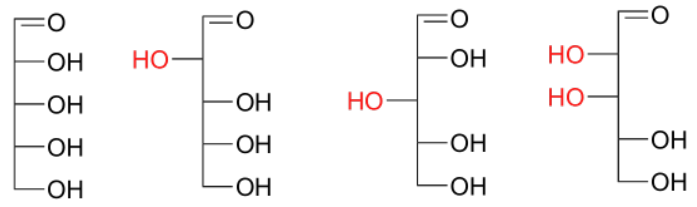


Below are three representations of the open chain form of D-glucose: in the conventional Fischer projection, a wedge/dash version of a Fischer projection, and finally in the 'zigzag' style that is preferred by many organic chemists.



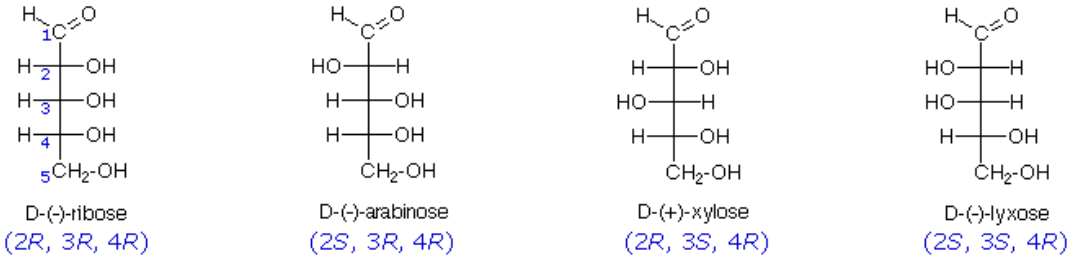
D-Glucose

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.



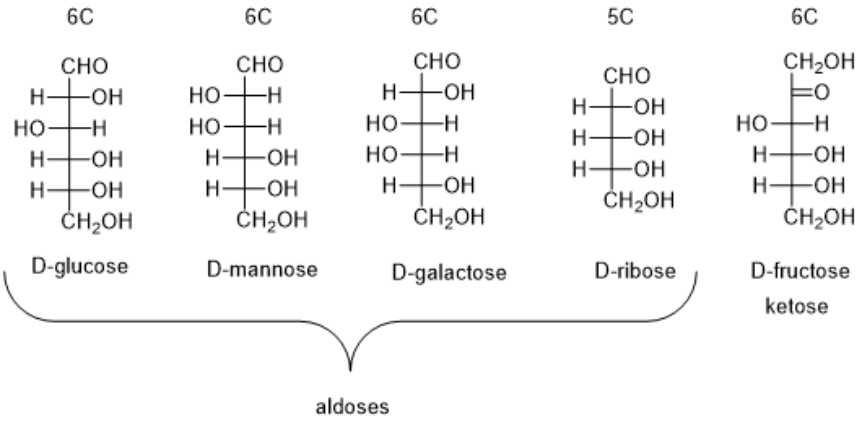
The usefulness of this notation to Fischer, in his carbohydrate studies, is evident in the following diagram. There are eight stereoisomers of 2,3,4,5-tetrahydroxypentanal, a group of compounds referred to as the aldopentoses (aldo- since the oxidized carbon is an aldehyde and -pentose since the molecules 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



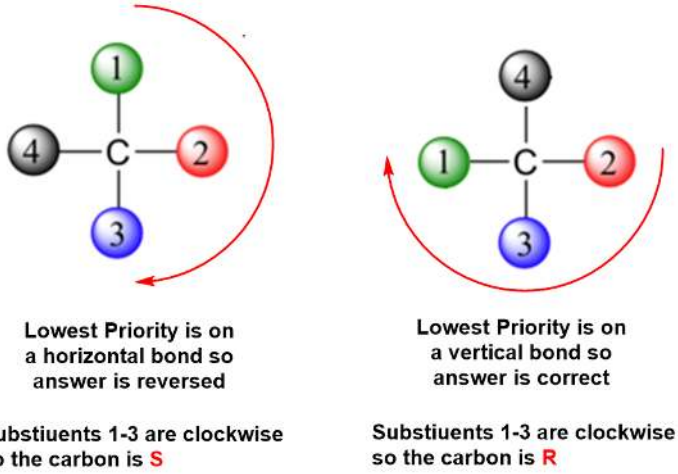
The aldopentose structures drawn above are all diastereomers. A more selective term, **epimer**, is used to designate diastereomers that differ in configuration at only one chiral center. Thus, ribose and arabinose are epimers at C-2, and arabinose and lyxose are epimers at C-3. However, arabinose and xylose are not epimers, since their configurations differ at both C-2 and C-3.

The Fisher structures of the most common monosaccharides (other than glyceraldehyde and dihydroxyacetone), which you will encounter most frequently are shown below.



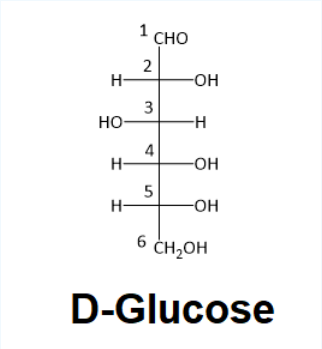
Determining R and S in Fischer Projections

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.



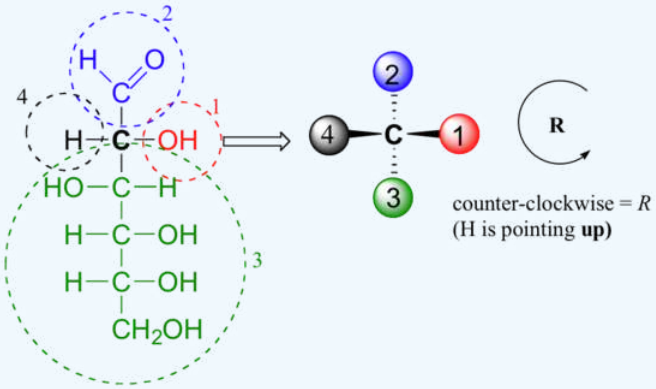
Worked Example 6.3.1

Determine if carbon #2 in D-glucose is R or S.



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.



How to make Fischer Projections

To make a Fischer Projection, it is easier to show through examples than through words. Lets start with the first example, turning a 3D structure of ethane into a 2D Fischer Projection.

Exercise 6.3.1

Start by mentally converting a 3D structure into a Dashed-Wedged Line Structure. Remember, the atoms that are pointed toward the viewer would be designated with a wedged lines and the ones pointed away from the viewer are designated with dashed lines.

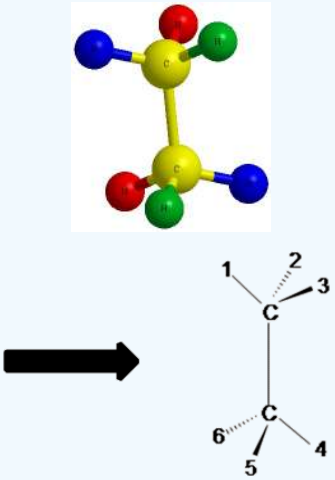


Figure B

Notice the red balls (atoms) in Figure A above are pointed away from the screen. These atoms will be designated with dashed lines like those in Figure B by number 2 and 6. The green balls (atoms) are pointed toward the screen. These atoms will be designated with wedged lines like those in Figure B by number 3 and 5. The blue atoms are in the plane of the screen so they are designated with straight lines.

Now that we have our Dashed- Wedged Line Structure, we can convert it to a Fischer Projection. However, before we can convert this Dashed-Wedged Line Structure into a Fischer Projection, we must first convert it to a "flat" Dashed-Wedged Line Structure. Then from there we can draw our Fischer Projection. Lets start with a more simpler example. Instead of using the ethane shown in Figure A and B, we will start with a methane. The reason being is that it allows us to only focus on one central carbon, which make things a little bit easier.

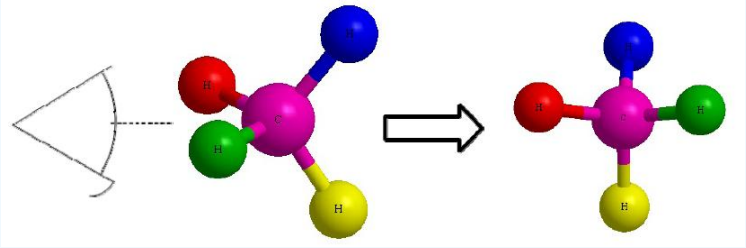
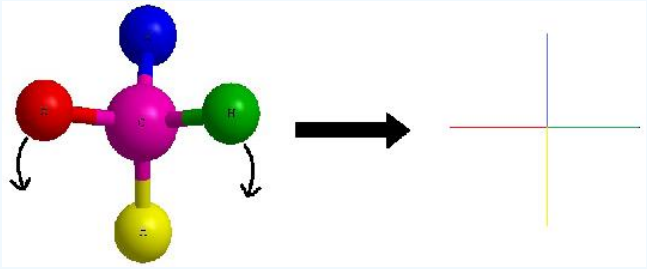


Figure D

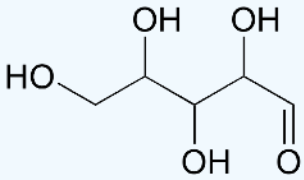
Lets start with this 3D image and work our way to a dashed-wedged image. Start by imagining yourself looking directly at the central carbon from the left side as shown in Figure C. It should look something like Figure D. Now take this Figure D and flatten it out on the surface of the paper and you should get an image of a cross.



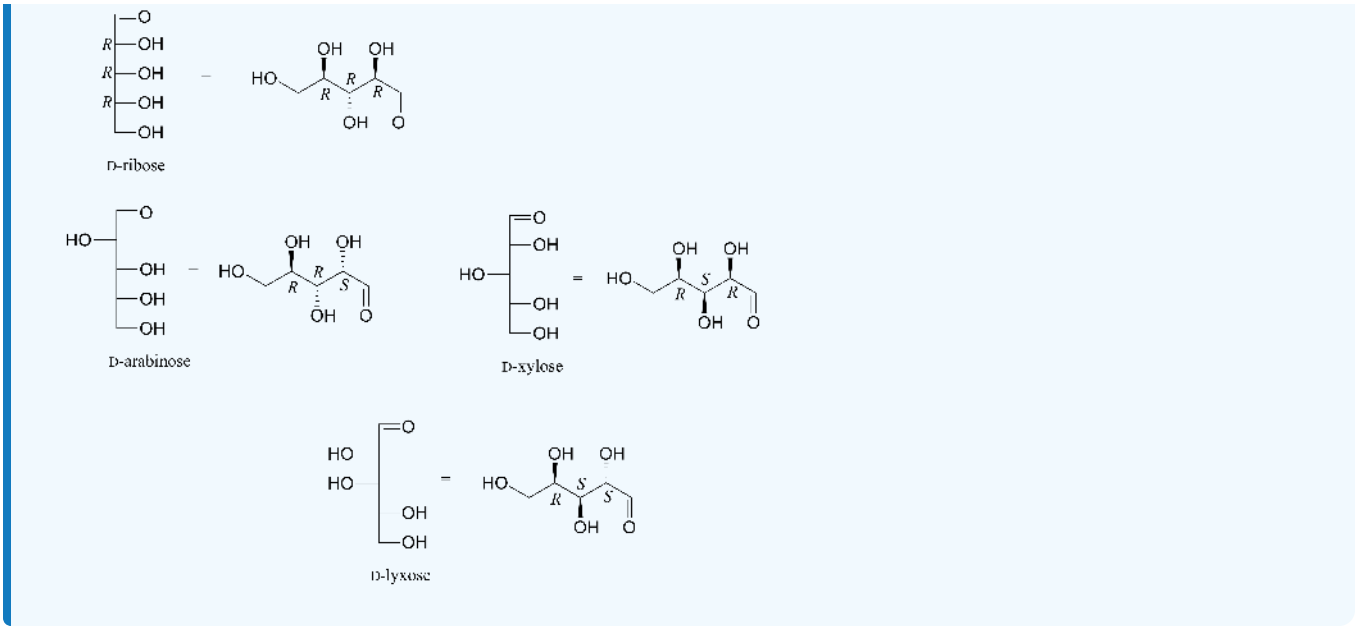
As a reminder, the horizontal line represents atoms that are coming out of the paper and the vertical line represents atoms that are going into the paper. The cross image to the right of the arrow is a Fischer projection.

? Exercise 6.3.1

Draw 'zigzag' structures (using the solid/dash wedge convention to show stereochemistry) for the four sugars in the figure below. Label all stereocenters *R* or *S*.



Answer



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6.4: 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.

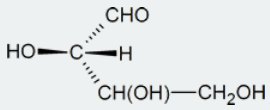
- D sugar
- L sugar

Study Notes

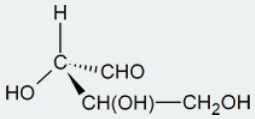
If you find that you have forgotten the meanings of terms such as dextrorotatory and polarimeter, refer back to Section 5.3 in which the fundamentals of optical activity were introduced.

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?

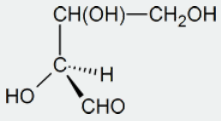
One approach is to focus on the carbon atom of interest and sketch a three-dimensional representation of the configuration around that atom, remembering the convention used in Fischer projections: vertical lines represent bonds going into the page, and horizontal lines represent bonds coming out of the 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.

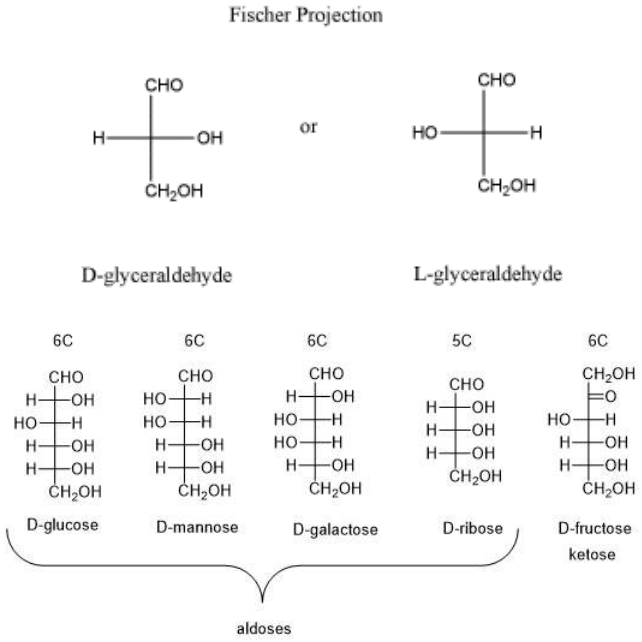


The Cahn-Ingold-Prelog order of priority for the three remaining groups is OH > CHO > $CH(OH)CH_2OH$; thus, we see that we could trace out a counterclockwise path going from the highest-priority group to the second- and third-highest, and we

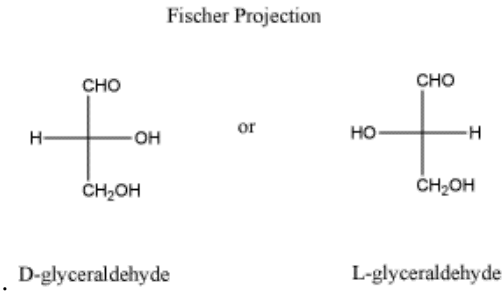
conclude that the central carbon atom has an *S* configuration.

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.



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 arrangement around all of the chiral centers (horizontal lines) in the Fischer project of D-glucose need to be opposite to make L-glucose.



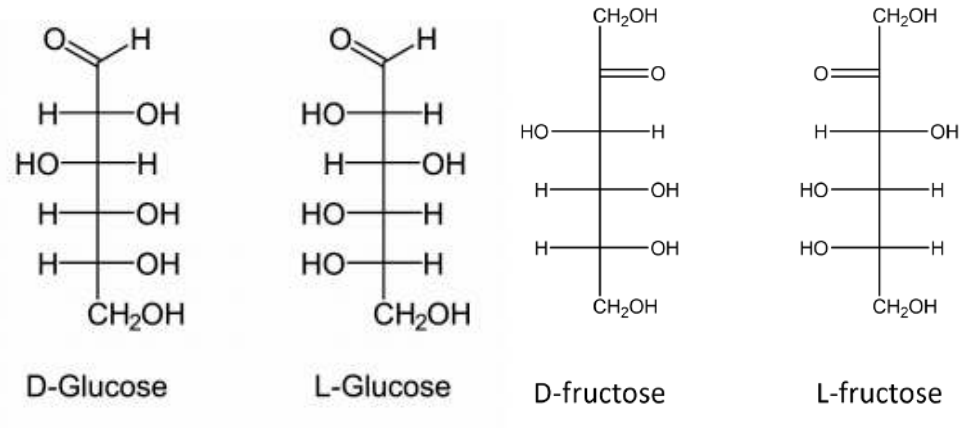


Figure 6. Fischer projections of enantiomers of glucose (left) and fructose (right).

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 6.4.1

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)

Answer

a) From top to bottom, 2R, 3R, and it is a D sugar.

b) From top to bottom, 2S, 3R, 4S, and it is an L sugar.

c) From to to bottom, 3R, 4S, and it is an L sugar.

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6.5: 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.

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.

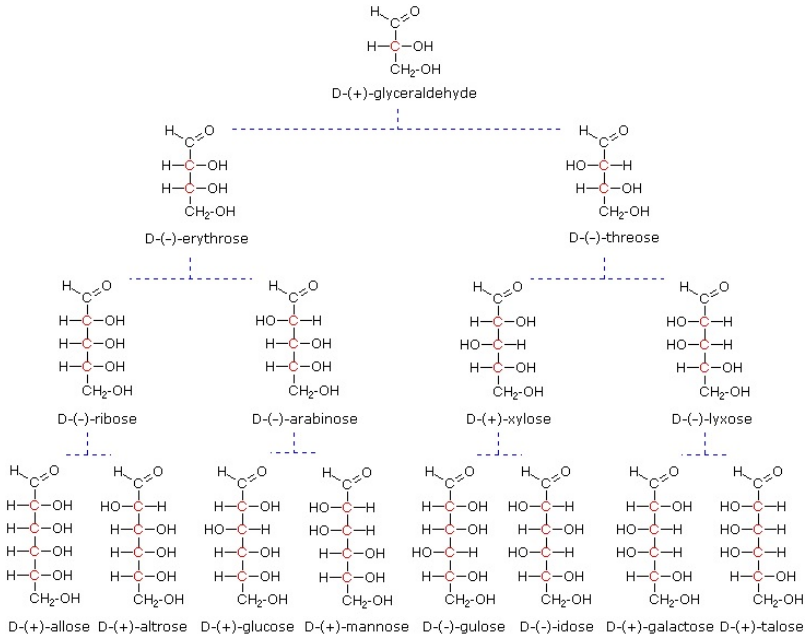
Aldotrioses: 3 carbon sugars with one chiral center. Aldotrioses have two (2^1) possible stereoisomers. A pair of enantiomers called D-gylceraldehyde and L-glyceraldehyde.

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.

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. Remember that only D-aldoses are represented below. Each D-aldose has an L-aldose enantiomer which is not shown. The L-aldose versions can be draw by inverting all of the chiral centers in the D-aldose's Fischer projection as discussed in the previous section.



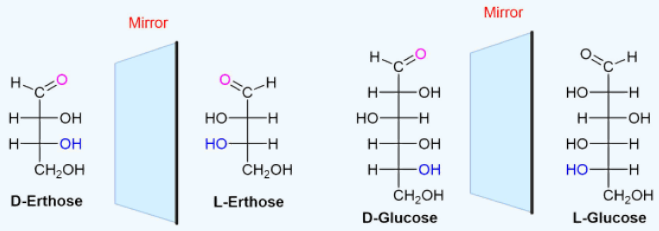
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Worked Example 6.5.1

Draw the Fisher projection of L-erythrose and L-Glucose

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.

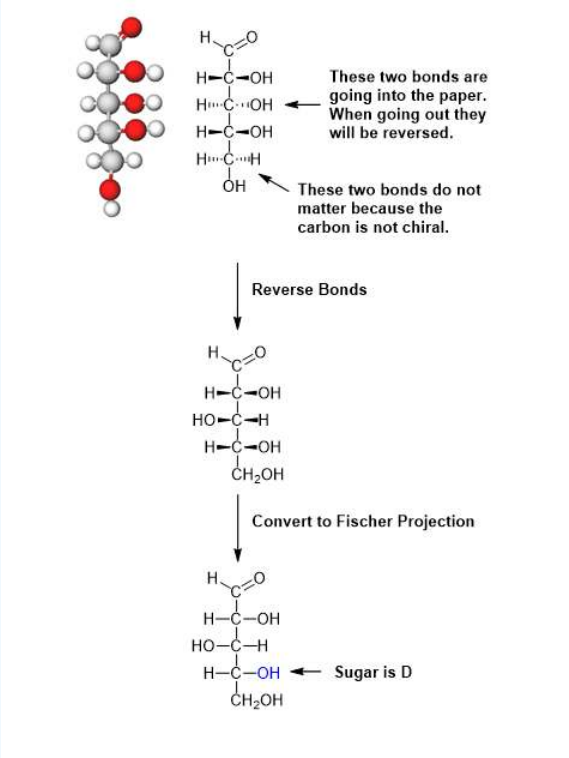


Worked Example 6.5.2

Please draw the Fischer projection fo the following aldopentose and determine if the sugars is D or L.

Solution

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.

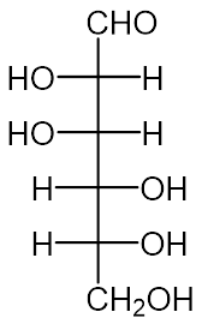


Exercise 6.5.1

For the following model of a sugar, please draw its Fischer projection and name it.

Answer

D-Mannose



Exercise 6.5.2

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.

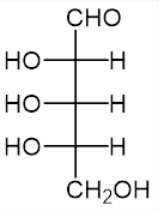
Exercise 6.5.3

Draw the Fischer projection of the following sugars.

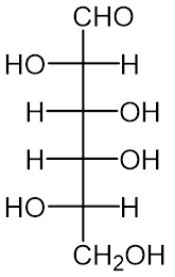
a. L-Ribose
b. L-Galactose
c. L-Talose

Answer

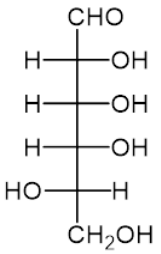
a)



b)



c)



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6.6: 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.

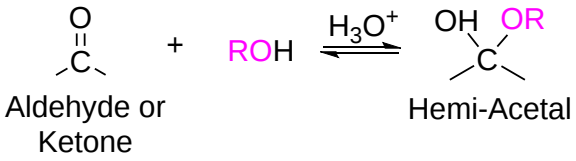
- alpha anomer
- anomer
- anomeric centre
- beta anomer
- furanose
- mutarotation
- pyranose

Study Notes

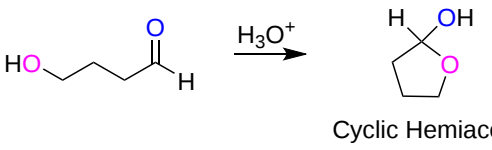
If necessary, before you attempt to study this section, review the formation of hemiacetals discussed in Section 19.10.

Cyclic Monosaccharides

In Section 19-10 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).



Molecules which have both an alcohol and a carbonyl can undergo an intramolecular version of the same reaction forming a 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.

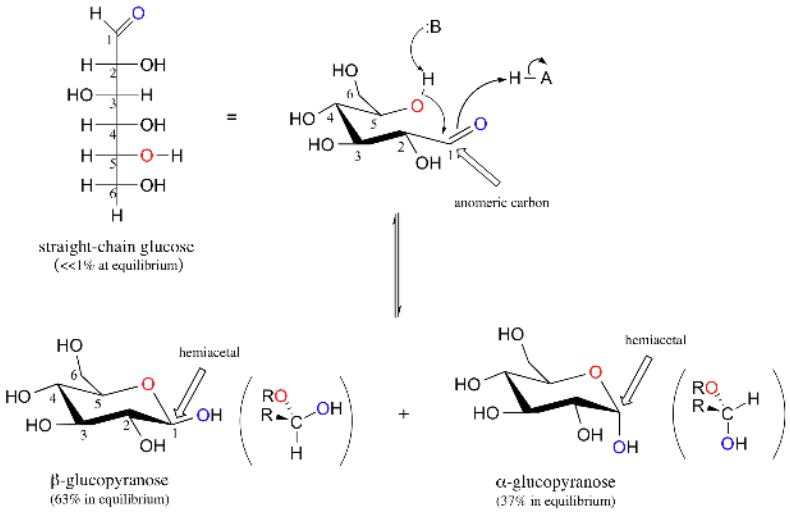


Furan (5-membered ring) and pyran (6-membered ring) structures

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.

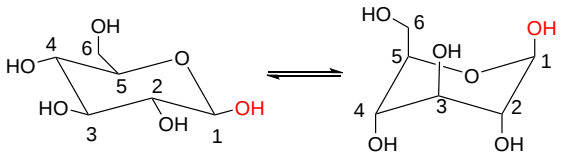
Aldohexoses usually form pyranose rings and their pentose homologs tend to prefer the furanose form, but there are many counter examples. At equilibrium less than 1% of glucose is in an open chain form with the rest being almost exclusively in its cyclic pyranose form. The pyranose ring is formed by attack of the hydroxyl on carbon 5 of glucose to the aldehyde carbon (carbon #1, also called the anomeric carbon in carbohydrate terminology). The cyclic form of glucose is called glucopyranose. Notice that for glucose and other aldohexoses the hydroxyl that forms the cyclic hemiacetal is also the one that determines the D/L designation of a sugar.

Pyranose rings are often drawn in a chair conformation like cyclohexane rings (**Section 4-6)** with substituents being either an axial or equatorial position. Pyranose rings are even capable of undergoing a ring flip to change between chair conformations. By convention the ring oxygen is placed to the right and to the rear of the structure (top right of the drawing). Groups which go to the right in a Fischer projection will be orientend 'down' of the pyranose ring while groups to the left are oriented 'up' in the chair structure. Also, the terminal -CH_2OH group is oriented up on the pyranose ring for D-sugars and down for L-Sugars.



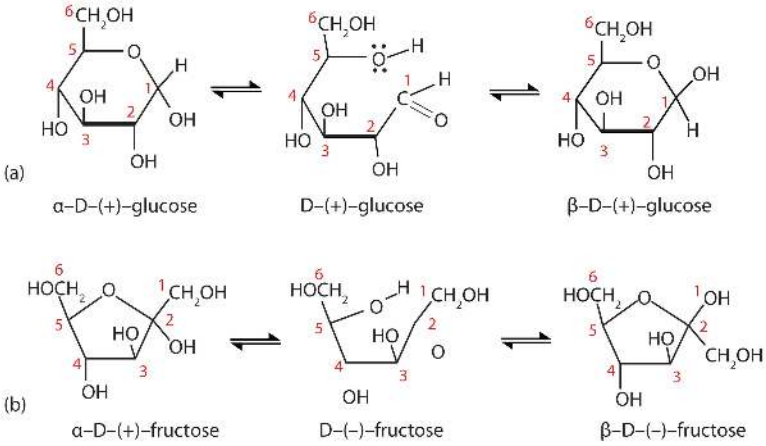
When D-glucose cyclizes it forms a 37/63 mixture of the alpha and beta anomer respectively. The beta anomer is preferred because β-D-glucopyranose is the only aldohexose which can be drawn with all its bulky substituents (-OH and -CH_2OH) in equatorial positions, making it the most stable of the eight D-aldohexoses, which probably accounts for its widespread prevalence in nature.

Conformational Isomers

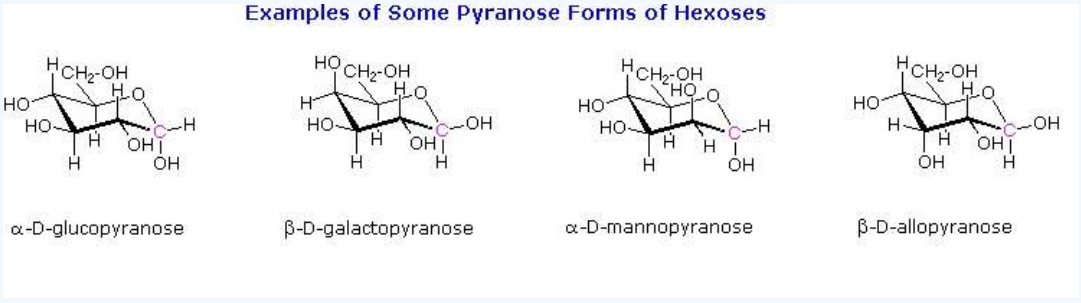


b-D-glucopyranose

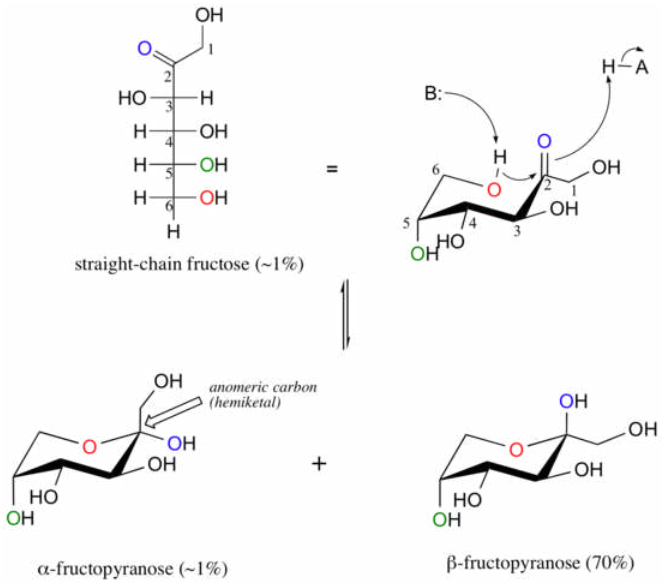
It is possible to obtain a sample of crystalline glucose in which all the molecules have the α structure or all have the β structure. The α form melts at 146°C and has a specific rotation of +112°, while the β form melts at 150°C and has a specific rotation of +18.7°. When the sample is dissolved in water, however, a mixture is soon produced containing both anomers as well as the straight-chain form, in dynamic equilibrium. You can start with a pure crystalline sample of glucose consisting entirely of either anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then re-close 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 (Latin *mutare*, meaning "to change"). 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°.



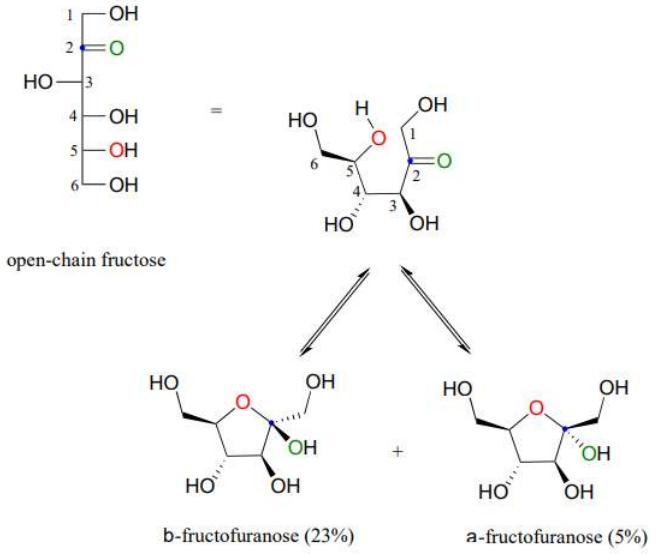
? Example 6.6.1



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 in the minor α anomer the bulkier -CH_2OH group occupies 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.



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. 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.

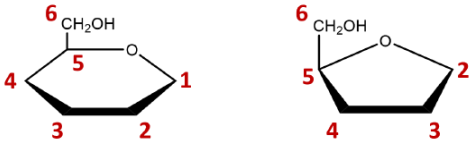
Although we have been looking at specific examples for glucose and fructose, other five- and six-carbon monosaccharides also exist in solution as equilibrium mixtures of open chains and cyclic hemiacetals and hemiketals. Shorter monosaccharides are unlikely to undergo analogous ring-forming reactions, however, due to the inherent instability of three and four-membered rings.

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.

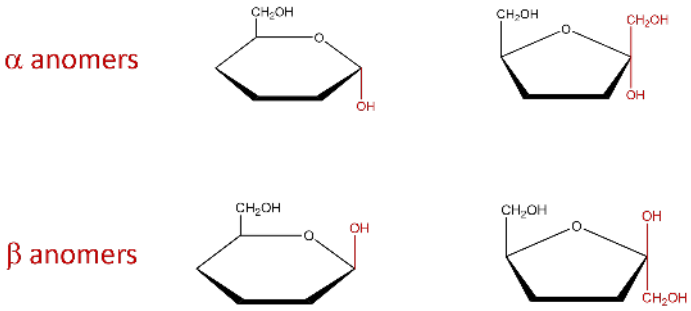
Figure: Conversion of the Fischer projection of D-glucose to the Haworth projection of ß-D-glucose.

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 a ketohexose, the **furanose** ring is typically used. The furanose ring contains four carbon atoms and an oxygen.

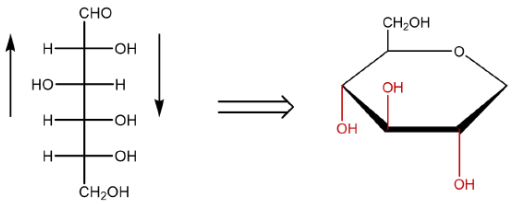


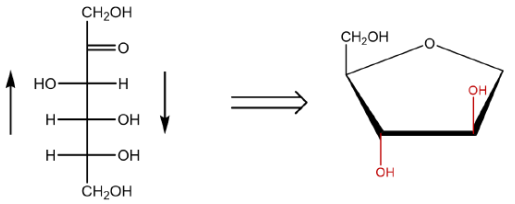
pyranose furanose

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.

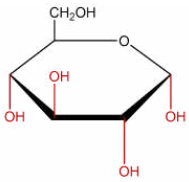


3. The remaining chiral centers (carbons 2, 3 and 4 of the pyranose or carbons 3 and 4 of the furanose) are arranged based on the directions of the hydroxyl from the Fischer projection structures. Groups to the left of the Fischer projection would point up (top face), while groups to the right would point down (bottom face).

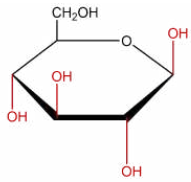




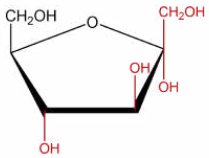
Since the Fischer Projection of any given carbohydrate is always the same, the Haworth Projection is essentially always the same. The only differences between the Haworth Projection of the alpha or beta form of a single carbohydrate, is how the OH (and carbon 1 if furanose ring) is arranged around the anomeric carbon to determine whether the molecule is alpha or beta.



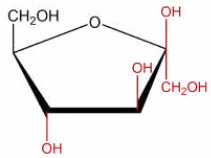
α-D-glucose
(or α-D-glucopyranose)



β-D-glucose
(or β-D-glucopyranose)



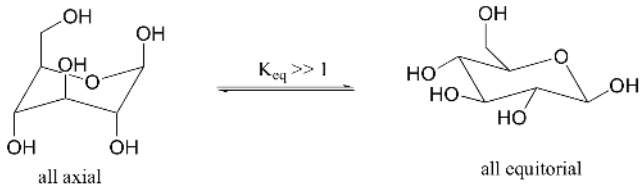
α-D-fructose
(or α-D-fructofuranose)



β-D-fructose
(or β-D-fructofuranose)

Stability of Chair Conformation in Pyranose Sugars

Previously, we have seen the six ring atoms of cyclic glucose drawn in two dimensions. A more accurate depiction shows that the molecule adopts, as expected, a chair conformation.

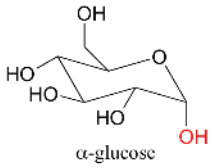


all axial

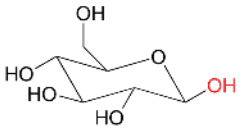
all equitorial

The conformation in which all substituents are equatorial is lower in energy. The two isomeric forms are referred to by the Greek letters alpha (α) and beta (β).

https://chem.libretexts.org/@go/page/396361



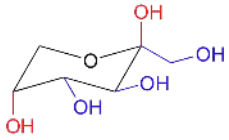
α-glucose



β-glucose

We have not learned about stereoisomerism quite yet, but you can still recognize that the bonding configuration on one carbon is different. On the alpha isomer, one of the hydroxyl groups is axial – this isomer is not able to adopt a chair conformation in which all non-hydrogen substituents are equatorial. The lower energy conformation is the one in which four of the five substituents are equatorial, but the presence of the one axial hydroxyl group means that the alpha isomer is, overall, less stable than the beta isomer.

The most abundant form of fructose in aqueous solution is also a six-membered ring.



fructose
(major form)

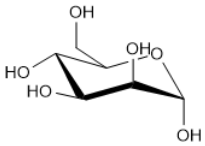
The lower energy chair conformation is the one with three of the five substituents (including the bulky $–CH_2OH$ group) in the equatorial position.

Exercise 6.6.1

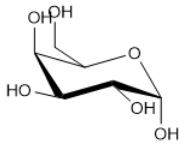
Draw the following in their most stable chair conformation: α-D-galactopyranose and α-D-mannopyranose. Which is expected to be the more stable?

Answer

Because the both have two axial OH's their chair conformations should be roughly the same stability.



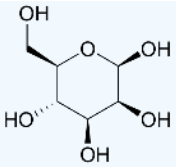
a-D-Mannose



a-D-Galactose

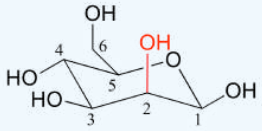
Exercise 6.6.2

Draw the two chair conformations of the sugar called 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.

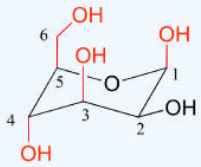


mannose

Answer



major chair form of mannose
(only one substituent axial)

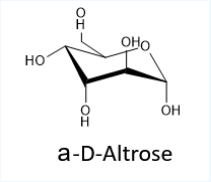


minor chair form of mannose
(four substituents axial)

Exercise 6.6.3

Draw the cyclic structure of α-D-altrose.

Answer

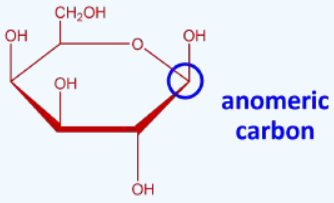


a-D-Altrose

Exercise 6.6.4

Draw the cyclic structure for β-D-galactose. Identify the anomeric carbon.

Answer

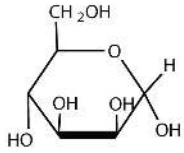


To identify the structure, we should first start with the Fischer projection of D-galactose. Since it is an aldohexose, we will start with the pyranose ring. The beta anomer was requested, so the OH on the anomeric carbon (C1) is cis to C6. Since C6 is top face (pointing up), the OH will be top face. 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 6.6.5

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.

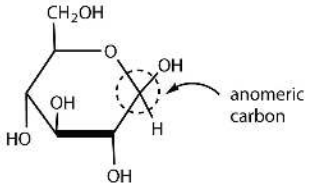
Answer



Exercise 6.6.6

Draw the cyclic structure for β-D-glucose. Identify the anomeric carbon.

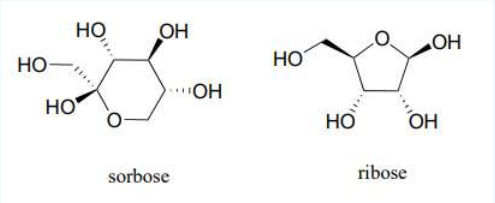
Answer



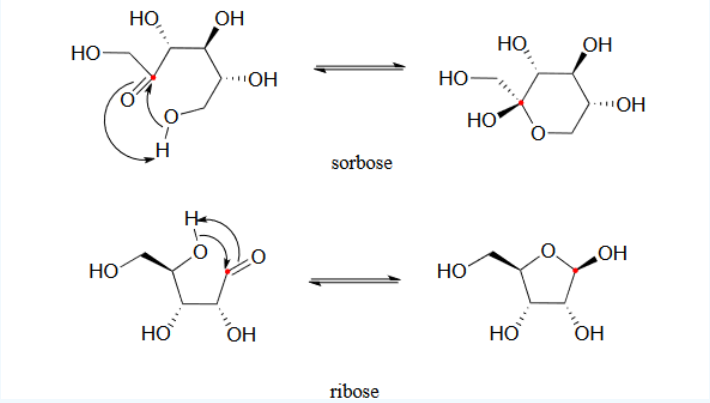
Exercise 6.6.7

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 cyclization of the open-chain forms to the cyclic forms shown.



Answer

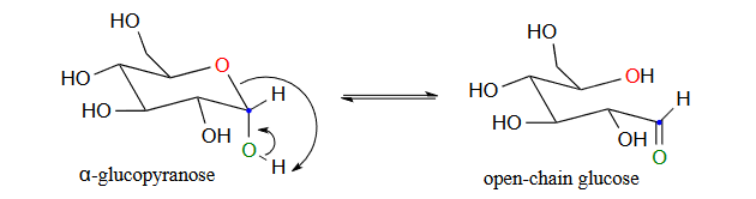


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Exercise 6.6.8

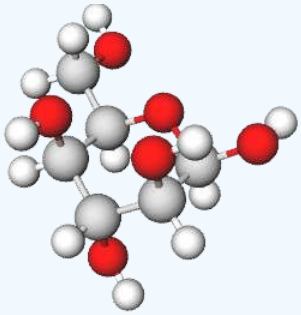
Draw a mechanism for the conversion of α-glucopyranose to open-chain glucose.

Answer



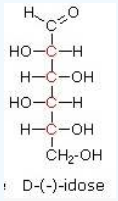
Exercise 6.6.9

Identify the following monosaccharide, write its full name, and draw its open-chain form as a Fischer projection.



Answer

β-D-idopyranose.



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6.7: 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
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

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 19.10

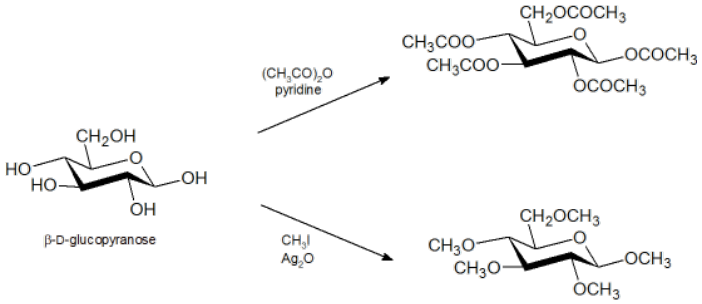
Monosaccharides contain both alcohol and carbonyl functional groups. This allows monosaccharides to undergo many of the reactions typical for these functional groups. In particular, alcohols can be converted to esters, converted to ethers, converted to acetals, or oxidized. Carbonyls can be reacted with 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.

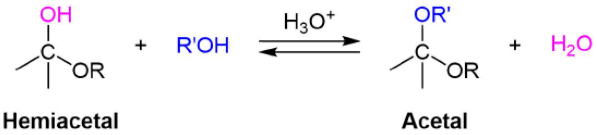
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5) in the presence of a base. During these reactions all of the -OH groups are converted to esters. The monosaccharide, D-glucopyranose can be coverted to the pentacetate through reaction with acetic anhydride.

Treatment of carbohydrates with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the formation of ethers. The strongly basic conditions typically used for the Williamson ether synthesis can degrade some sugar molecules. Instead, milder bases or silver oxide (Ag_2O) are used to provide ethers in high yields. The monosaccharide, D-glucopyranose can be converted to the pentamethyl ether through reaction with iodomethane and silver oxide.

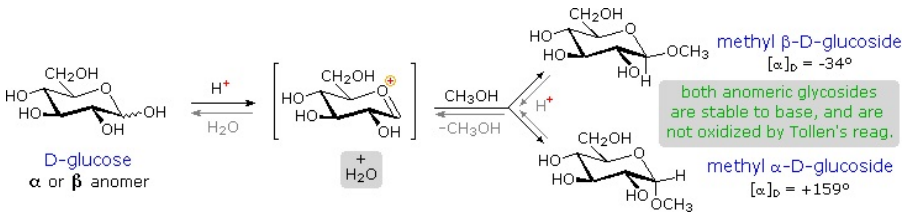


Glycoside Formation

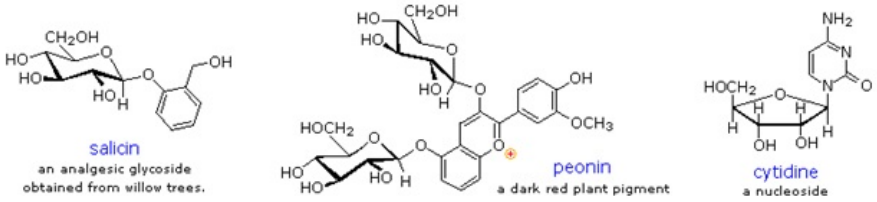
Reacting a hemiacetal with an alcohol and an acid catalyst produces an acetal in which the anomeric hydroxide has been replaced by an ether group.



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. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. This reaction is illustrated below for D-glucopyranose and methanol which forms a mixture of alpha and beta methyl-glucopyranosides. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The acetal product is stable to base and alkaline oxidants such as Tollen's reagent. They are not in equilibrium with the open-chain form and thus do not undergo mutarotation. Since this acid-catalyzed reaction is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.



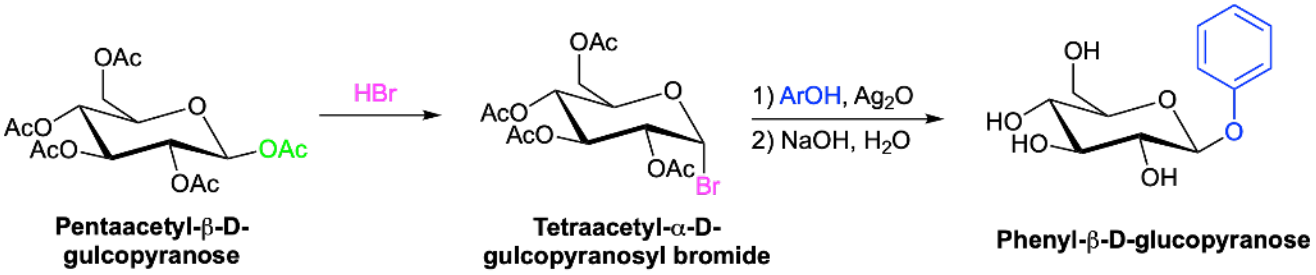
Two examples of naturally occurring glycosides and one example of an amino derivative are displayed below.



- 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

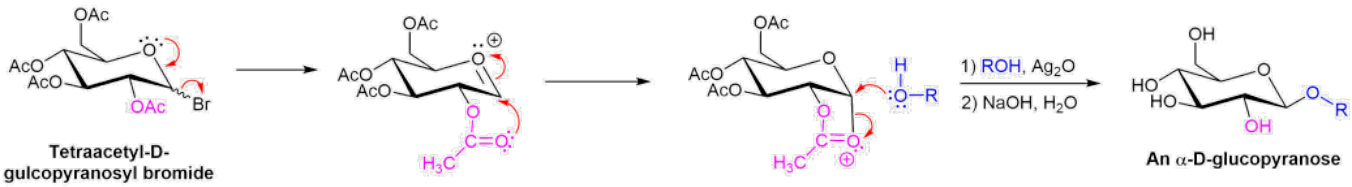
The presence of multiple -OH groups on a sugar molecular makes the synthesis of glycosides particularly difficult. One of the oldest glycosylation reactions, called the **Koenigs–Knorr reaction**, is effective for preparing the beta-glycosides of glucose. The pathway starts with the reaction of glucose pentaacetate with HBr to form a pyranosyl bromide. Addition of silver oxide allows for the nucleophilic addition of the chosen alcohol. Hydrolysis of the remaning 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.

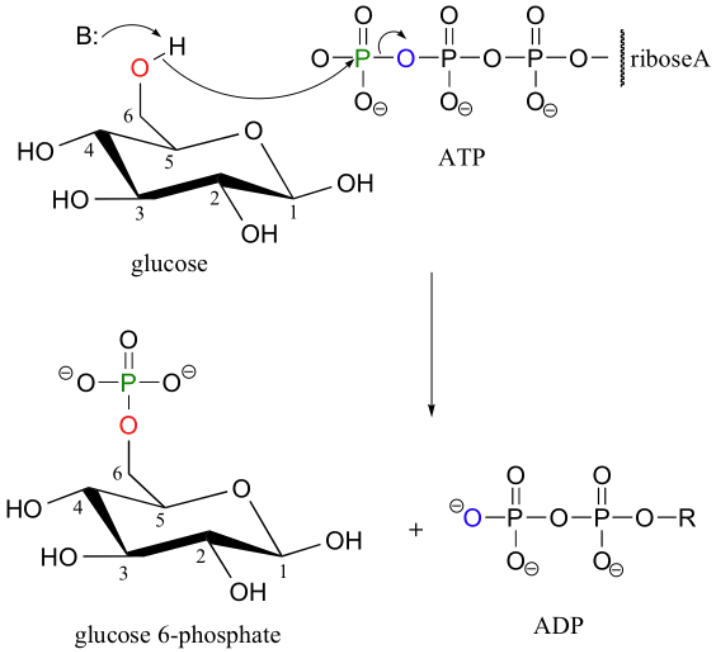
Koenigs–Knorr Reaction Mechanism

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**.



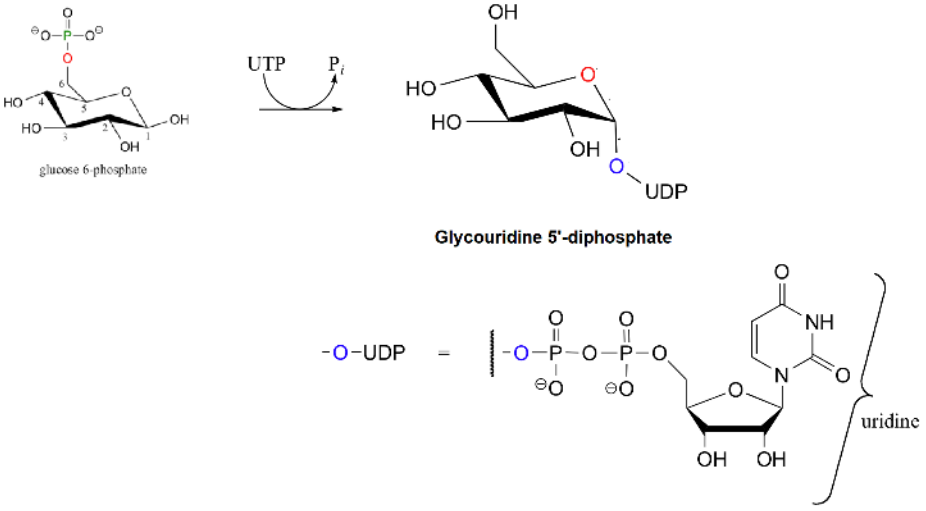
Biological Ester Formation: Phosphorylation

Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP.

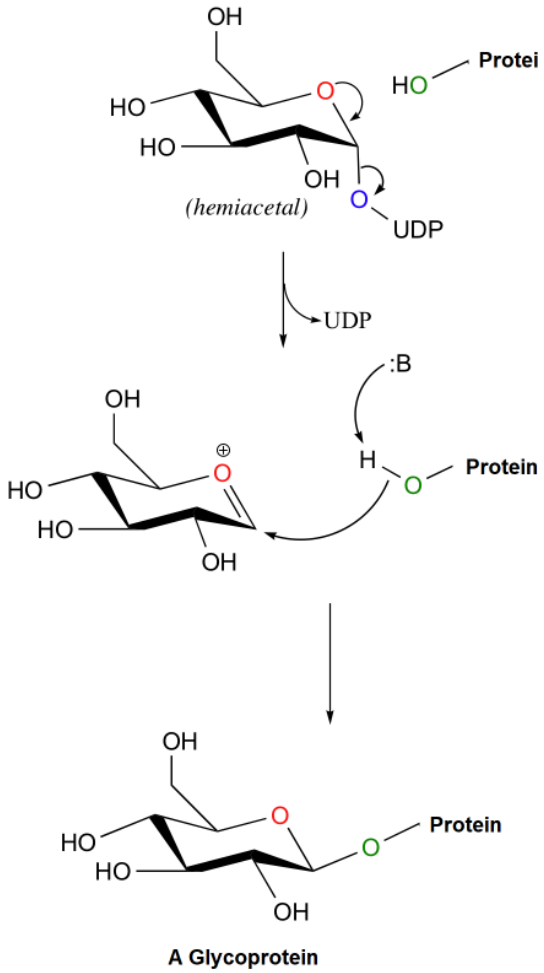


Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins. Called glycoconjugates these sugar bonded molecules are often found in biological membranes, to which they are anchored through covalent bonds. These compounds are crucial to determine to how different cell types recognized one another which will be discussed further in **Section 25.11**.

Glycoconjugate formation begins with the formation of a phosphorylated sugar such as glucose-6-phosphate which is then reacted with uridine triphosphate (UTP), to give a glycosyl uridine diphosphate. The phosphorylation makes the anomeric -OH of the sugar a better leaving group. During nucleophilic substitutions reaction with a protein or a lipid to form a glycoconjugate the anomeric -OH does not leave as a water molecule, but rather as part of a uridine nucleotide diphosphate group.



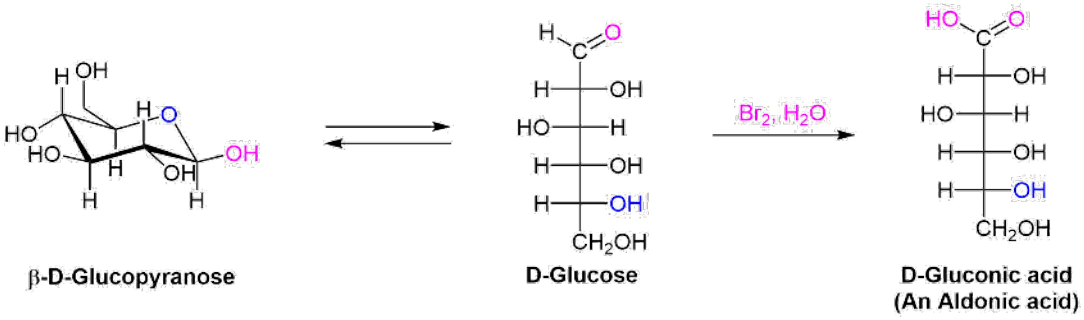
To form a glycoprotein the anomeric carbon of a glucopyranose-UDP derivative is attacked from above by an -OH of -NH_2 group from a protein. The UDP leaving group is displaced, and inversion of stereochemistry results at the anomeric carbon.



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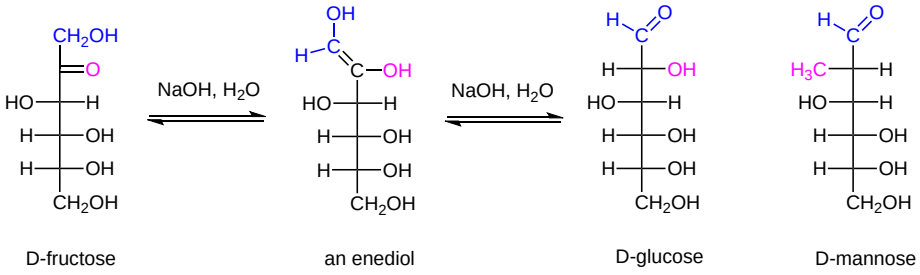
Oxidation of Monosaccharides

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.

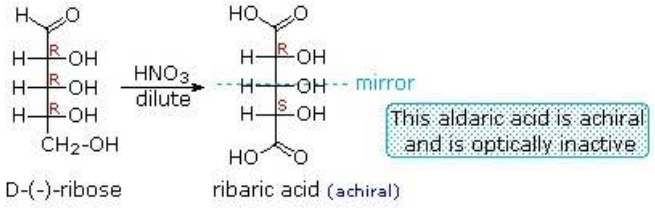


Historically sugars have been classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'** (Ag^+ in NH_3) or **Benedict's** (Cu^{2+} and sodium citrate) reagents. If a sugar is oxidized by these reagents it is called a reducing sugar, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) 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.

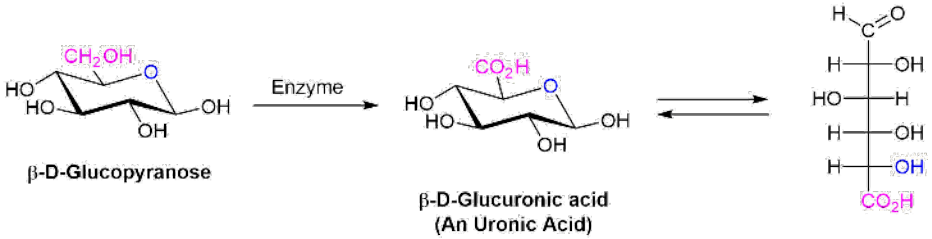
Becuase aldoses contain an aldehyde group they are reducing sugars and will be oxidized by Tollen's and Benedict's reagent. Some ketoses are also reducing sugars. Despite not having an aldehyde groups, fructose is capable of isomerizing to glucose and mannose by keto-enol tautomerism under basic conditions. Once formed, these aldoses are capable of being oxidized by Tollens reagent.



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.

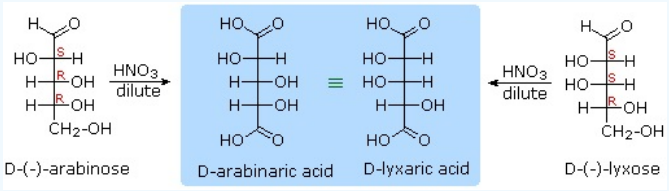


Exercise 6.7.1

D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

Answer

1) Remember, a Fischer projection formula may be rotated by 180º in the plane of projection without changing its configuration.



Exercise 6.7.2

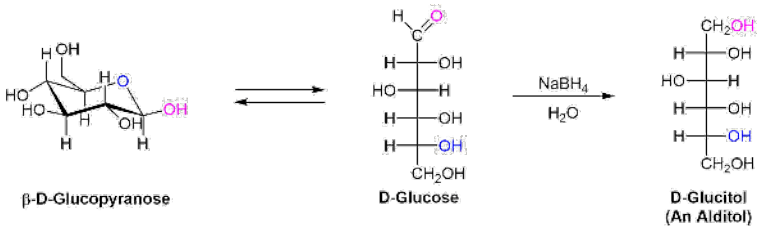
Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer

D-Allose and D-galactose.

Reduction of Monosaccarides

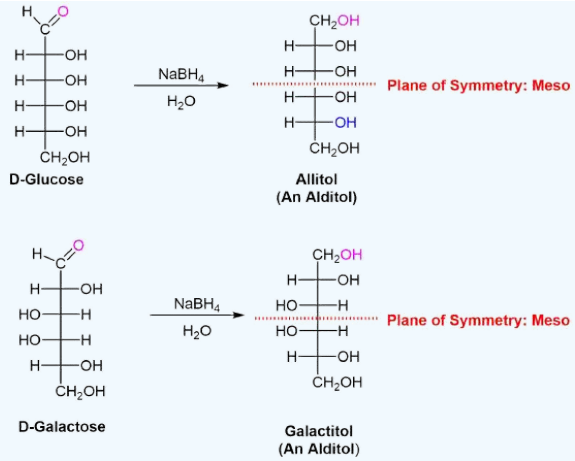
Treatment of an aldose or ketose with sodium borohydride reduces it to a polyalcohol called an alditol. The reduction occurs by reaction of the open-chain form. Although only a small amount of the open-chain form is present at any given time, that small amount is reduced, more is produced by opening 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 6.7.3

Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

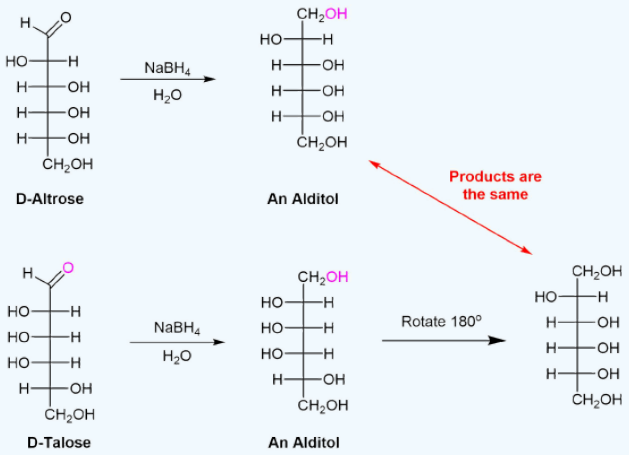
Answer



Exercise 6.7.4

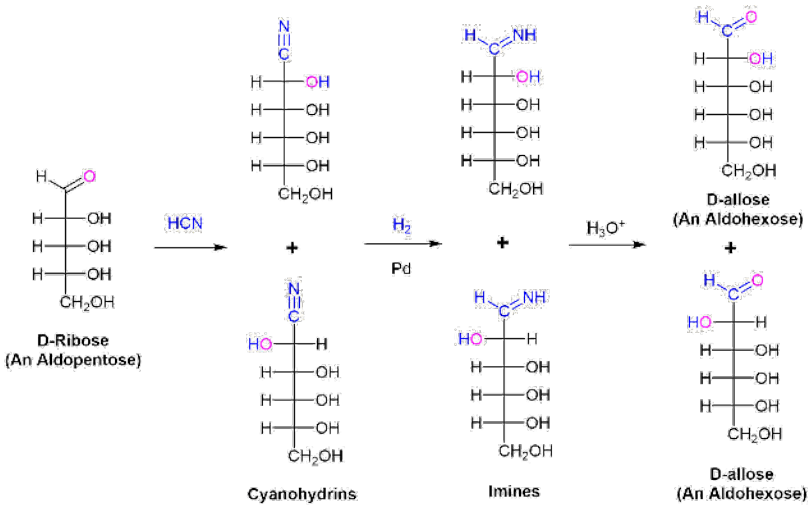
Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer



Chain Lengthening: The Kiliani–Fischer Synthesis

The Kiliani–Fischer synthesis lengthens the carbon chain of an aldose by one carbon atom. In doing this two new sugar epimers are created. 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. The nitrile group of the cyanohydrin is reduced to an imine intermediate by hydrogenation over a palladium catalyst. 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 6.7.5

What products would you expect from Kiliani–Fischer reaction of D-xylose?

Answer

D-Gluose and D-idose

? Exercise 6.7.6

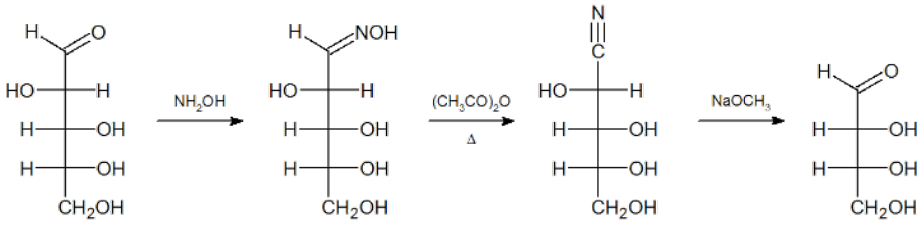
What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

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 19-8) 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. The following equation illustrates the application of this procedure to the aldopentose, D-arabinose to form the aldotetrose, D-erythrose.



? Exercise 6.7.7

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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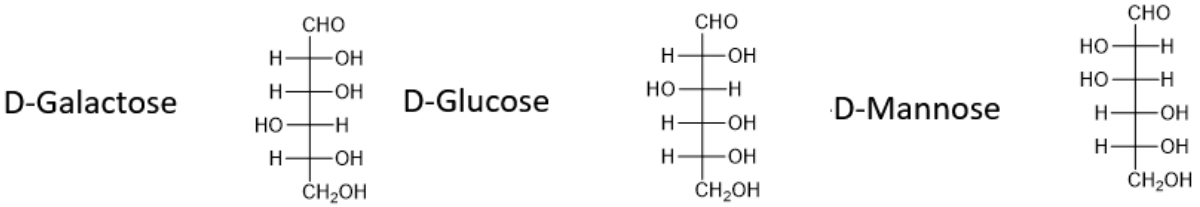
6.8: The Eight Essential Monosaccharides

Objectives

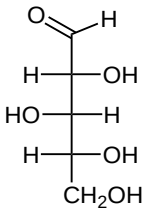
1. identify and draw the eight essential monosaccharides

Eight monosaccharides are required for the proper functioning of human beings. Although they are typically supplied through a healthy diet, they can be biosynthesized if required. The eight monosaccharides are L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine, D-glucose, D-mannose, N-acetyl-D-neuraminic acid, and D-xylose.

D-Galactose, D-Glucose, and D-Mannose are commonly found aldohexoses:

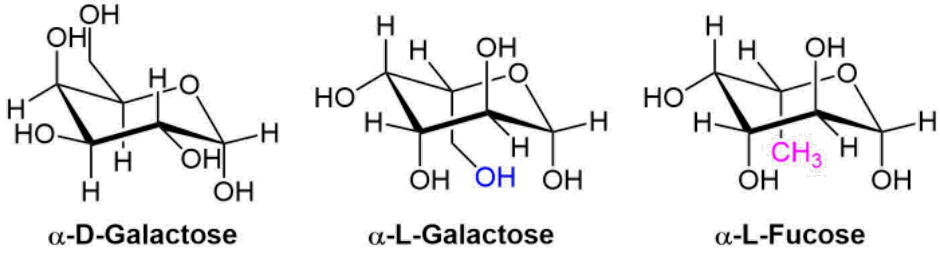


D-Xylose is a common aldopentose.

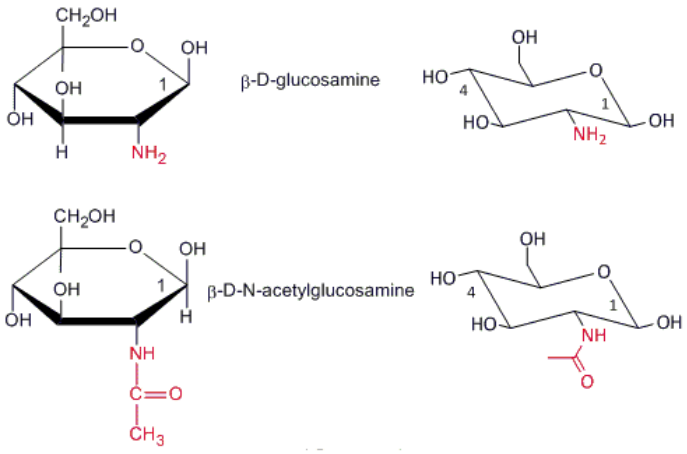


D-Xylose

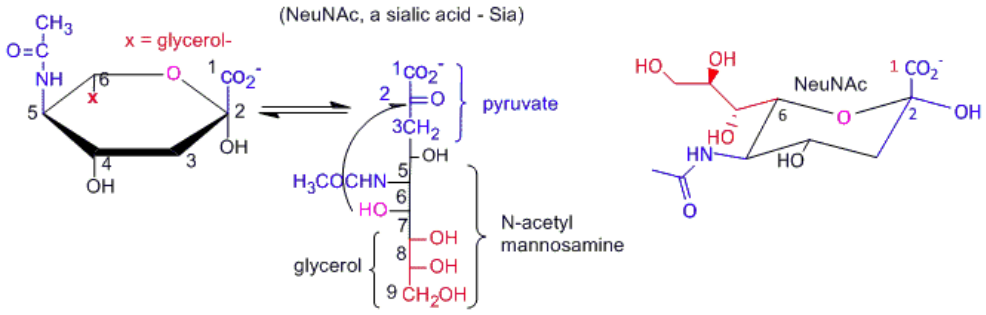
L-Fucose is a deoxy sugar. Fucose is is the monosaccaride L-galactose with the -OH group on C6 replaced with an -H.



N-acetylgalactosamine and N-acetylglucosamine are derivatives where the corresponding amino sugars have been converted to amides by N-acylation. Amino sugars have had their -OH groups at C2 replaced by an -NH_2.

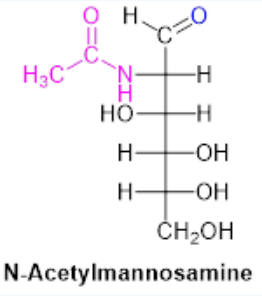


N-Acetylneuraminic acid is nine carbon sugar created by an aldol reaction between N-acetymannosamine and pyruvate. N-acetylneuaminic acid forms a pyranose ring by a intramolecular hemiacetal formation between the -OH on C6 and the ketone functional group in the pyruvate moiety.



Exercise 6.8.1

1) Please show the mechanism of the aldol reaction between *N*-acetylmannosamine and pyruvate to form neuraminic acid.



Answer

1)



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6.9: 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.

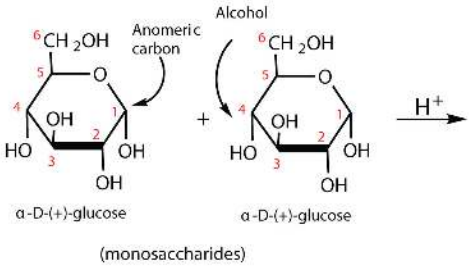
Previously, you learned that monosaccharides can form cyclic structures by the reaction of the carbonyl group with an OH group. These cyclic molecules can in turn react with another alcohol to form a glycoside. When the alcohol component of a glycoside is provided by a hydroxyl function on another monosaccharide, 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.

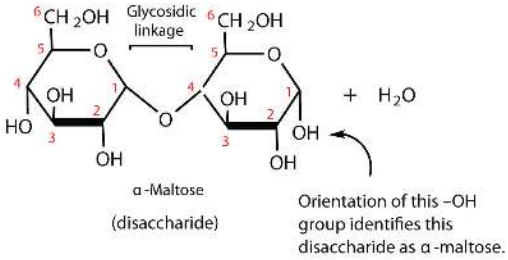
Maltose

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

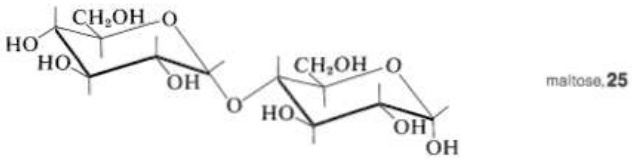
The glucopyranose units in maltose are joined in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucopyranose molecule to the fourth carbon atom of the second glucopyranose molecule (an α-1,4-glycosidic linkage). The bond

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.

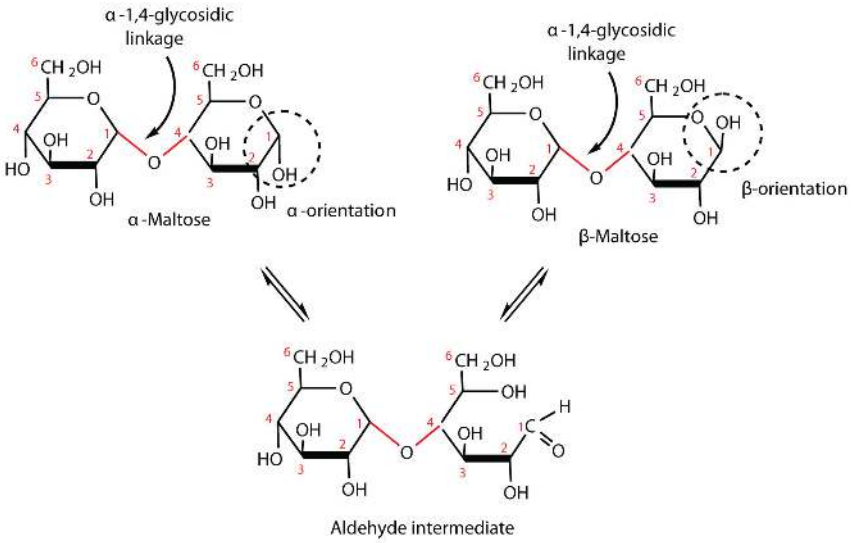




Cellobiose is a disaccharide made up of two D-glucopyranose molecules linked with a β-1,4-glycosidic linkage. Like maltose, the OH group on the anomeric carbon of the second glucopyranose of cellobiose can be in either the α or the β position. Although the difference between maltose and cellobiose seems small they have vastly different biological properties. Maltose can be digested by humans whereas cellobiose cannot.



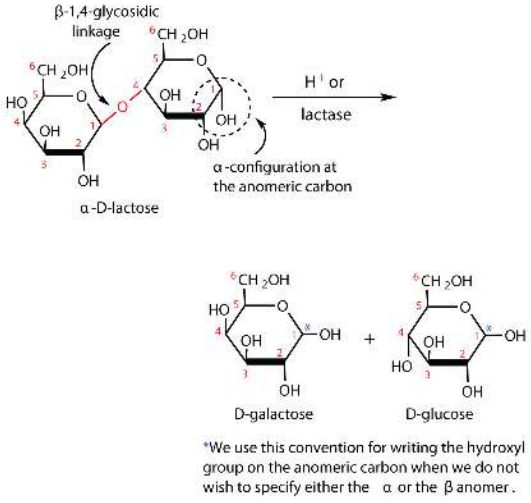
Maltose is a reducing sugar. Thus, its two D-glucopyranose molecules must be linked in such a way as to leave one anomeric carbon that can open to form an aldehyde group. Although one anomeric carbon in maltose and cellobiose is used to form the 1,4-glycosidic linkage, the anomeric carbons on the second 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.



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 in the manufacture of cheese. It is important as an infant food and in the production of penicillin.

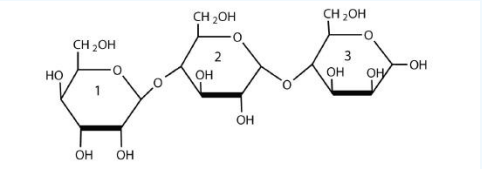
Lactose is a disaccharide composed of one molecule of D-galactopyranose and one molecule of D-glucopyranose joined by a β-1,4-glycosidic bond between the 1 of D-galactopyranose and the C4 of glucose. Lactose is a reducing sugar and undergoes mutarotation to exhibit both anomers of the D-glucopyranose 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.

Example 1

For this trisaccharide, indicate whether each glycosidic linkage is α or β.



Solution

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.

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 enzyme increases with age. Up to 20% of the US population suffers 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.

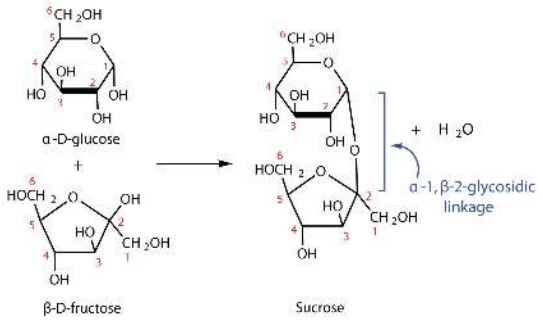
The symptoms disappear if milk or other sources of lactose are excluded from the diet or consumed only sparingly. Alternatively, many food stores now carry special brands of milk that have been pretreated with lactase to hydrolyze the lactose. Cooking or fermenting milk causes at least partial hydrolysis 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.

Summary

Maltose is composed of two molecules of glucose joined by an α-1,4-glycosidic linkage. It is a reducing sugar that is found in sprouting grain. Lactose is composed of a molecule of galactose joined to a molecule of glucose by a β-1,4-glycosidic linkage. It is a reducing sugar that is found in milk. Sucrose is composed of a molecule of glucose joined to a molecule of fructose by an α-1,β-2-glycosidic linkage. It is a nonreducing sugar that is found in sugar cane and sugar beets.

? Exercise 6.9.1

What monosaccharides are obtained by the hydrolysis of each disaccharide?

a. sucrose
b. maltose
c. lactose

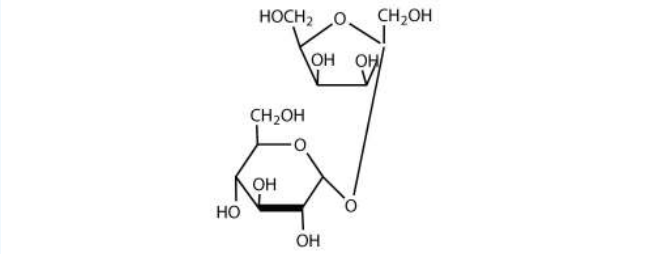
Answer

a. D-glucose and D-fructose
b. two molecules of D-glucose
c. D-glucose and D-galactose

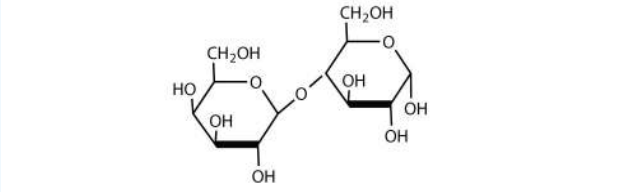
? Exercise 6.9.2

For each disaccharide, indicate whether the glycosidic linkage is α or β.

a)

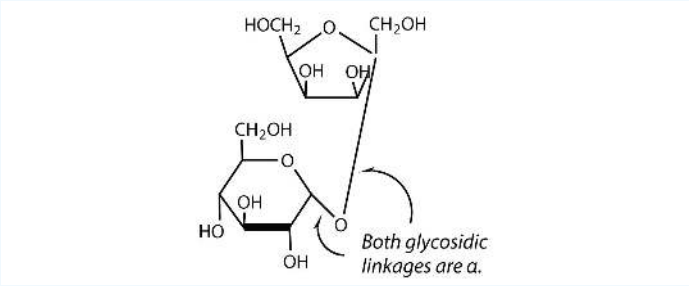


b)

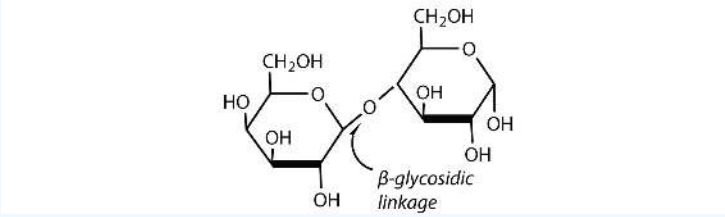


Answer

a)



b)



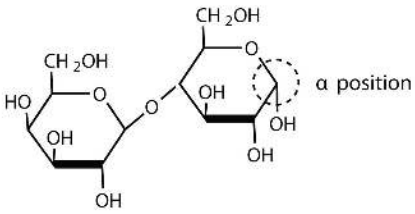
Exercise 6.9.3

Identify each disaccharide 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

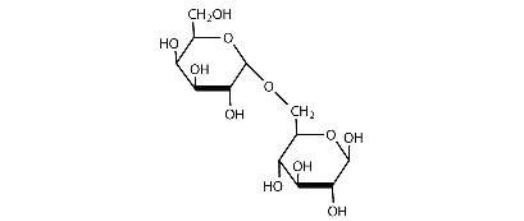
a) nonreducing

b) reducing



Exercise 6.9.4

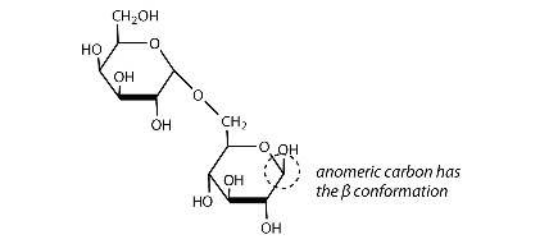
Melibiose is a disaccharide that occurs in some plant juices. Its structure is as follows:



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.

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6.10: 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.

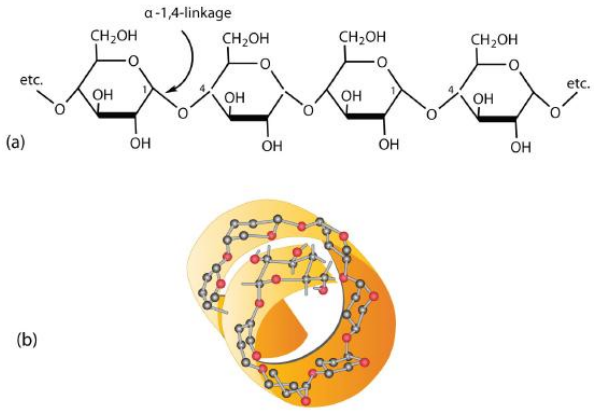


Figure 6.10.1: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

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 6.10.1). 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 6.10.1). 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.

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 6.10.2). 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.

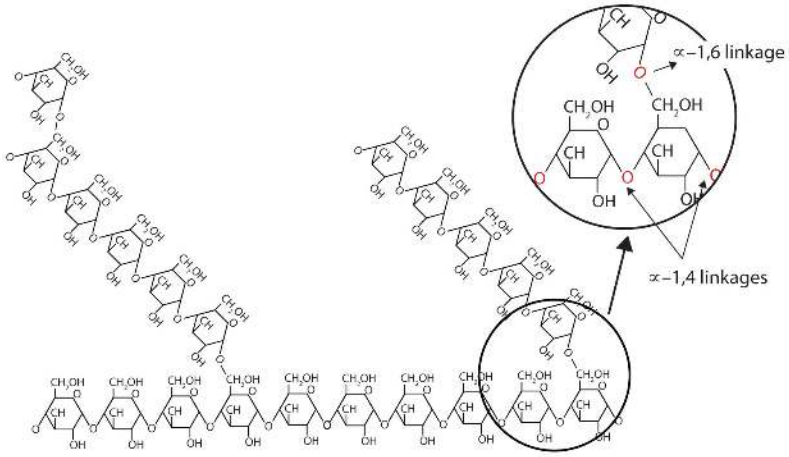


Figure 6.10.2: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

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.

Glycogen is structurally quite similar to amylopectin, although glycogen is more highly branched (8–12 glucose units between branches) and the branches are shorter. 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.

> 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.

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 6.10.3). 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 6.10.3). 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.

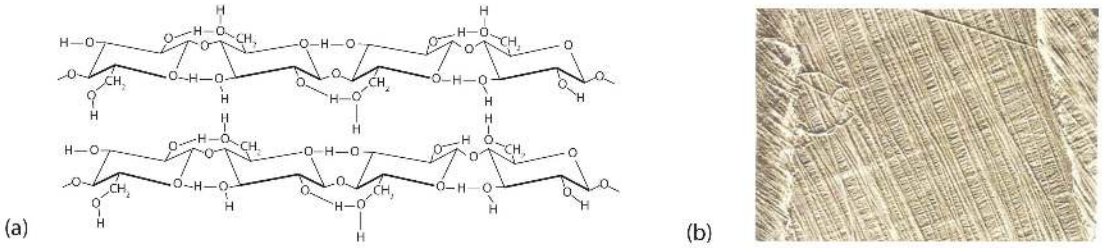
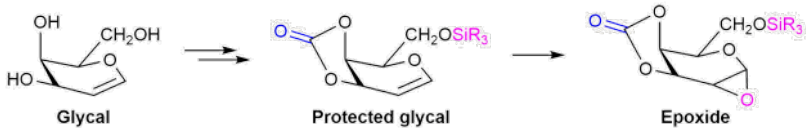


Figure 6.10.3: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

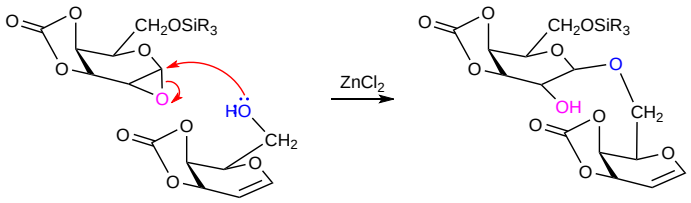
Cellulose yields D-glucose after complete acid hydrolysis, yet humans are unable to metabolize cellulose as a source of glucose. Our digestive juices lack enzymes that can hydrolyze the β-glycosidic linkages found in cellulose, so although we can eat potatoes, we cannot eat grass. However, certain microorganisms 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.



Disaccaride glycal

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6.11: Other Important Carbohydrates

Objectives

After completing this section, you should be able to identify deoxy and amino sugars, given their structures.

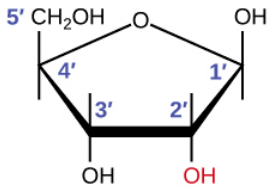
Key Terms

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

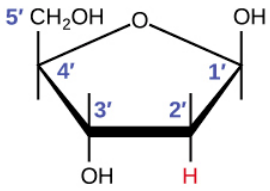
- amino sugar
- deoxy sugar

Deoxy Sugars

As shown in **Section 25-7**, 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).

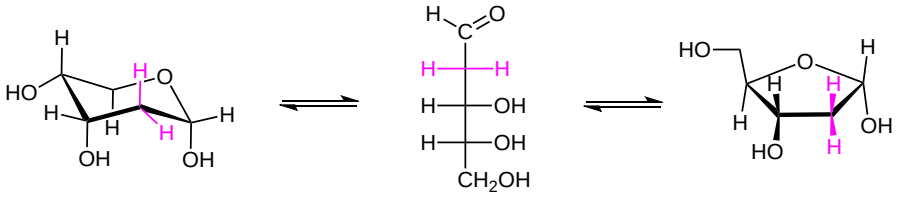


Ribose



Deoxyribose

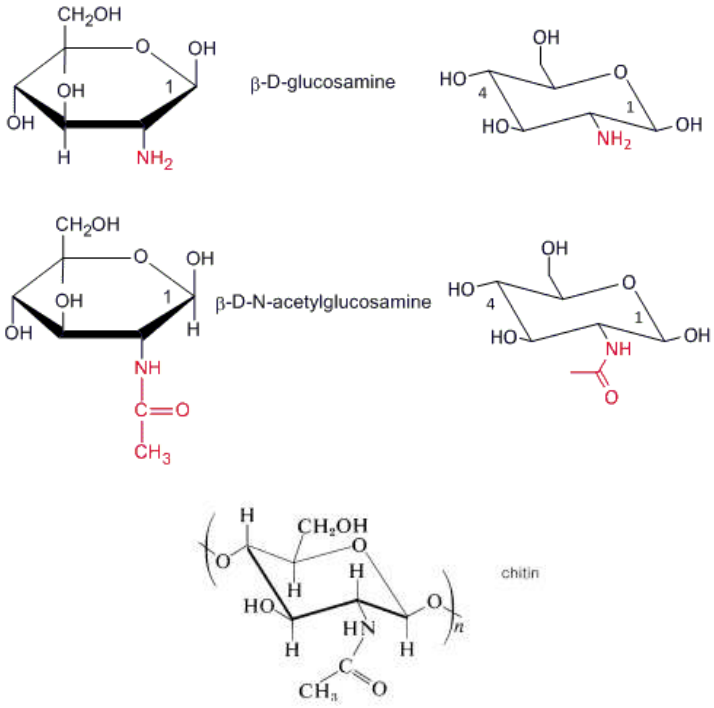
In water, 2-deoxyribose is an equilibrium mixture of both the furanose and pyranose ring forms. The pyranose form the most stable (40% alpha anomer and 35% beta anomer), followed by the furanose structures (13% alpha anomer and 12% beta), with the uncyclized form making up the remaining 0.7%.



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) and is 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. Amino sugars are also found in antibiotics such as amikacin and tobramicin.

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6.12: 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 a component 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 by through nonpolar interactions. What is the function of these carbohydrates? Two are apparent. First, glycosylation of proteins helps protect the protein from degradation by enzyme catalysts within 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.

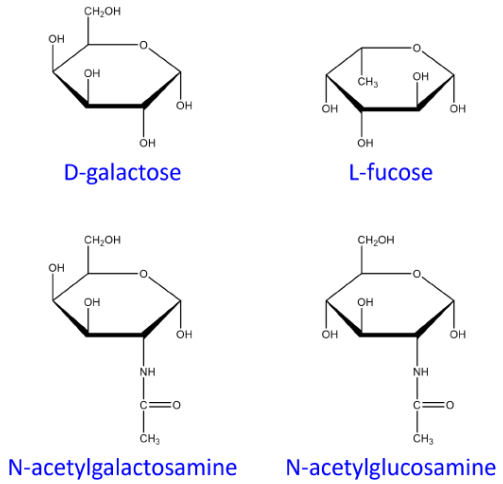


Figure 6.12.1: Structures of monosaccharide units present in ABO blood markers

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 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.

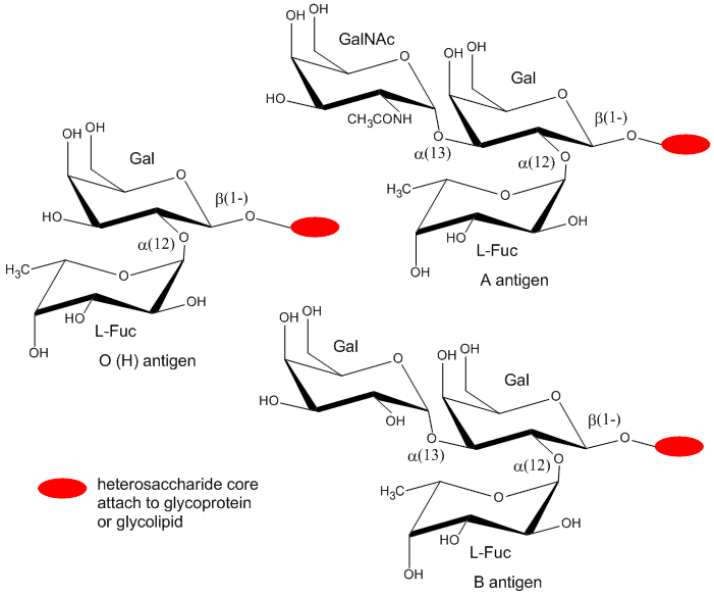


Figure 6.12.2: ABO blood types.

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 a simple yet deadly virus. 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: in addition to HA is the enzyme neuraminidase. Two viral strains which have been often discussed are H5N1 and H1N1 which stands 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.

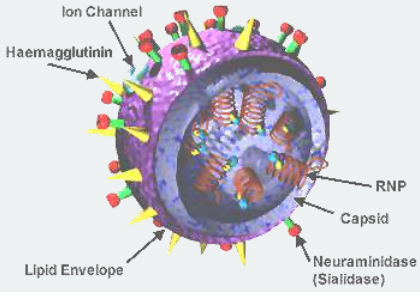
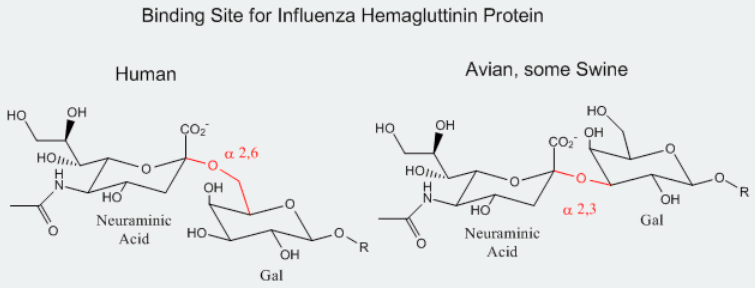
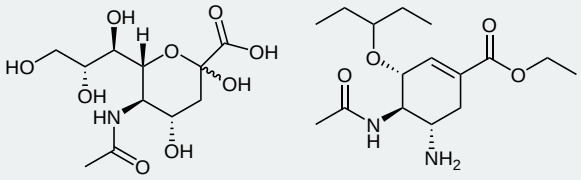


Figure 6.12.3: Structure (3D) of the Influenza Virus: The image depicts the major components of the virus structure, including the neuraminidase. (Public Domain; National Institutes of Health via Wikipedia)

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.



The virus, before it leaves the cell, forms a bud on the intracellular side of the cell with the HA and NA in the cell membrane of the host cell. The virus in this state would not leave the cell since its HA molecules would interact with sialic acid residues in the host cell membrane, holding the virus in the membrane. Neuraminidase hydrolyzes sialic acid from cell surface glycoproteins, allowing the virus to complete the budding process 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 work against N1 of the present 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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6.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.

25.1 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.

25.2 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.

25.3 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.

25.4 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.

25.5 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.

25.6 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.

25.7 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 the monosaccharides, which is why some sugars are classified as reducing.
- 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.

25.8 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.

25.9 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 is 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.

25.10 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.

25.11 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.

25.12 Cell-Surface Carbohydrates and Influenza Viruses

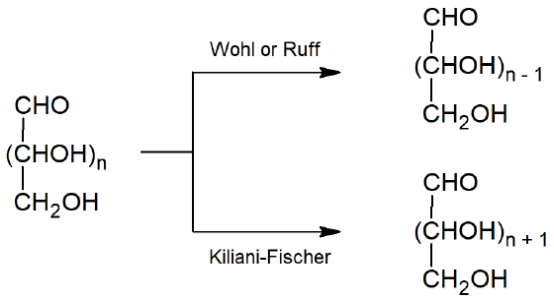
- Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins.
- Glycoproteins and glycolipids are often found in biological membranes that allow other biomolecules to interact and bind to the protein.
- Bacteria and 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

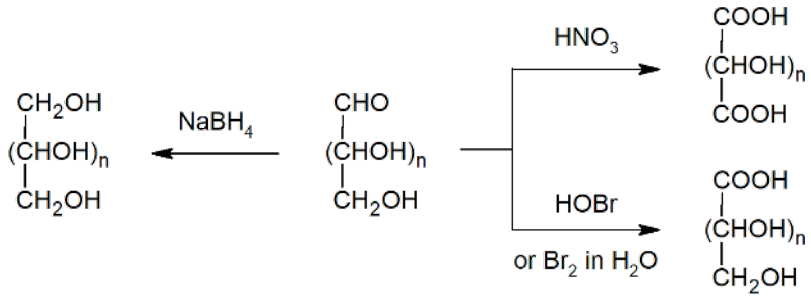
- Skill 25.1 Determine which molecules can be classified as carbohydrates.
- Skill 25.2 Distinguish between monosaccharide, disaccharide, and trisaccharides given the structure.
- Skill 25.3 Classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.
- Skill 25.4 Draw the Fischer projection of a monosaccharide, given its wedge-and-broken-line structure or a molecular model.
- Skill 25.5 Draw the wedge-and-broken-line structure of a monosaccharide, given its Fischer projection or a molecular model.
- Skill 25.6 Construct a molecular model of a monosaccharide, given its Fischer projection or wedge-and-broken-line structure.
- Skill 25.7 Identify a specific enantiomer of a monosaccharide as being D or L, given its Fischer projection.
- Skill 25.8 Assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
- Skill 25.9 Draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
- Skill 25.10 Draw configurations of aldoses.
- Skill 25.11 Determine whether a given monosaccharide will exist as a pyranose or furanose.
- Skill 25.12 Draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
- Skill 25.13 Determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
- Skill 25.14 Describe the phenomenon known as mutarotation.
- Skill 25.15 Explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
- Skill 25.16 Predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
- Skill 25.17 Identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
- Skill 25.18 Predict the product that would be produced by the Wohl degradation of a given aldose.
- Skill 25.19 Identify the aldose that would yield a given product following Wohl degradation synthesis.
- Skill 25.20 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 25.21 Identify the two monosaccharide units in a given disaccharide.
- Skill 25.22 Identify the type of glycoside link (e.g., 1,4′-β) present in a given disaccharide structure.
- Skill 25.23 Draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.
- Skill 25.24 Identify the products formed from the hydrolysis of a given disaccharide.

Summary of Reactions

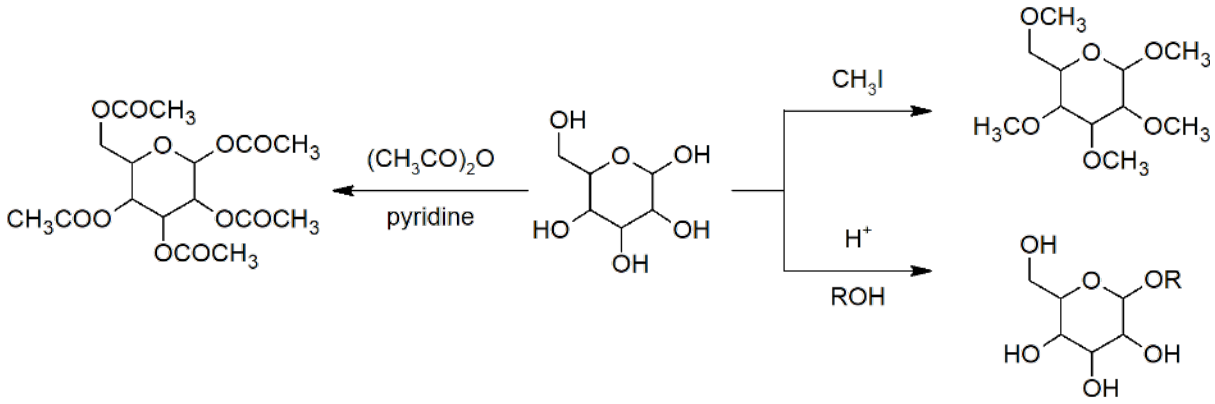
Chain Length



Oxidation - Reduction



Ester and Ether Formation



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CHAPTER OVERVIEW

7: Biomolecules- Amino Acids, Peptides, and Proteins

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.

7.1: Introduction
7.2: Structures of Amino Acids
7.3: Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points
7.4: Synthesis of Amino Acids
7.5: Peptides and Proteins
7.6: Peptide Synthesis
7.7: Protein Structure
7.8: Enzymes and Coenzymes
7.9: How do Enzymes Work? Citrate Synthase
7.10: Chapter Objectives
7.11: Amino Acid Analysis of Peptides
7.12: The Edman Degradation
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7: Biomolecules- Amino Acids, Peptides, and Proteins is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

7.1: 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

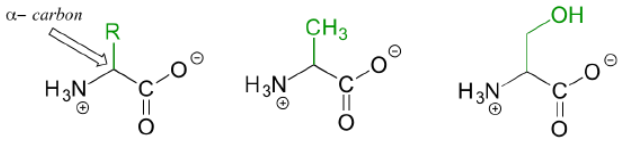
Make certain that you can define, and use in context, the key terms below.

- amino acid
- enzyme
- peptide bond
- protein

Study Notes

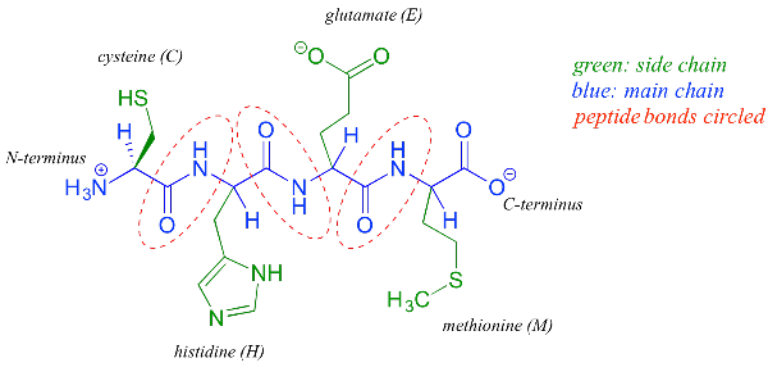
The “peptide bond” or “peptide linkage” that is formed between the amino group of one amino acid and the carboxyl group of a second amino acid is identical to the C$\ce{-}$N bond present in amides (see Section 21.7). We shall review the nature of such bonds in Section 26.4.

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.



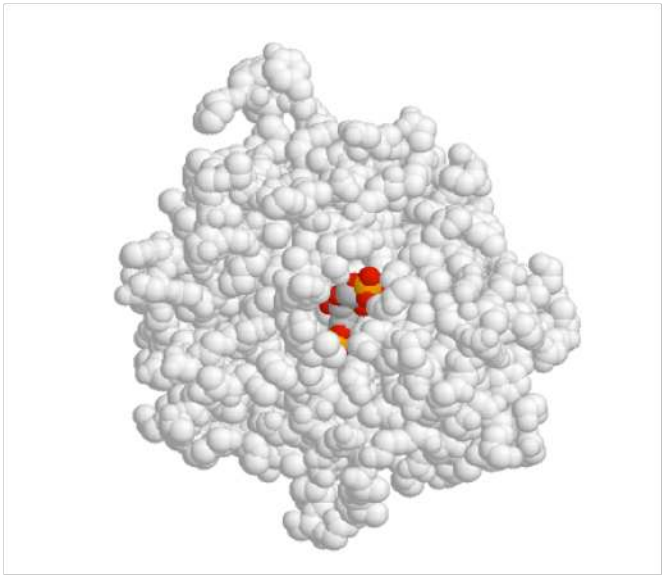
CHEM peptide

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)

Intro to nucleic acids ⇒

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7.2: 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: You are not expected to remember the detailed structures of all these amino acids, but you should 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: To do so, you must remember that 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.

Introduction to Amino Acids

Amino acids form polymers through a nucleophilic attack by the amino group of an amino acid at the electrophilic carbonyl carbon of the carboxyl group of another amino acid. The carboxyl group of the amino acid must first be activated to provide a better leaving group than OH^-. (We will discuss this activation by ATP later in the course.) The resulting link between the amino acids is an amide link which biochemists call a peptide bond. In this reaction, water is released. In a reverse reaction, the peptide bond can be cleaved by water (hydrolysis).

- Structure and Property of the Naturally-Occurring Amino Acids (Too large to include in text: print separately)

When two amino acids link together to form an amide link, the resulting structure is called a dipeptide. Likewise, we can have tripeptides, tetrapeptides, and other polypeptides. At some point, when the structure is long enough, it is called a protein. There are many different ways to represent the structure of a polypeptide or protein, each showing differing amounts of information.

Figure: Different Representations of a Polypeptide (Heptapeptide)

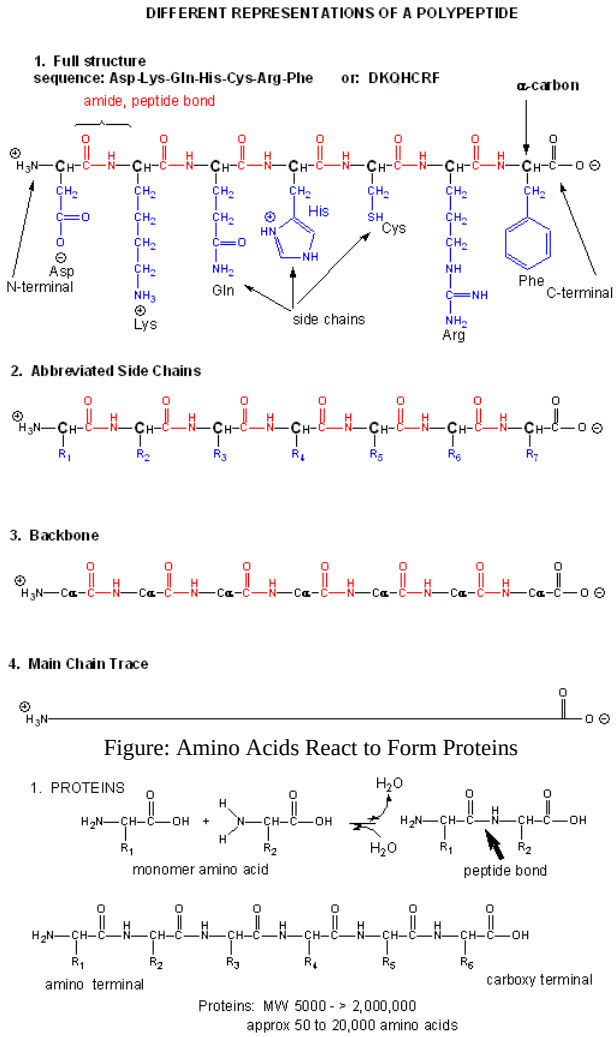


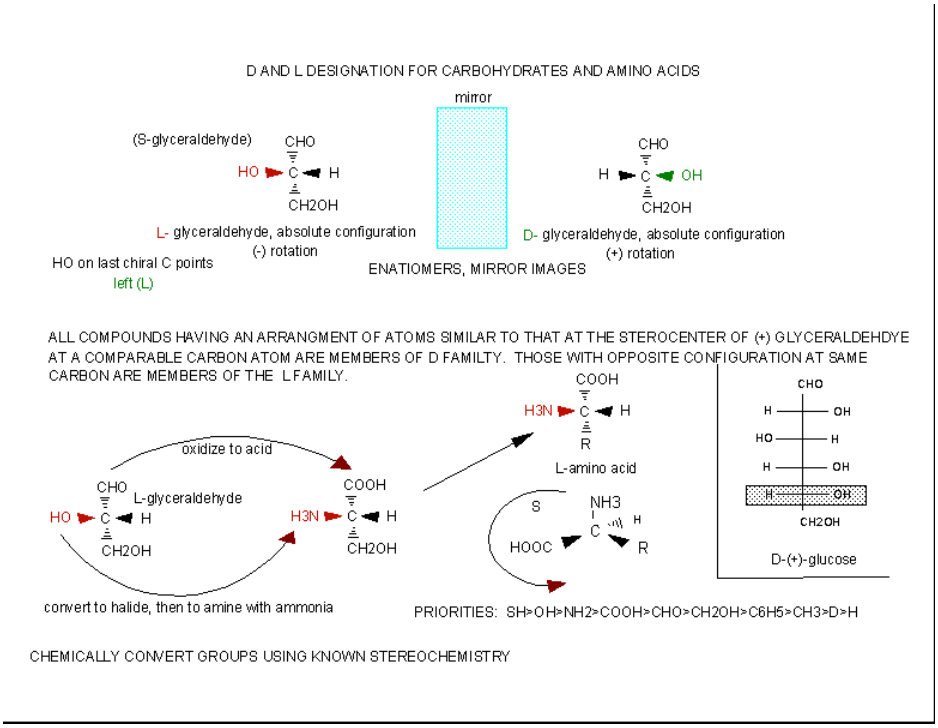
Figure: Amino Acids React to Form Proteins

(Note: above picture represents the amino acid in an unlikely protonation state with the weak acid protonated and the weak base deprotonated for simplicity in showing removal of water on peptide bond formation and the hydrolysis reaction.) Proteins are polymers of twenty naturally occurring amino acids. In contrast, nucleic acids are polymers of just 4 different monomeric nucleotides. Both the sequence of a protein and its total length differentiate one protein from another. Just for an octapeptide, there are over 25 billion different possible arrangements of amino acids. Compare this to just 65536 different oligonucleotides of 8 monomeric units (8mer). Hence the diversity of possible proteins is enormous.

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 occuring proteins from all living organisms consist of L amino acids. 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 the amino acids can be shown with the H pointed to the rear, the COOH groups pointing out to the left, the R group to the right, and the NH_3 group upwards. You can remember this with the anagram CORN.

Figure: *Stereochemistry of Amino Acids.*



Why do biochemists still use D and L for sugars and amino acids? This explanation (taken from the link below) seems reasonable.

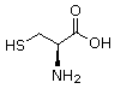
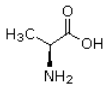
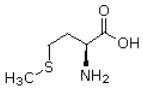
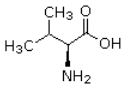
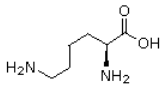
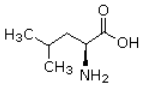
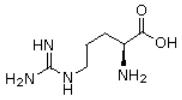
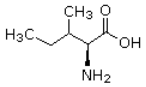
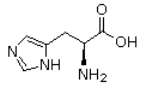
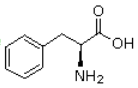
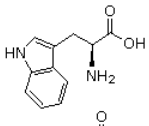
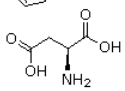
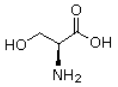
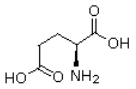
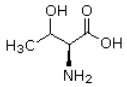
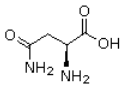
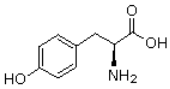
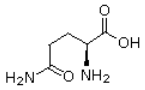
"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied 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), but this just reflects the human decision to give a sulphur 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. "

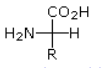
Natural α-Amino Acids

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. Those amino acids having green colored names are **essential** diet components, since they are not synthesized by human metabolic processes. The best food source of these nutrients is protein, but it is important to recognize that not all proteins have equal nutritional value. For example, peanuts have a higher weight content of protein than fish or eggs, but the proportion of essential amino acids in peanut protein is only a third of that from the two other sources. For reasons that will become evident when discussing the structures of proteins and peptides, each amino acid is assigned a one or three letter abbreviation.

Natural α-Amino Acids

Name	Formula	Abbreviations		Name	Formula	Abbreviations	
Glycine		Gly	G	Cysteine		Cys	C
Alanine		Ala	A	Methionine		Met	M
Valine		Val	V	Lysine		Lys	K
Leucine		Leu	L	Arginine		Arg	R
Isoleucine		Ile	I	Histidine		His	H
Phenylalanine		Phe	F	Tryptophan		Trp	W
Proline		Pro	P	Aspartic Acid		Asp	D
Serine		Ser	S	Glutamic Acid		Glu	E
Threonine		Thr	T	Asparagine		Asn	N
Tyrosine		Tyr	Y	Glutamine		Gln	Q

Some common features of these amino acids should be noted. With the exception of proline, they are all 1º-amines; and with the exception of glycine, they are all chiral. 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 R-substituent in this structure is the remaining structural component that varies from one amino acid to another, and in proline R is a three-carbon chain that joins the nitrogen to the alpha-carbon in a five-membered ring. Applying the Cahn-Ingold-Prelog notation, all these natural chiral amino acids, with the exception of cysteine, have an **S**-configuration. For the first seven compounds in the left column the R-substituent is a hydrocarbon. The last three entries in the left column have hydroxyl functional groups, and the first two amino acids in the right column incorporate thiol and sulfide groups respectively. Lysine and arginine have basic amine functions in their side-chains; histidine and tryptophan have less basic nitrogen heterocyclic rings as substituents. Finally, carboxylic acid side-chains are substituents on aspartic and glutamic acid, and the last two compounds in the right column are their corresponding amides.


L-Amino Acid

The formulas for the amino acids written above are simple covalent bond representations based upon previous understanding of mono-functional analogs. **The formulas are in fact incorrect**. 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

Compound	Formula	Mol.Wt.	Solubility in Water	Solubility in Ether	Melting Point	pK_a
isobutyric acid	$(CH_3)_2CHCO_2H$	88	20g/100mL	complete	-47 ºC	5.0
lactic acid	$CH_3CH(OH)CO_2H$	90	complete	complete	53 ºC	3.9
3-amino-2-butanol	$CH_3CH(NH_2)CH(OH)CH_3$	89	complete	complete	9 ºC	10.0
alanine	$CH_3CH(NH_2)CO_2H$	89	18g/100mL	insoluble	ca. 300 ºC	9.8

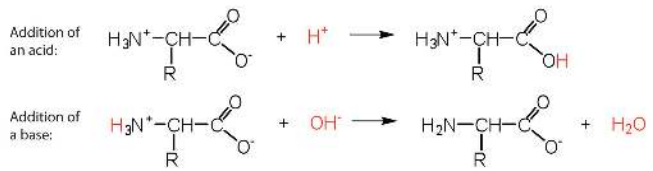
Zwitterion

These differences above all point to internal salt formation by a proton transfer from the acidic carboxyl function to the basic amino group. The resulting ammonium carboxylate structure, commonly referred to as a **zwitterion**, is also supported by the spectroscopic characteristics of alanine.

$CH_3CH(NH_2)CO_2H$	$\rightleftharpoons$	$CH_3CH(NH_3)^{(+)}CO_2^{(-)}$

As expected from its ionic character, the alanine zwitterion is high melting, insoluble in nonpolar solvents and has the acid strength of a 1º-ammonium ion. Examples of a few specific amino acids may also be viewed in their favored neutral zwitterionic form. Note that in lysine the amine function farthest from the carboxyl group is more basic than the alpha-amine. Consequently, the positively charged ammonium moiety formed at the chain terminus is attracted to the negative carboxylate, resulting in a coiled conformation.

The structure of an amino acid allows it to act as both an acid and a base. An amino acid has this ability because at a certain pH value (different for each amino acid) nearly all the amino acid molecules exist as zwitterions. If acid is added to a solution containing the zwitterion, the carboxylate group captures a hydrogen (H^+) ion, and the amino acid becomes positively charged. If base is added, ion removal of the H^+ ion from the amino group of the zwitterion produces a negatively charged amino acid. In both circumstances, the amino acid acts to maintain the pH of the system—that is, to remove the added acid (H^+) or base (OH^-) from solution.

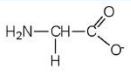


Example 26.1

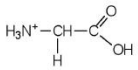
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

a. The base removes H^+ from the protonated amine group.

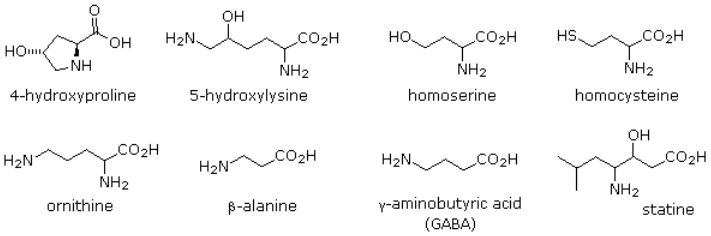


The acid adds H^+ to the carboxylate group.



Other Natural Amino Acids

The twenty alpha-amino acids listed above are the primary components of proteins, their incorporation being governed by the genetic code. Many other naturally occurring amino acids exist, and the structures of a few of these are displayed below. Some, such as hydroxylysine and hydroxyproline, are simply functionalized derivatives of a previously described compound. These two amino acids are found only in collagen, a common structural protein. Homoserine and homocysteine are higher homologs of their namesakes. The amino group in beta-alanine has moved to the end of the three-carbon chain. It is a component of pantothenic acid, $HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2CO_2H$, a member of the vitamin B complex and an essential nutrient. Acetyl coenzyme A is a pyrophosphorylated derivative of a pantothenic acid amide. The gamma-amino homolog GABA is a neurotransmitter inhibitor and antihypertensive agent.



Many unusual amino acids, including D-enantiomers of some common acids, are produced by microorganisms. These include ornithine, which is a component of the antibiotic bacitracin A, and statin, found as part of a pentapeptide that inhibits the action of the digestive enzyme **pepsin**.

Exercises

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7.3: Amino Acids, the Henderson-Hasselbalch Equation, 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. Here, the pK_a represents the acidity of a specific conjugate acid function (HA). When the pH of the solution equals pK_a, the concentrations of HA and $A^{(-)}$ must be equal (log 1 = 0).

$$pK_a = pH + \log_{10} \frac{[HA]}{A^-]}$$

The titration curve for alanine in Figure 7.3.2 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 concentration. 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.

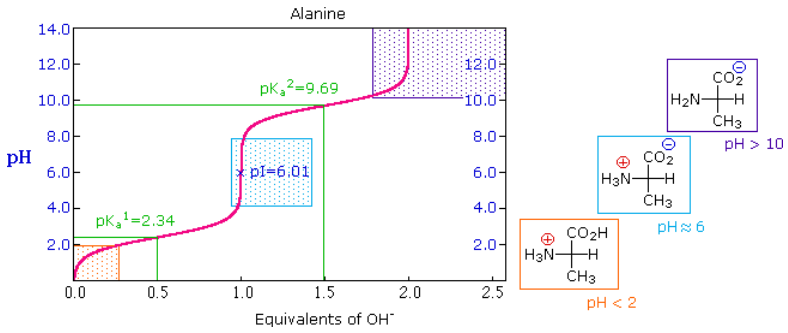


Figure 7.3.1: Titration curves for many other amino acids may be examined at a useful site provided by The University of Virginia in Charlottesville.

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 7.3.2). 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.

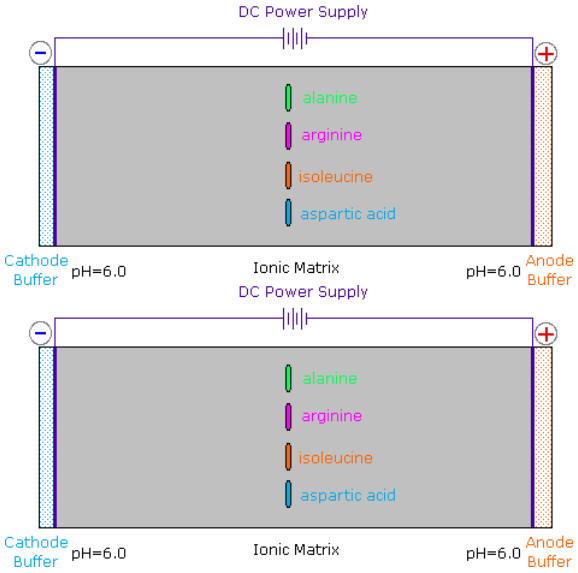
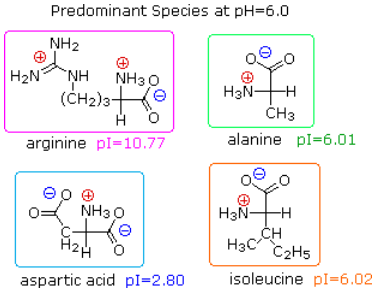


Figure 7.3.2: In the example shown here, four different amino acids are examined simultaneously in a pH 6.00 buffered medium. To see the result of this experiment, click on the illustration. Note that the colors in the display are only a convenient reference, since these amino acids are colorless.

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.



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.

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 2º-amino acid proline, pK_a^2 is 10.6, reflecting the greater basicity of 2º-amines.

Table 7.3.1: 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

Amino Acid	α-CO_2H pK_a^1	α-NH_3 pK_a^2	Side Chain pK_a^3	pI
Tyrosine	2.2	9.1	10.1	5.7

Some amino acids have additional acidic or basic functions in their side chains. These compounds are listed in Table 7.3.1. 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. As expected, such compounds display three inflection points in their titration curves, illustrated by the titrations of arginine and aspartic acid (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.

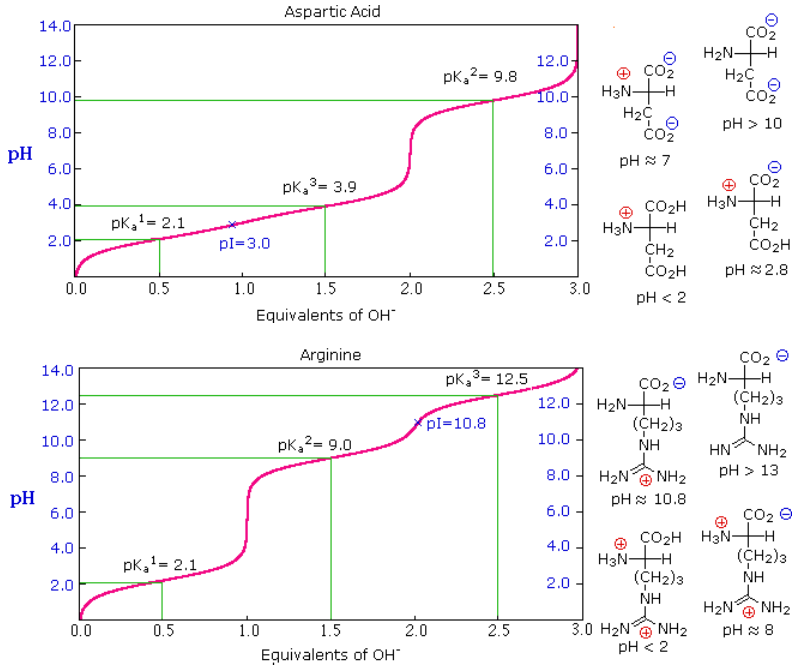


Figure 7.3.3

The Isoelectric Point

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. 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, 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, 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

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7.4: 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.

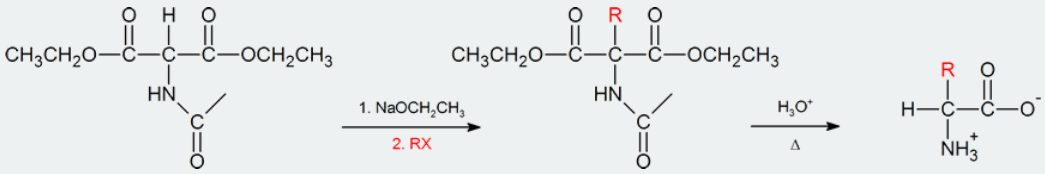
- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

Study Notes

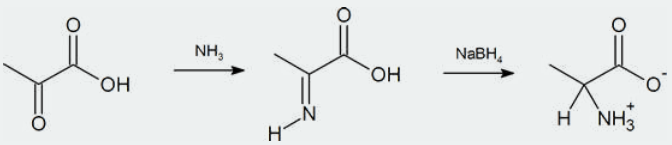
Do not be alarmed by the number of methods to synthesize amino acids described in this section.You have seen many of these reactions in previous sections and should already be familiar with the approaches discussed here.

To fulfill the requirements of Objective 1, review the Hell-Volhard-Zelinskii reaction (Section 22.4) and the Gabriel phthalimide synthesis (Section 24.6).

The **amidomalonate synthesis** is a simple variation of the malonic ester synthesis (Section 22.7). A base abstracts a proton from the alpha carbon, which is then alkylated with an alkyl halide. Then both the hydrolysis of the esters and the amide protecting group under aqueous acidic conditions generates the α-amino acid.



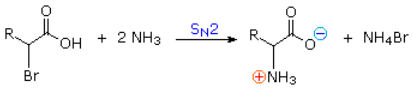
Another method of getting to the α-amino acid is by **reductive amination** of the α-keto acid which you have also previously encountered (Section 24.6).



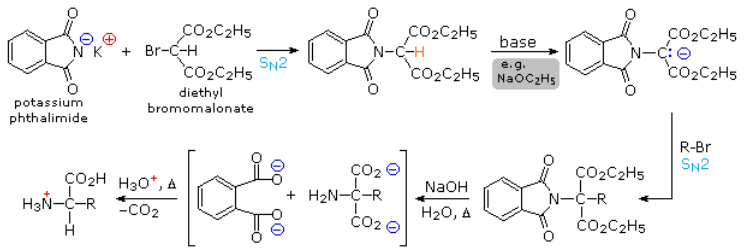
Synthesis of α-Amino Acids

1) Amination of alpha-bromocarboxylic acids, illustrated by the following equation, provides a straightforward method for preparing alpha-aminocarboxylic acids. The bromoacids, in turn, are conveniently prepared from carboxylic acids by reaction with Br_2 + PCl_3. Although this direct approach gave mediocre results when used to prepare simple amines from alkyl halides, it is more

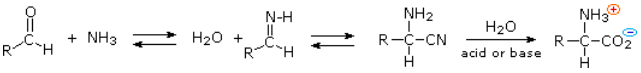
effective for making amino acids, thanks to the reduced nucleophilicity of the nitrogen atom in the product. Nevertheless, more complex procedures that give good yields of pure compounds are often chosen for amino acid synthesis.



2) 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).

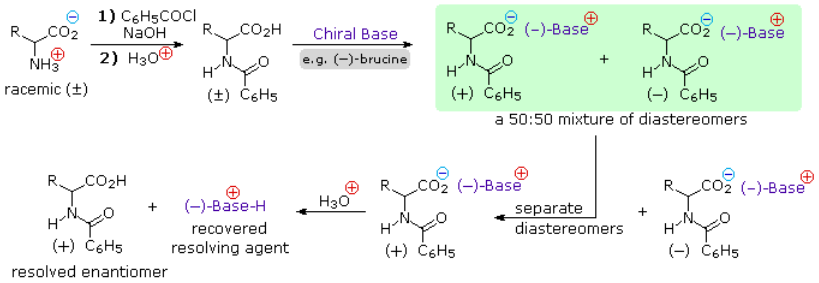


3) An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this way can then be hydrolyzed to an amino acid by either acid or base catalysis.

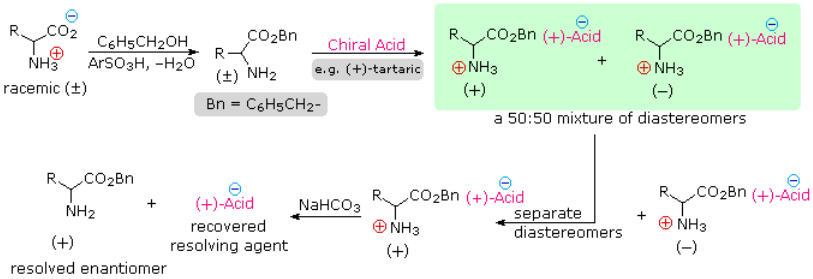


4) Resolution The three synthetic procedures described above, and many others that can be conceived, give racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve these racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation 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 diastereomeric salt formation. 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.



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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 aminoacid 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

Till now all of the synthetic routes to α-amino acids we have discussed yield a racemic mixture. Once produced one could resolve the mixture to obtain pure **L** or **D** enantiomers. However, enantioselective synthetic methods to produce pure compounds directly are being developed. For instance, several catalysts are now available for reduction of C=C to expose enantiopure amino acids. 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 production of almost pure L-DOPA.

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7.5: 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$\ce{-}$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.

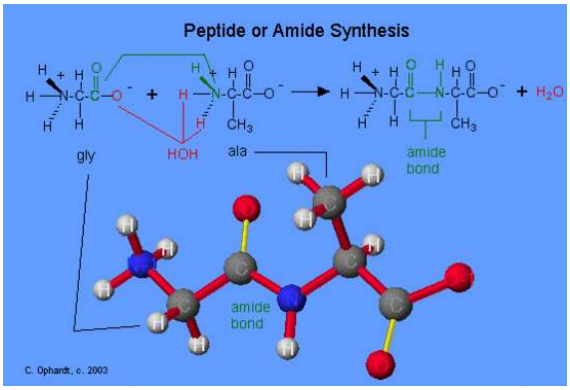
- C-terminal amino acid
- N-terminal amino acid
- peptides
- residues

Study Notes

If necessary, review the discussion of the delocalization of the nitrogen lone-pair electrons in amides that was presented in Section 24.3. Similarly, you may wish to refer back to Section 18.8 to review the interconversion of thiols and disulfides.

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. The reaction of glycine with alanine to form the dipeptide glyclalanine is written as shown in the graphic on the left. Oxygen (red) from the acid and hydrogens (red) on the amine form a water molecule. The carboxyl oxygen (green) and the amine nitrogen (green) join to form the amide bond.



If the order of listing the amino acids is reversed, a different dipeptide is formed such as alaninylglycine.

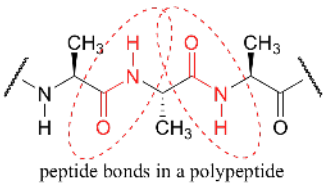
Exercise 7.5.1

Write the reactions for:

a. ala + gly ---> Answer graphic
b. phe + ser ----> Answer graphic

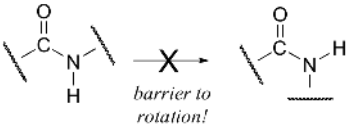
Resonance contributors for the peptide bonds

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.

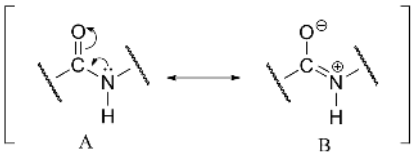


peptide bonds in a polypeptide

Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, the C-N bond in a peptide linkage has a significant barrier to rotation, almost as if it were a double bond.



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.



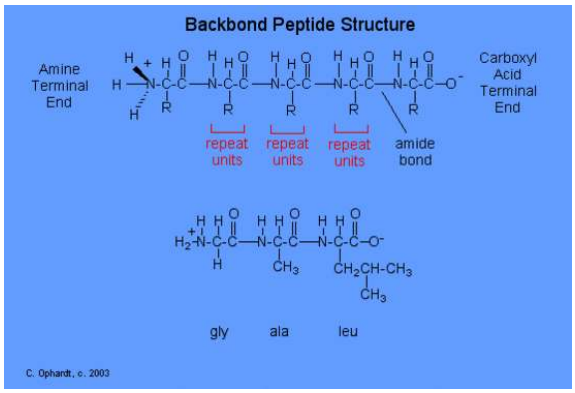
Although B is a minor contributor due to the separation of charges, it is still very relevant in terms of peptide and protein structure – our proteins would simply not fold up properly if there was free rotation about the peptide C-N bond.

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.

The peptide backbone consists of repeating units of "N-H 2, CH, C double bond O; N-H 2, CH, C double bond O; etc. See the graphic on the left .

After the backbone is written, go back and write the specific structure for the side chains as represented by the "R" as gly-ala-leu for this example. The amine end (N terminal) of an amino acid is always on the left (gly), while the acid end (C terminal) is on the right (leu).



? Exercise 7.5.2

Write the tripeptide structure for val-ser-cys. First write the "backbone" and then add the specific side chains.

Solution

Answer graphic

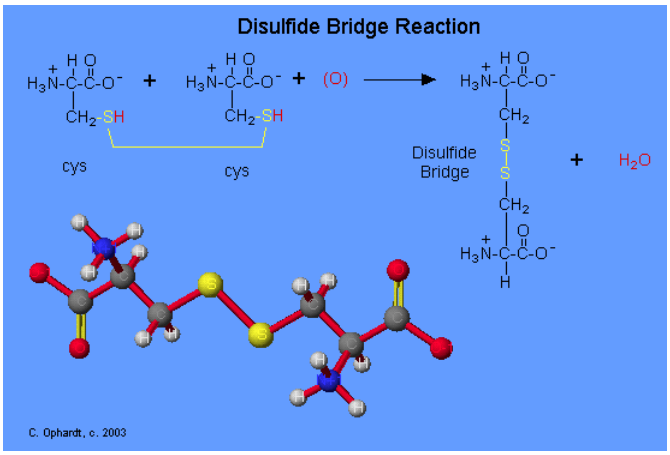
QUES. Write the structure for the tripeptide:

2 a) glu-cys-gly ---> Answer graphic

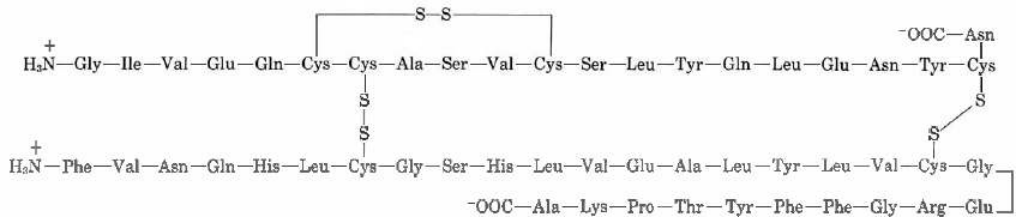
2 b) phe-tyr-asn ---> Answer graphic

Disulfide Bridges and Oxidation-Reduction

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 hydrogens. The **oxidation** of two cysteine amino acids is shown in the graphic. An unspecified oxidizing agent (O) provides an oxygen which reacts with the hydrogen (red) on the -SH group to form water. The sulfurs (yellow) join to make the **disulfide bridge**. This is an important bond to recognize in protein tertiary structure. The reduction of a disulfide bond is the opposite reaction which again leads to two separate cysteine molecules. Remember that reduction is the addition of hydrogen.



Cysteine residues in the the peptide chain can form a loop buy 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 the primary structure to comprise of two chains linked by two cysteine disulfide bridges. Also note the first peptide chain possesses an internal loop.



Insulin

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7.6: Peptide Synthesis

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. write a detailed mechanism for 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 in order to form a dipeptide from two given amino acids.

In order to synthesize a peptide from its component amino acids, two obstacles must be overcome. The first of these is statistical in nature, and is illustrated by considering the dipeptide Ala-Gly as a proposed target. If we ignore the chemistry involved, a mixture of equal molar amounts of alanine and glycine would generate four different dipeptides. These are: **Ala-Ala, Gly-Gly, Ala-Gly & Gly-Ala**. In the case of tripeptides, the number of possible products from these two amino acids rises to eight. Clearly, some kind of selectivity must be exercised if complex mixtures are to be avoided.

The second difficulty arises from the fact that carboxylic acids and 1º or 2º-amines do not form amide bonds on mixing, but will generally react by proton transfer to give salts (the intermolecular equivalent of zwitterion formation).

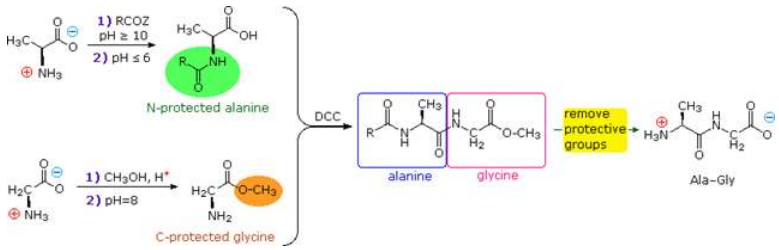
From the perspective of an organic chemist, peptide synthesis requires selective acylation of a free amine. To accomplish the desired amide bond formation, we must first deactivate all extraneous amine functions so they do not compete for the acylation reagent. Then we must selectively activate the designated carboxyl function so that it will acylate the one remaining free amine. Fortunately, chemical reactions that permit us to accomplish these selections are well known.

First, the basicity and nucleophilicity of amines are substantially reduced by amide formation. Consequently, the acylation of amino acids by treatment with acyl chlorides or anhydrides at pH > 10, as described earlier, serves to protect their amino groups from further reaction.

Second, acyl halide or anhydride-like activation of a specific carboxyl reactant must occur as a prelude to peptide (amide) bond formation. This is possible, provided competing reactions involving other carboxyl functions that might be present are precluded by preliminary ester formation. Remember, esters are weaker acylating reagents than either anhydrides or acyl halides, as noted earlier.

Finally, dicyclohexylcarbodiimide (DCC) effects the dehydration of a carboxylic acid and amine mixture to the corresponding amide under relatively mild conditions. The structure of this reagent and the mechanism of its action have been described. Its application to peptide synthesis will become apparent in the following discussion.

The strategy for peptide synthesis, as outlined here, should now be apparent. The following example shows a selective synthesis of the dipeptide Ala-Gly.



An important issue remains to be addressed. Since the N-protective group is an amide, removal of this function might require conditions that would also cleave the just formed peptide bond. Furthermore, the harsh conditions often required for amide hydrolysis might cause extensive racemization of the amino acids in the resulting peptide. This problem strikes at the heart of our strategy, so it is important to give careful thought to the design of specific N-protective groups. In particular, three qualities are desired:

1. The protective amide should be easy to attach to amino acids.

2. The protected amino group should not react under peptide forming conditions.
3. The protective amide group should be easy to remove under mild conditions.

A number of protective groups that satisfy these conditions have been devised; and two of the most widely used, **carbobenzoxy** (Cbz) and **t-butoxycarbonyl** (BOC or t-BOC), are described here.

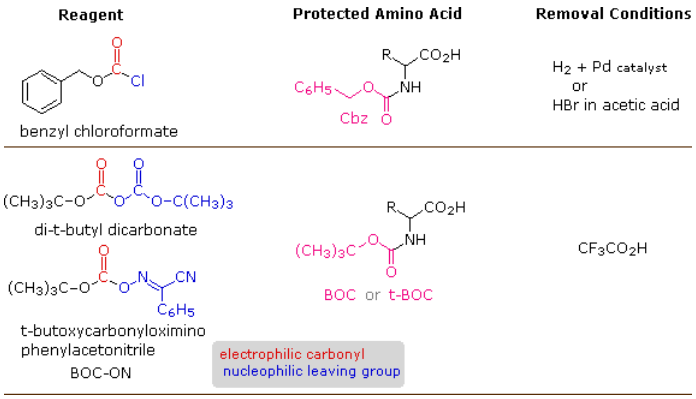


Figure_3.png" />

The reagents for introducing these N-protective groups are the acyl chlorides or anhydrides shown in the left portion of the above diagram. Reaction with a free amine function of an amino acid occurs rapidly to give the "protected" amino acid derivative shown in the center. This can then be used to form a peptide (amide) bond to a second amino acid. Once the desired peptide bond is created the protective group can be removed under relatively mild non-hydrolytic conditions. Equations showing the protective group removal will be displayed above by are shown above. Cleavage of the reactive benzyl or tert-butyl groups generates a common carbamic acid intermediate (HOCO-NHR) which spontaneously loses carbon dioxide, giving the corresponding amine. If the methyl ester at the C-terminus is left in place, this sequence of reactions may be repeated, using a different N-protected amino acid as the acylating reagent. Removal of the protective groups would then yield a specific tripeptide, determined by the nature of the reactants and order of the reactions.

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7.7: 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.

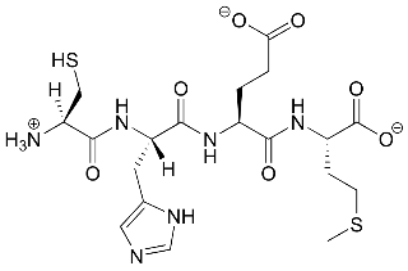
- α helix
- β pleated sheet
- primary structure
- quaternary structure
- secondary structure
- tertiary structure

Study Notes

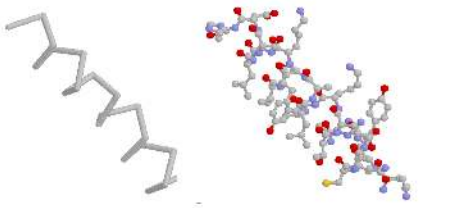
Note that in a diagram of the α-helical structure of a protein, the C-terminal of the protein is at the bottom of the diagram and the N-terminal is at the top. In an α helix, such as the one shown in Figure 26.9.1, the bulky R groups are all found on the outside of the helix, where they have the most room.

The four levels of protein 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)

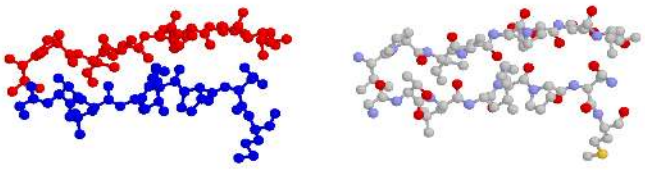


Secondary structure is three-dimensional, but is a local phenomenon, confined to a relatively short stretch of amino acids. For the most part, there are three important elements of secondary structure: helices, beta-sheets, and loops. In a helix, the main chain of the protein adopts the shape of a clockwise spiral staircase, and the side chains point out laterally.



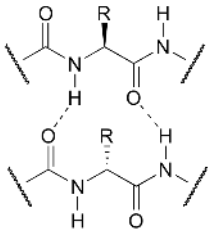
main chain view main chain + side chain

In a beta-sheet (or beta-strand) structure, two sections of protein chain are aligned side-by-side in an extended conformation. The figure below shows two different views of the same beta-sheet: in the left-side view, the two regions of protein chain are differentiated by color.



Loops are relatively disordered segments of protein chain, but often assume a very ordered structure when in contact with a second protein or a smaller organic compound.

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

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

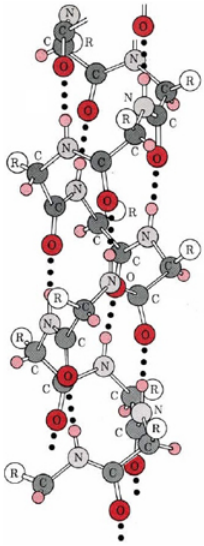


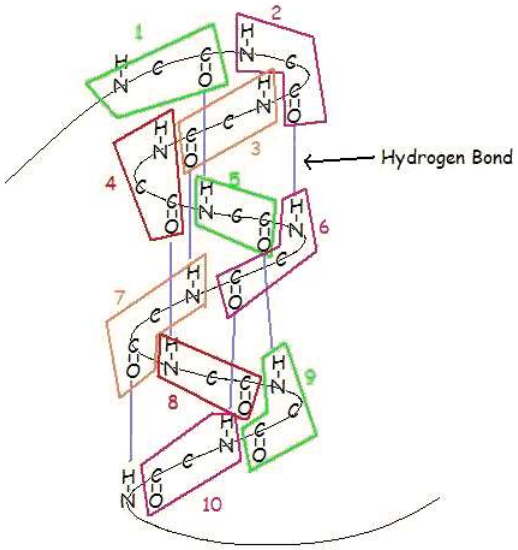
Figure 26.9.1 *Ball-and-stick model of the α helix. Hydrogen bonds are shown as dotted bonds. Note that R groups extend almost perpendicular from the axis.*

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 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.

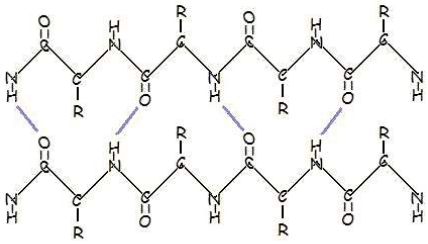
The structural integrity of an α-helix is in part dependent on correct steric configuration. Amino acids whose R-groups are too large (tryptophan, tyrosine) or too small (glycine) destabilize α-helices. Proline also destabilizes α-helices because of its irregular geometry; its R-group bonds back to the 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 entire helix due to 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.



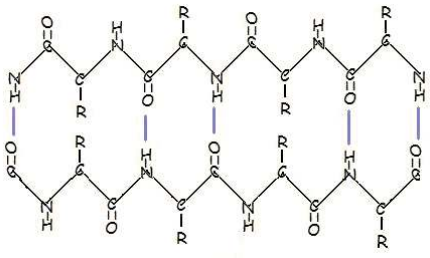
BETA-PLEATED SHEETS

This structure occurs when two (or more, e.g. ψ-loop) segments of a polypeptide chain overlap one another and form a row of hydrogen bonds with each other. This can happen in a parallel arrangement:



Parallel

Or in anti-parallel arrangement:



Anti-Parallel

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

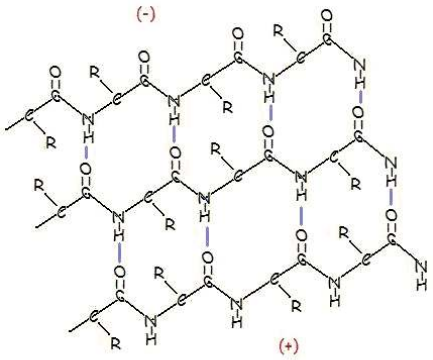
arrangement, the C-terminus end and the N-terminus end are on the same sides for both segments. The "pleat" occurs because of the alternating planes of the peptide bonds between amino acids; the aligned amino and carbonyl group of each opposite segment alternate their orientation from facing towards 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.

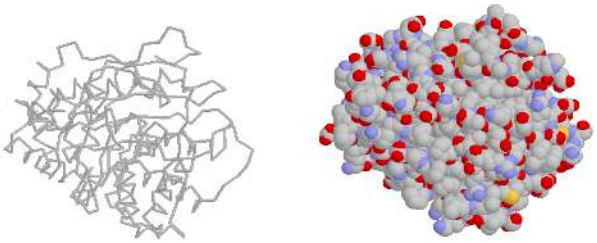
α-PLEATED SHEETS

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

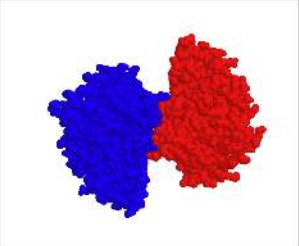
A protein's **tertiary structure** is the shape in which the entire protein chain folds together in three-dimensional space, and it is this level of structure that provides protein scientists with the most information about a protein's specific function.



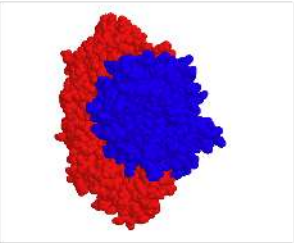
folded protein chain
(main chain view)

folded protein chain
('space-filling' view)

While a protein's secondary and tertiary structure is defined by how the protein chain folds together, **quaternary structure** is defined by how two or more folded protein chains come together to form a 'superstructure'. Many proteins consist of only one protein chain, or **subunit**, and thus have no quaternary structure. Many other proteins consist of two identical subunits (these are called homodimers) or two non-identical subunits (these are called heterodimers).

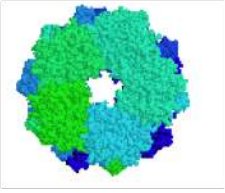


a homodimer

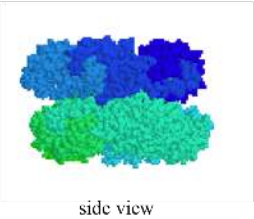


a heterodimer

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):



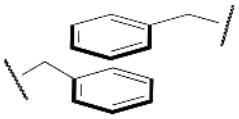
top view



side view

The molecular 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 same basic noncovalent forces that we talked about in chapter 2: ion-ion, ion-dipole, dipole-dipole, hydrogen bonding, and hydrophobic (van der Waals) interactions. 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.



Hydrogen bonding networks are extensive within proteins, with both side chain and main chain atoms participating. Ionic interactions often play a role in protein structure, especially on the protein surface, as negatively charged residues such as aspartate interact with positively-charged groups on lysine or arginine.

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 caused to come unfolded (through exposure to heat, for example, or extremes of pH), it will usually lose its solubility and form solid precipitates, as the 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.

In recent years, scientists have become increasing 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 is 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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7.8: 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. 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

Study Notes

You should have a general knowledge of the function of enzymes, but you need not memorize specific names or the classification system.

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. 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 7.8.1.

Table 7.8.1: ***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 subst 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.

Class	Type of Reaction Catalyzed	Examples
isomerases	reactions in which a compound is converted to its isomer	Isomerases may catalyze the conversion of an aldose to a ketose, and mutases catalyze reactions in which a functional group is tr 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-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 7.8.1). 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 7.8.2):

$$S + E \rightleftharpoons E\text{–}S \tag{7.8.1}$$

$$E\text{–}S \rightarrow P + E \tag{7.8.2}$$

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 7.8.1).

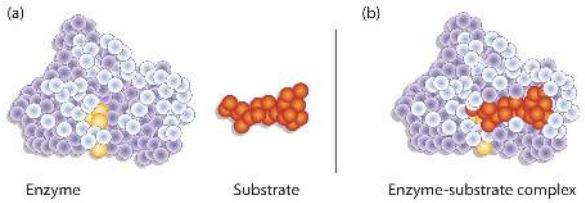


Figure 7.8.1: *Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.*

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 7.8.2). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

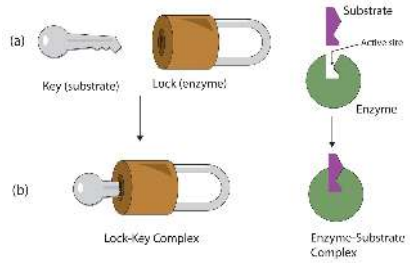


Figure 7.8.2: The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate complex.

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 theinduced-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 7.8.3. After catalysis, the enzyme resumes its original structure.

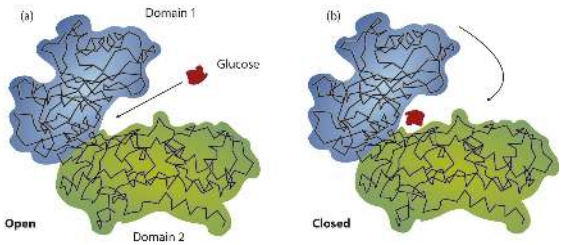


Figure 7.8.3: The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and glucose.

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 7.8.1

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 7.8.1

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.

Enzyme Cofactors and Vitamins

Many enzymes are simple proteins consisting entirely of one or more amino acid chains. Other enzymes contain a nonprotein component called a **cofactor** that is necessary for the enzyme's proper functioning. There are two types of cofactors: inorganic ions [e.g., zinc or Cu(I) ions] and organic molecules known as coenzymes. Most **coenzymes** are vitamins or are derived from vitamins.

Vitamins are organic compounds that are essential in very small (trace) amounts for the maintenance of normal metabolism. They generally cannot be synthesized at adequate levels by the body and must be obtained from the diet. The absence or shortage of a vitamin may result in a vitamin-deficiency disease. In the first half of the 20th century, a major focus of biochemistry was the identification, isolation, and characterization of vitamins. Despite accumulating evidence that people needed more than just carbohydrates, fats, and proteins in their diets for normal growth and health, it was not until the early 1900s that research established the need for trace nutrients in the diet.

Table 7.8.2: Fat-Soluble Vitamins and Physiological Functions

Vitamin	Physiological Function	Effect of Deficien
vitamin A (retinol)	formation of vision pigments; differentiation of epithelial cells	night blindness; continued deficiency
vitamin D (cholecalciferol)	increases the body's ability to absorb calcium and phosphorus	osteomalacia (softening of the bones); kn
vitamin E (tocopherol)	fat-soluble antioxidant	damage to cell memb
vitamin K (phylloquinone)	formation of prothrombin, a key enzyme in the blood-clotting process	increases the time required fo

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 7.8.2), which include vitamins A, D, E, and K, and the *water-soluble vitamins*, which are the B complex vitamins and vitamin C (Table 7.8.3). 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 7.8.3: ***Water-Soluble Vitamins and Physiological Functions***

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease

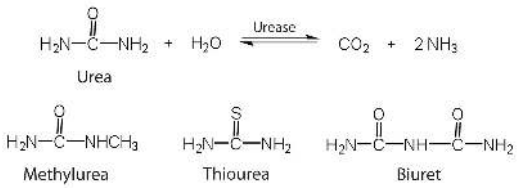
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Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
vitamin B_1 (thiamine)	thiamine pyrophosphate	decarboxylation reactions	beri-beri
vitamin B_2 (riboflavin)	flavin mononucleotide or flavin adenine dinucleotide	oxidation-reduction reactions involving two hydrogen atoms	—
vitamin B_3 (niacin)	nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate	oxidation-reduction reactions involving the hydride ion (H^-)	pellagra

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
vitamin B_6 (pyridoxine)	pyridoxal phosphate	variety of reactions including the transfer of amino groups	—
vitamin B_{12} (cyanocobalamin)	methylcobalamin or deoxyadenoxylcobalamin	intramolecular rearrangement reactions	pernicious anemia
biotin	biotin	carboxylation reactions	—
folic acid	tetrahydrofolate	carrier of one-carbon units such as the formyl group	anemia

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
pantothenic Acid	coenzyme A	carrier of acyl groups	—
vitamin C (ascorbic acid)	none	antioxidant; formation of collagen, a protein found in tendons, ligaments, and bone	scurvy

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.

Concept Review Exercises

1. Distinguish between the lock-and-key model and induced-fit model of enzyme action.
2. Which enzyme has greater specificity—urease or carboxypeptidase? Explain.

Answers

1. 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.
2. Urease has the greater specificity because it can bind only to a single substrate. Carboxypeptidase, on the other hand, can catalyze the removal of nearly any amino acid from the carboxyl end of a peptide or protein.

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

1. 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. $CH(CH_3)_2$
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. SH
   b. NH_2
   c. C_6H_5
   d. COO^-
3. For each functional group in Exercise 1, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.
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.

Answers

1. a. hydrogen bonding
   b. ionic bonding
   c. hydrogen bonding
   d. dispersion forces
3. 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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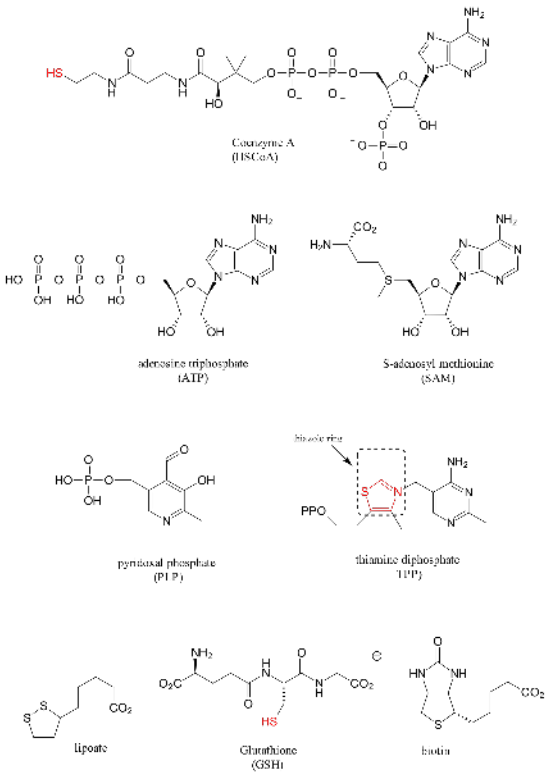
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7.9: How do Enzymes Work? Citrate Synthase

Objectives

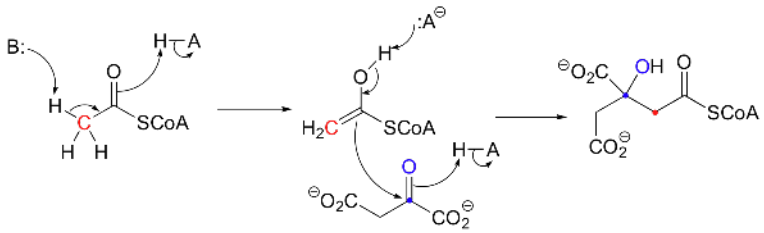
After completing this section, you should be able to

1. describe and explain the general function of an enzyme like citrate synthase in a reaction.
2. identify the structures of ten common coenzymes.



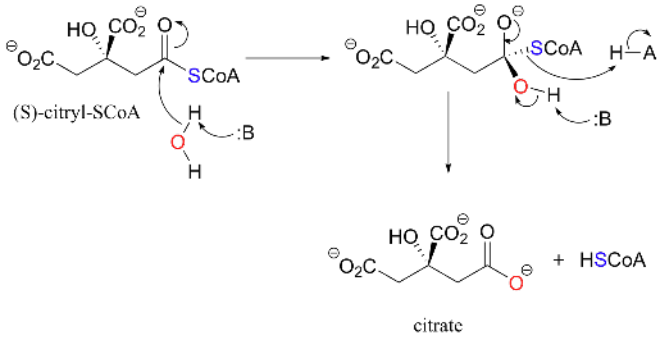
Oxaloacetate to Citrate Catalyzed by Citrate Synthase

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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7.10: Chapter Objectives

placeholder

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7.11: Amino Acid Analysis of Peptides

Objectives

After completing this section, you should be able to describe, briefly, how the identity and amounts of each amino acid residue present in a peptide of unknown structure may be determined.

Key Terms

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

- amino acid analyzer

Study Notes

You need not memorize the reaction between ninhydrin and an α-amino acid.

Ion-exchange chromatography

When a protein is to be analysed, it is first heated with acid to hydrolyse all the peptide bonds. When such a mixture of amino acids is to be purified and estimated quantitatively, ion-exchange chromatography is the technique of choice. Fully automated amino acid analyzers are now available, which are equipped with a solvent pump to deliver the required buffer(s) in a programmed manner. There is a column, filled with Dowex 50 resin (Fig 26.5.1). This solid support is made up of polymeric beads. Chemically speaking they are polymers bearing arylsulfonic acid groups. The cation exchange resin helps in the separation of amino acids. In a typical run (Fig 26.5.2), the eluent is a buffer. The pH value of the buffer could be varied as step elution or as gradient elution. The chromatogram shown in Fig 26.5.2 is a chromatogram run with gradient elution technique, using **ninhydrin** as the post column treatment. The detector is a UV detector scanning the wavelengths 570 nm and 440 nm.

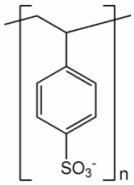


Fig 26.5.1: A Cation Rasin like Dowex 50 is a polymeric bead bearing aryl sulfonic acid groups

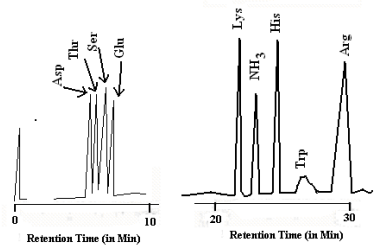
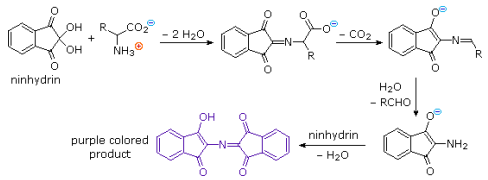


Fig 26.5.2: Some typical chromatograms from an amino acid analyzer

The Ninhydrin Reaction

Alpha-amino acids show reactivity at their the carboxylic acid and amine sites typical of those functional groups. In addition to these common reactions of amines and carboxylic acids, common alpha-amino acids, except proline, undergo a unique reaction with the triketohydrindene hydrate known as ninhydrin. Among the products of this unusual reaction (shown on the left below) is a purple colored imino derivative, which provides as a useful color test for these amino acids, most of which are colorless. A common application of the ninhydrin test is the visualization of amino acids in paper chromatography. As shown in the graphic on the right, samples of amino acids or mixtures thereof are applied along a line near the bottom of a rectangular sheet of paper (the baseline). The bottom edge of the paper is immersed in an aqueous buffer, and this liquid climbs slowly toward the top edge. As the solvent front passes the sample spots, the compounds in each sample are carried along at a rate which is characteristic of their functionality, size and interaction with the cellulose matrix of the paper. Some compounds move rapidly up the paper, while others may scarcely move at all. The ratio of the distance a compound moves from the baseline to the distance of the solvent front from the baseline is defined as the retardation (or retention) factor R_f. Different amino acids usually have different R_f's under suitable conditions. In the example on the right, the three sample compounds (1, 2 & 3) have respective R_f values of 0.54, 0.36 & 0.78.



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7.12: The Edman Degradation

Objectives

After completing this section, you should be able to

1. describe how an Edman degradation is used to determine the sequence of the amino acid residues in peptides containing up to 20 such residues.
2. describe, briefly, how the procedure is modified to deal with peptides and proteins containing more than 20 amino acid residues.
3. write a detailed mechanism for the Edman degradation.
4. determine the structure of a peptide, given a list of the fragments that are produced by a partial acid hydrolysis.
5. determine the structure of a peptide, given a list of the fragments that are produced when the peptide is cleaved by a specific enzyme and the details of the types of bonds cleaved by that enzyme.
6. predict the fragments that would be produced when a peptide of known structure is cleaved by a specific enzyme, given sufficient information about the types of bonds that are cleaved by the enzyme in question.

Key Terms

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

- Edman degradation

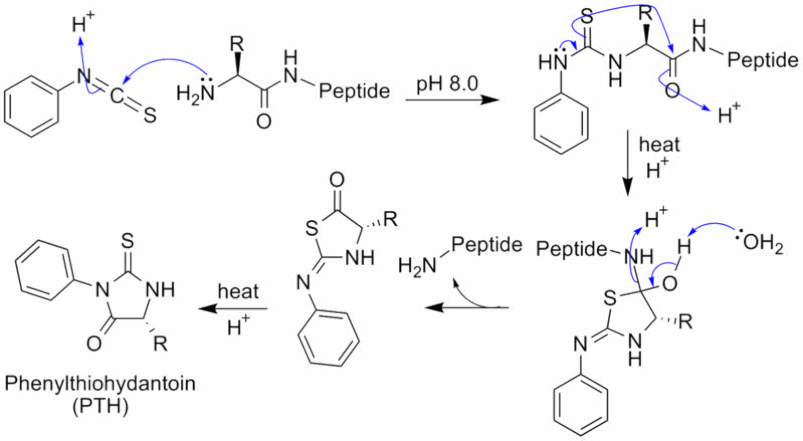
Study Notes

The reagent used in the Edman degradation is phenyl isothiocyanate. You may find it helpful to review the relationship between cyanates, isocyanates, thiocyanates and isothiocyanates.

R–O–C≡N	cyanate (such compounds do not exist)
R–N=C=O	isocyanate
R–S–C≡N	thiocyanate
R–N=C=S	isothiocyanate

You need not memorize the specific peptide bonds that are broken by the enzymes trypsin and chymotrypsin.

Edman degradation is the process of purifying protein by sequentially removing one residue at a time from the amino end of a peptide. To solve the problem of damaging the protein by hydrolyzing conditions, Pehr Edman created a new way of labeling and cleaving the peptide. Edman thought of a way of removing only one residue at a time, which did not damage the overall sequencing. This was done by adding Phenyl isothiocyanate, which creates a phenylthiocarbamoyl derivative with the N-terminal. The N-terminal is then cleaved under less harsh acidic conditions, creating a cyclic compound of phenylthiohydantoin PTH-amino acid. This does not damage the protein and leaves two constituents of the peptide. This method can be repeated for the rest of the residues, separating one residue at a time.



Edman degradation is very useful because it does not damage the protein. This allows sequencing of the protein to be done in less time. Edman sequencing is done best if the composition of the amino acid is known. As we saw in Section 26.5, to determine the composition of the amino acid, the peptide must be hydrolyzed. This can be done by denaturing the protein and heating it and adding HCl for a long time. This causes the individual amino acids to be separated, and they can be separated by ion exchange chromatography. They are then dyed with ninhydrin and the amount of amino acid can be determined by the amount of optical absorbance. This way, the composition but not the sequence can be determined

Sequencing Larger Proteins

Larger proteins cannot be sequenced by the Edman sequencing because of the less than perfect efficiency of the method. A strategy called divide and conquer successfully cleaves the larger protein into smaller, practical amino acids. This is done by using a certain chemical or enzyme which can cleave the protein at specific amino acid residues. The separated peptides can be isolated by chromatography. Then they can be sequenced using the Edman method, because of their smaller size.

In order to put together all the sequences of the different peptides, a method of overlapping peptides is used. The strategy of divide and conquer followed by Edman sequencing is used again a second time, but using a different enzyme or chemical to cleave it into different residues. This allows two different sets of amino acid sequences of the same protein, but at different points. By comparing these two sequences and examining for any overlap between the two, the sequence can be known for the original protein.

For example, trypsin can be used on the initial peptide to cleave it at the carboxyl side of arginine and lysine residues. Using trypsin to cleave the protein and sequencing them individually with Edman degradation will yield many different individual results. Although the sequence of each individual cleaved amino acid segment is known, the order is scrambled. Chymotrypsin, which cleaves on the carboxyl side of aromatic and other bulky nonpolar residues, can be used. The sequence of these segments overlap with those of the trypsin. They can be overlapped to find the original sequence of the initial protein. However, this method is limited in analyzing larger sized proteins (more than 100 amino acids) because of secondary hydrogen bond interference. Other weak intermolecular bonding such as hydrophobic interactions cannot be properly predicted. Only the linear sequence of a protein can be properly predicted assuming the sequence is small enough.

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7.13: The Merrifield 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)

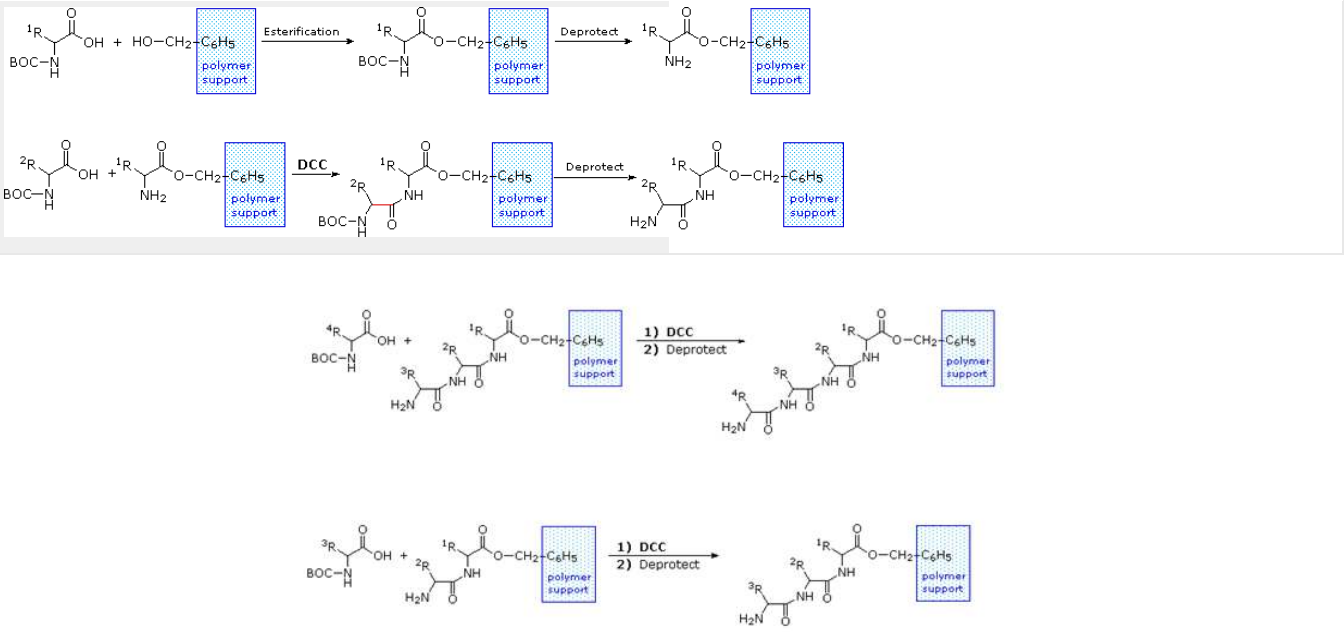
Study Notes

The solid-phase used in this method is a polymer support. You will not be examined on the details of the Merrifield solid-phase method; however, you should be prepared to write a couple of paragraphs describing this important process.

For his work on the synthesis of peptides, Bruce Merrifield was awarded the 1984 Nobel Prize in chemistry.

The synthesis of a peptide of significant length (e.g. ten residues) by this approach 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, a clever modification of this strategy has been developed. This procedure, known as the **Merrifield Synthesis** after its inventor R. Bruce Merrifield, involves attaching the C-terminus of the peptide chain to a polymeric solid, usually having the form of very small beads. Separation and purification is simply 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 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 may be viewed below. The final step, in which the completed peptide is released from the polymer support, is a simple benzyl ester cleavage. This is not shown in the display.

The Merrifield Peptide Synthesis



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Two or more moderately sized peptides can be joined together by selective peptide bond formation, provided side-chain functions are protected and do not interfere. In this manner good sized peptides and small proteins may be synthesized in the laboratory. However, even if chemists assemble the primary structure of a natural protein in this or any other fashion, it may not immediately adopt its native secondary, tertiary and quaternary structure. Many factors, such as pH, temperature and inorganic ion concentration influence the conformational coiling of peptide chains. Indeed, scientists are still trying to understand how and why these higher structures are established in living organisms.

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CHAPTER OVERVIEW

8: Biomolecules - Lipids

Learning Objectives

- When you have completed Chapter 27, 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.

8.1: Introduction to Lipids
8.2: Waxes, Fats, and Oils
8.3: Soap
8.4: Phospholipids
8.5: Terpenoids
8.6: Steroids
8.7: Biosynthesis of Steroids
8.8: Prostaglandins and Other Eicosanoids
8.S: Biomolecules - Lipids (Summary)

Contributors and Attributions

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8.1: Introduction to Lipids

Objectives

After completing this section, you should be able to identify fats and steroids as being examples of lipids.

Key Terms

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

- lipid

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. 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.

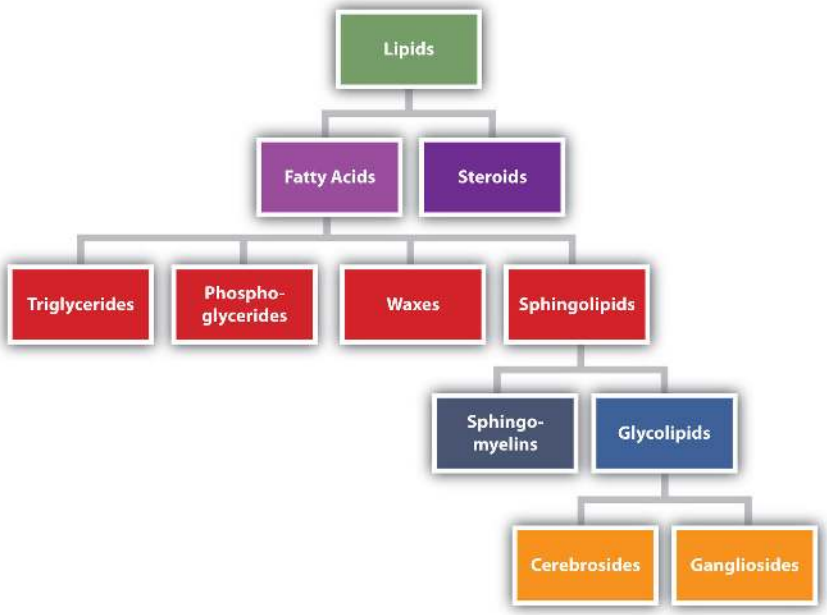


Figure 8.1.1: Lipid Organization Based on Structural Relationships

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 8.1.1 presents one scheme for classifying the various kinds of lipids.

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8.2: 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 8.2.1. The systematic names for these compounds are shown in the tables below.

Saturated Fatty Acids

Table 8.2.1: Systematic names of some common saturated fatty acids

Trivial Name	Systematic Name
lauric acid	dodecanoic acid
myristic acid	tetradecanoic acid
palmitic acid	hexadecanoic acid
stearic acid	octadecanoic acid
arachidic acid	eicosanoic acid

Unsaturated Fatty Acids

Table 8.2.2: Systematic names of some common unsaturated fatty acids

Trivial Name	Systematic Name
palmitoleic acid	(*Z*)-9-hexadecenoic acid
oleic acid	(*Z*)-9-octadecenoic acid
ricinoleic acid	(*Z*)-12-hydroxy-9-octadecenoic acid
linoleic acid	(*Z*,*Z*)-9,12-octadecadienoic acid
linolenic acid	(*Z*,*Z*,*Z*)-9,12,15-octadecatrienoic acid
arachidonic acid	(*Z*,*Z*,*Z*,*Z*)-5,8,11,14-eicosatetraenoic acid

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 20. You may wish to review the alkane names (Section 3.2) and the *E*,*Z* system (Section 7.5) 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 that are obtained from the hydrolysis of triacylglycerols.

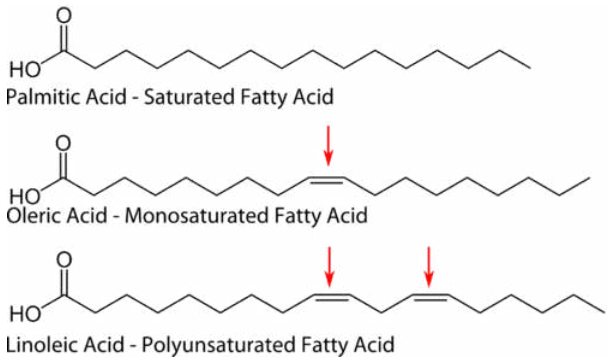
Fats play an important role in human nutrition, and most people are aware of the desirability of limiting their dietary intake of saturated fats, as these compounds have been associated with heart disease. Unsaturated fats are generally considered to be much more desirable from the point of view of good 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 thought to be essential nutrients, but recent research suggests that they can be synthesized in the body if sufficient linoleic acid is present.

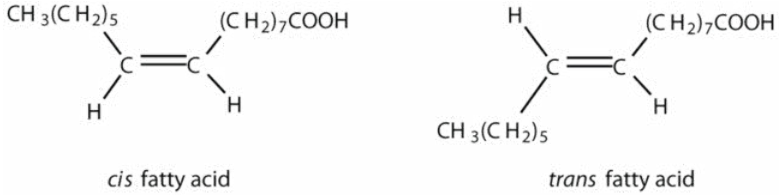
Fatty Acids

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).



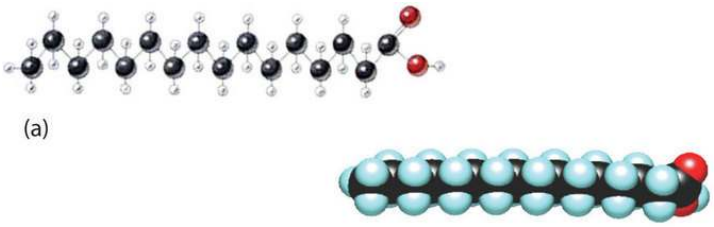
Each of the double bonds in unsaturated fatty acids can have either cis or trans stereochemistry and the type of fatty acid is further defined as a **cis fatty acid** or **trans fatty acid**. These are what are commonly referred to in food as cis or trans fats.



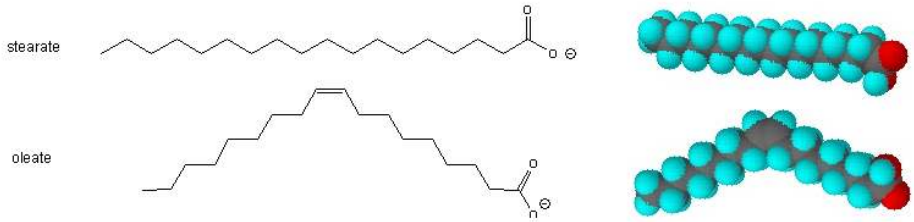
Saturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 °C
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 °C
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 °C
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 °C
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 °C

Unsaturated Fatty Acids		
Formula	Common Name	Melting Point
$CH_3(CH_2)_5CH=CH(CH_2)_7CO_2H$	palmitoleic acid	0 °C
$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H$	oleic acid	13 °C
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linoleic acid	-5 °C
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linolenic acid	-11 °C
$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 °C

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 into a crystal lattice, maximizing the strength of dispersion forces and causing fatty acids and the fats derived from them to have relatively high melting points.

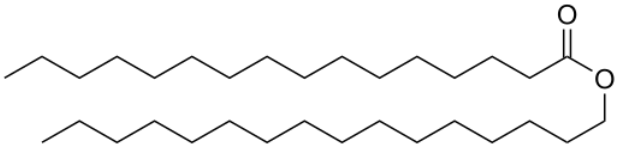


The cis-double bond(s) in the unsaturated fatty acids introduce a kink in their shape, which makes it more difficult to pack their molecules together in a stable repeating array or crystalline lattice. As a result, the intermolecular attractions of unsaturated fatty acids (and unsaturated fats) are weaker, causing these substances to have lower melting points. Most are liquids at room temperature.



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.

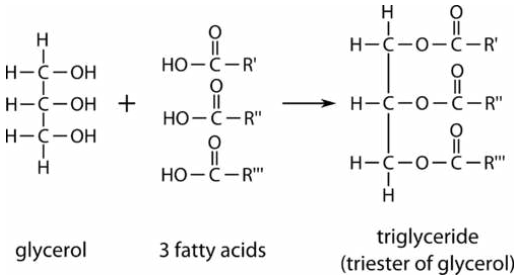
Waxes are widely distributed in nature. The leaves and fruits of many plants have waxy coatings, which may protect them from dehydration and small predators. The feathers of birds and the fur of some animals have similar coatings which serve as a water

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.

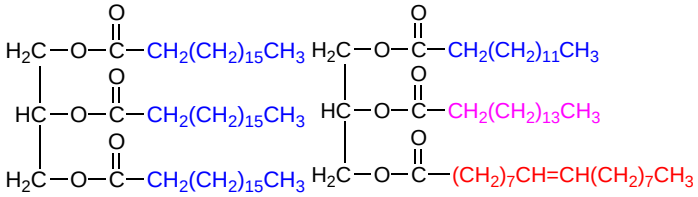
	Spermaceti	Beeswax	Carnauba wax
Alcohol	$CH_3(CH_2)_{14}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH
Fatty Acid	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{24}COOH$
Wax	$CH_3(CH_2)_{14}CO_2$-$(CH_2)_{15}CH_3$	$CH_3(CH_2)_{24}CO_2$-$(CH_2)_{29}CH_3$	$CH_3(CH_2)_{30}CO_2$-$(CH_2)_{33}CH_3$

Triglycerides

Fats 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)

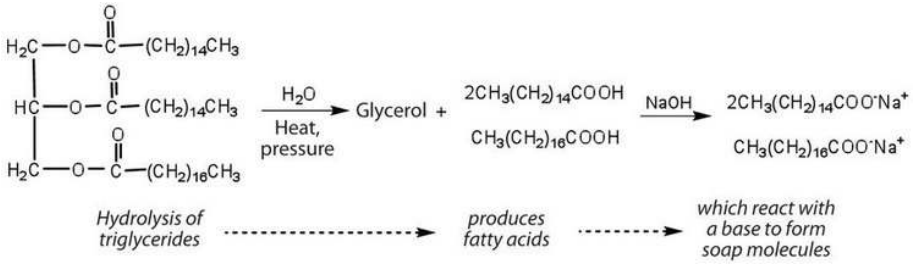
A triglyceride is called a **fat** if it is a solid at 25°C; it is called an **oil** if it is a liquid at that temperature. These differences in melting points reflect differences in the degree of unsaturation (as discussed above) and number of carbon atoms in the constituent fatty acids. Triglycerides 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 8.2.3: 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

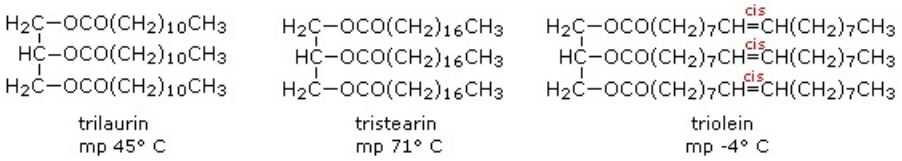
glycerides					
Vegetable Origin					
Corn oil	10	4	34	48	4
Soybean	7	3	25	56	9
Peanut	7	5	60	21	7
Olive	6	4	83	7	-

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 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):

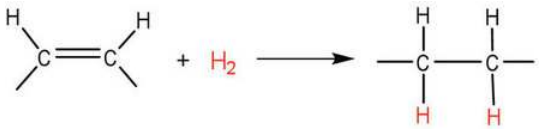


Chemical reaction of the saponification (base hydrolysis) of a triglyceride.

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.



The double bonds in fats and oils can undergo hydrogenation and also oxidation. 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.



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 being advised to use polyunsaturated oils and soft or liquid margarine and reduce their total fat consumption to less than 30% of their total calorie intake each day.

Exercise 8.2.1

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 8.2.2

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 8.2.3

Write the condensed structural formula for each fatty acid.

a. lauric acid
b. palmitoleic acid
c. linoleic acid

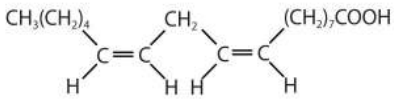
Answer

a. $CH_3(CH_2)_{10}COOH$
b. $CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
c. $CH_3(CH_2)_3(CH_2CH{=}CH)_2(CH_2)_7COOH$

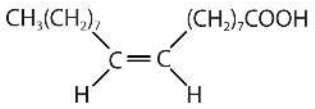
Exercise 8.2.4

Arrange these fatty acids (all contain 18 carbon atoms) in order of increasing melting point. Justify your arrangement.

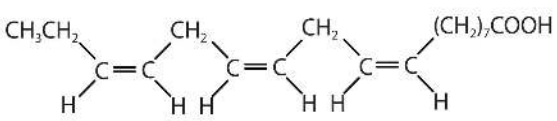
a)



b)



c)

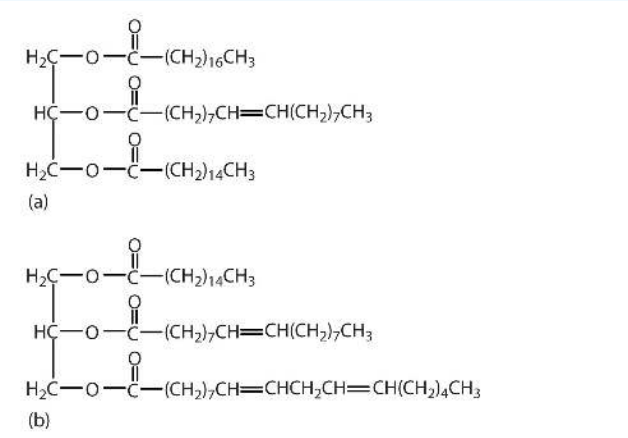


Answer

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 8.2.5

Which of these triglycerides would you expect to find in higher amounts in oils? In fats? Justify your choice.



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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8.3: 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.

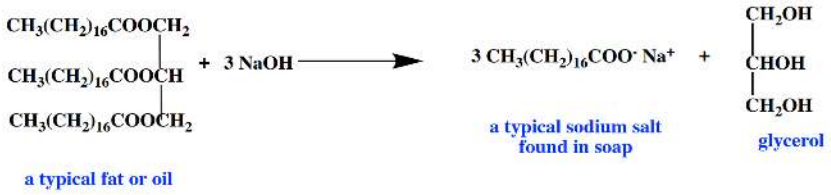
Key Terms

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

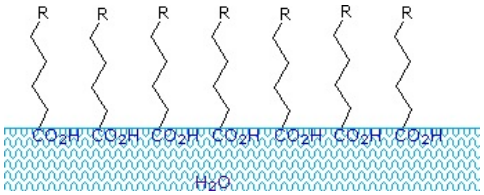
- hydrophilic
- lipophilic (hydrophobic)
- amphiphilic
- micelles

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.

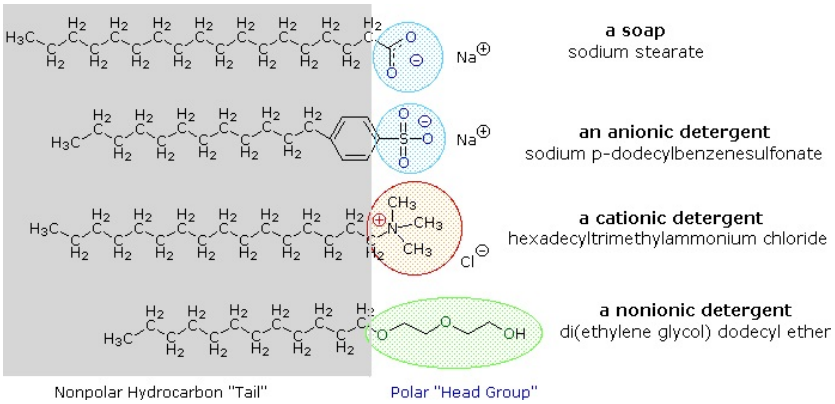
All soap is made from fats and oils, mixed with alkaline (basic) solutions. There are many kinds of fats and oils, both animal and vegetable. As previously discussed, fats are usually solid at room temperature, but many oils are liquid at room temperature. Liquid cooking oils originate from corn, peanuts, 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.



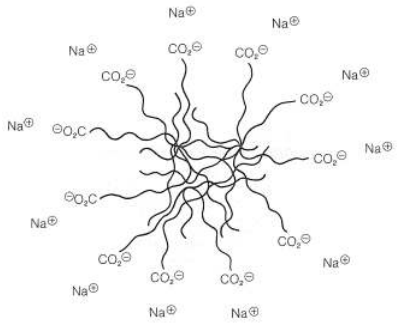
Carboxylic acids and salts having alkyl chains longer than eight carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed **amphiphilic** (Gk. amphi = both) or **amphipathic**. Fatty acids 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.

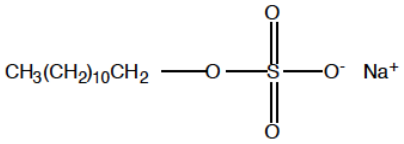


When minute amounts of soaps are put into water, instead of forming simple solutions, the molecules become concentrated at the surface of the water, with the saltlike ends sticking down into the water and the hydrocarbon chains forming a layer on the surface. This arrangement greatly reduces the surface 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.



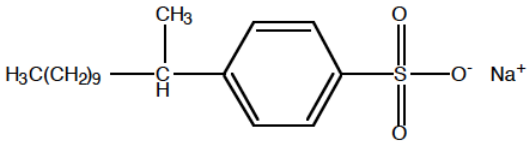
The importance of soap to human civilization is documented by history, but some problems associated with its use have been recognized. One of these is caused by the weak acidity (pKa ca. 4.9) of the fatty acids. Solutions of alkali metal soaps are slightly alkaline (pH 8 to 9) due to hydrolysis. If the 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.

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 that they work in both soft and hard water. By using a much stronger acid for the polar head group, water solutions of detergents are less sensitive to pH changes. Also the sulfonate functions used for virtually all anionic detergents confer greater solubility on micelles incorporating the alkaline earth cations found in hard water. 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.



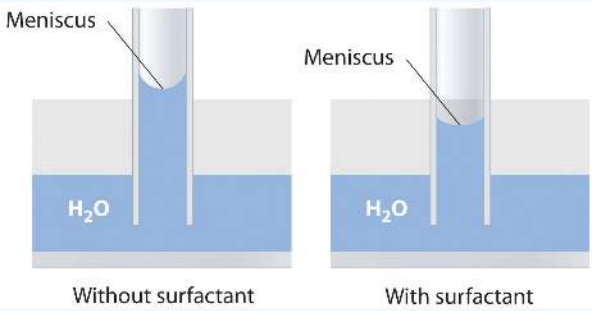
Sodium Laurylbenzenesulfonate (a biodegradable detergent)

? Exercise 8.3.1

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 8.3.2

Draw the structure of calcium stearate, a component of soap scum.

Answer

$(C_{17}H_{35}COO)_2Ca^{2+}$

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8.4: 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.

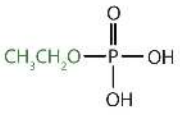
Key Terms

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

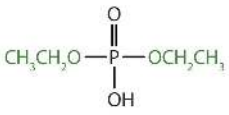
- phosphoglyceride
- phospholipid

Phosphate Esters

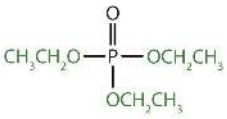
Similarly to carboxylic acids, inorganic acids such as nitric acid (HNO_3), sulfuric acid (H_2SO_4), and phosphoric acid (H_3PO_4) also can form esters. The esters of phosphoric acid are especially important in biochemistry. A phosphoric acid molecule can form a monoalkyl, a dialkyl, or a trialkyl ester by reaction with one, two, or three molecules of an alcohol.



Ethyl dihydrogen phosphate

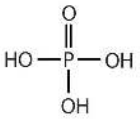


Diethyl hydrogen phosphate

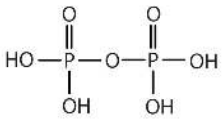


Triethyl phosphate

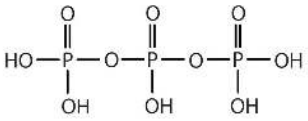
Esters of pyrophosphoric acid and triphosphoric acid are also important in biochemistry.



Phosphoric acid



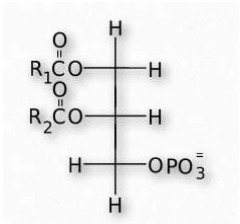
Pyrophosphoric acid



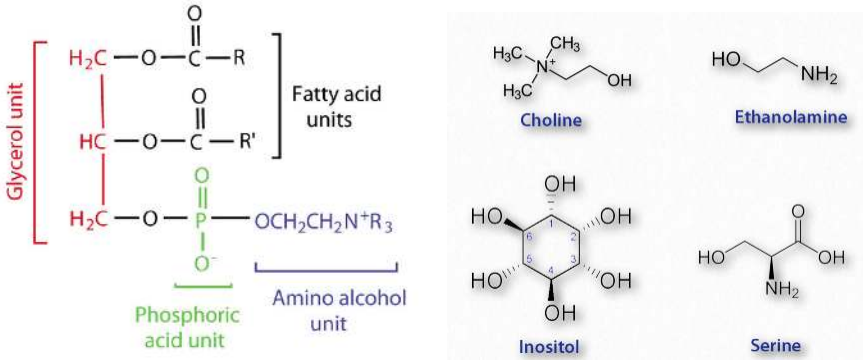
Triphosphoric acid

Phospholipids

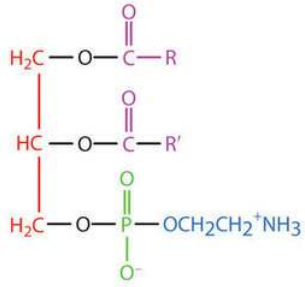
The two main types of phospholipids are **glycerophospholipids** and **sphingomyelins**. Glycerophospholipids are important components of the lipid bilayer of cellular membranes. Glycerophospholipids are structurally related to fats, as both are derived from phosphatidic acid, which has the basic structure 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.

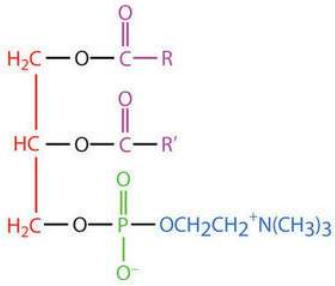


The **phosphatidylethanolamines** are found in all living cells and are one of the most common phosphatides. They are common constituents of brain tissue and in the spinal cord, making up as much as 45% of the total phospholipids. Phosphatidylethanolamines are asymmetrically distributed across membranes, being preferentially located on the inner leaflet (closest to the cytoplasm) of the plasma membrane.



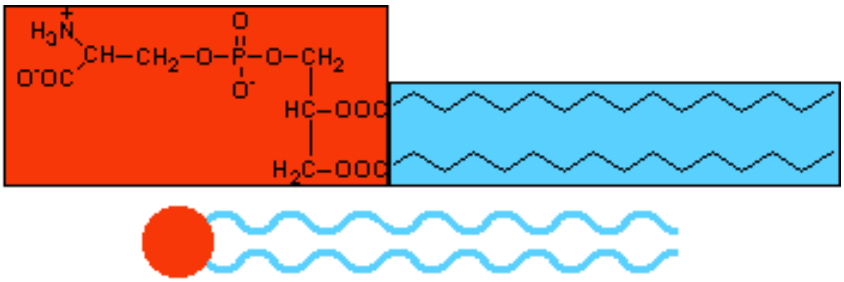
Phosphatidylethanolamine
(cephalin)

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).



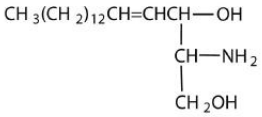
Phosphatidycholine
(lecithin)

Like the phosphatidylethanolamines, **phosphatidylserines** are preferentially located on the inner leaflet of the plasma membrane. 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.

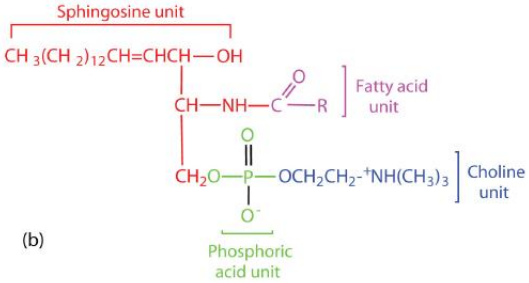


Phosphatidylserine, a polar phospholipid. A serine head group has been added on to a phosphate group on a glycerol functional group, all shown in orange. The fatty acid chains are in blue.

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.



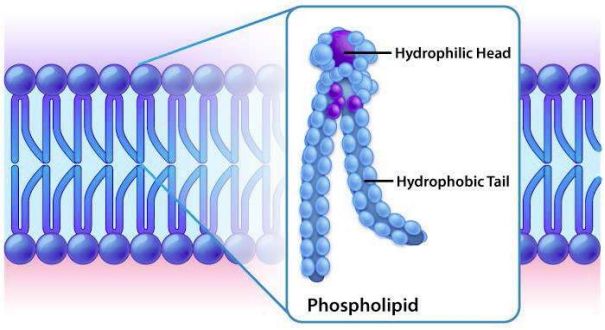
(a) Sphingosine



(b)

Lipid Bilayer

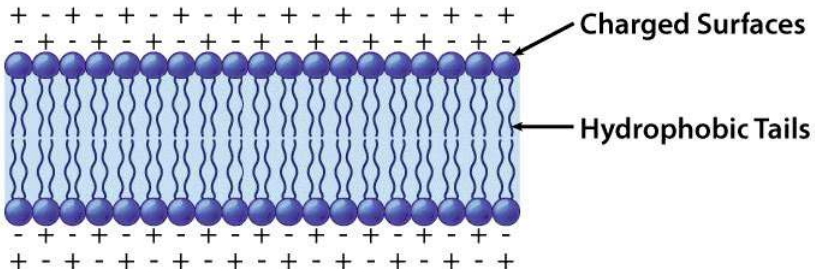
In one sense the polar lipids are like the anions of fatty acids, only more so. They contain two hydrophobic hydrocarbon tails and a head which may have several electrically charged sites. As in the case of soap and detergent molecules, the tails of polar lipids tend to avoid water and other polar substances, but the heads are quite compatible with such environments.



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.



Organization of the lipid bilayer Image by Aleia Ki

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 made in the laboratory have many properties in common 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 transport of ions and other molecules across the bilayer which could not cross otherwise.

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8.5: 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

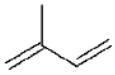
Make certain that you can define, and use in context, the key terms below.

- 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. Technically a terpenoid contains oxygen, while a terpene is a hydrocarbon. Often the two terms are used to refer collectively to both groups.



isoprene

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 incorporating most of the common functional groups are known, so this does not provide a useful means of classification. Instead, the number and structural organization of carbons is a definitive characteristic. 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.

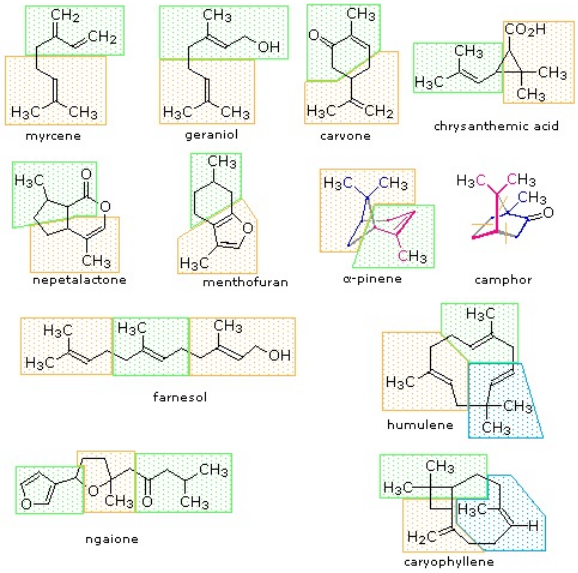


Figure 27.5.1: Monoterpenes and sesquiterpenes

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 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 center of the molecule cannot be dissected in this manner. Evidence exists 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 present location. This rearrangement is described in the biosynthesis section. Similar alkyl group rearrangements account for other terpenes that do not strictly follow the isoprene rule.

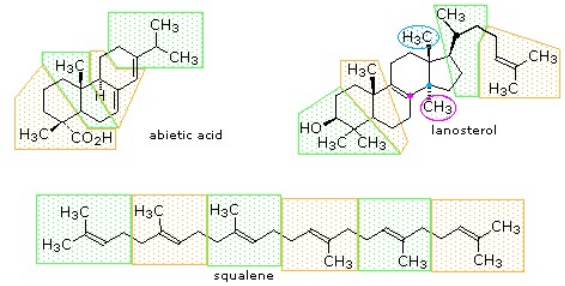
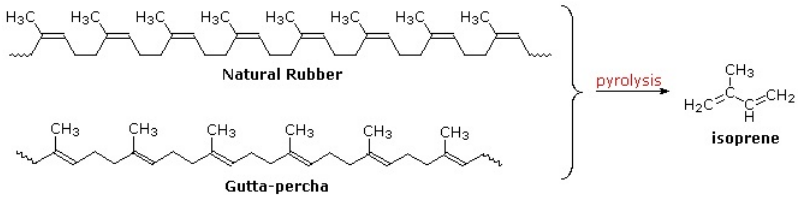


Figure 27.5.2: Triterpenes

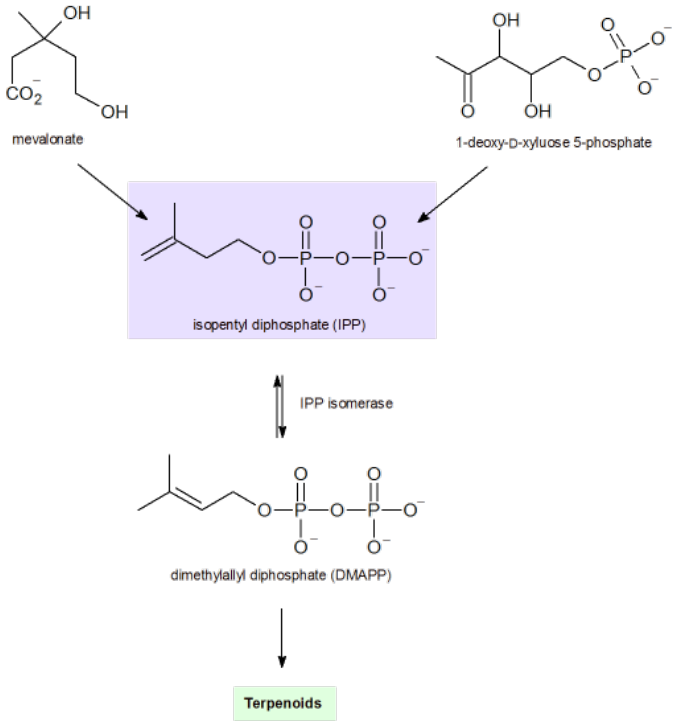
Polymeric isoprenoid hydrocarbons have also been identified. Rubber is undoubtedly the best known and most widely used compound of this kind. It occurs as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*). Rubber is a polyene, 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 ($CH_3COCH_2CH_2CO_2H$) 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 zig-zag or rod like conformation, which produces a more rigid and tough substance. Uses of gutta-percha include electrical insulation and the covering of golf balls.

Terpenoid Biosynthesis

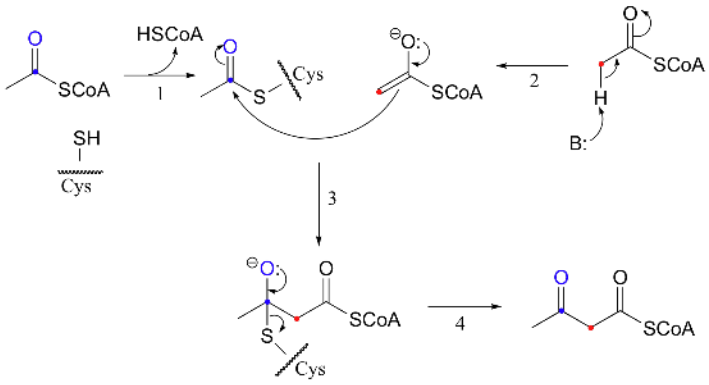
While we can identify isoprene units within a terpenoid structure and use that in its classification, the building block for terpenoid synthesis in nature is isopentenyl diphosphate (formerly called isopentenyl pyrophosphate and abbreviated IPP). There are two major routes to the synthesis of IPP; namely (1) the mevalonate pathway and (2) the 1-deoxyxylulose pathway.



Mevalonate Pathway

Step 1 - Claisen Condensation

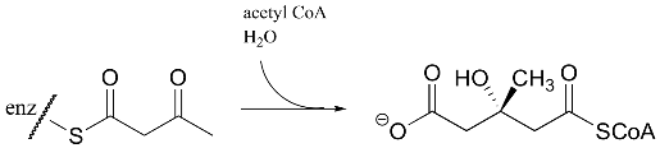
An early step in the biosynthesis of cholesterol and other ‘isoprenoid’ compounds is a Claisen condensation between two acetyl CoA molecules. An initial trans-thioesterase process transfers the acetyl group of the first acetyl CoA to an enzymatic cysteine (Reaction 1). In the Claisen condensation phase 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

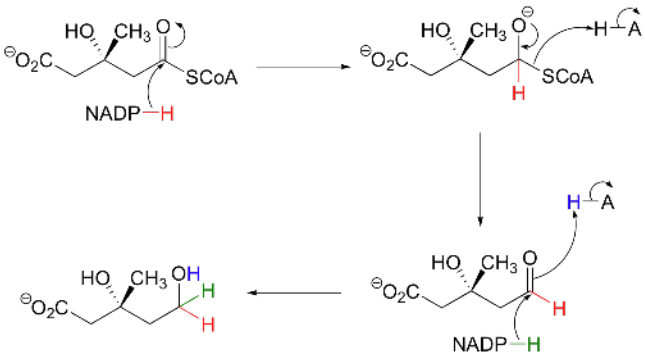
Acetyl CoA then reacts with the acetoacetyl CoA in an aldol-like addition. Subsequent hydrolysis produces (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).



Generating HMG-CoA

Step 3 - Reduction of the Thioester

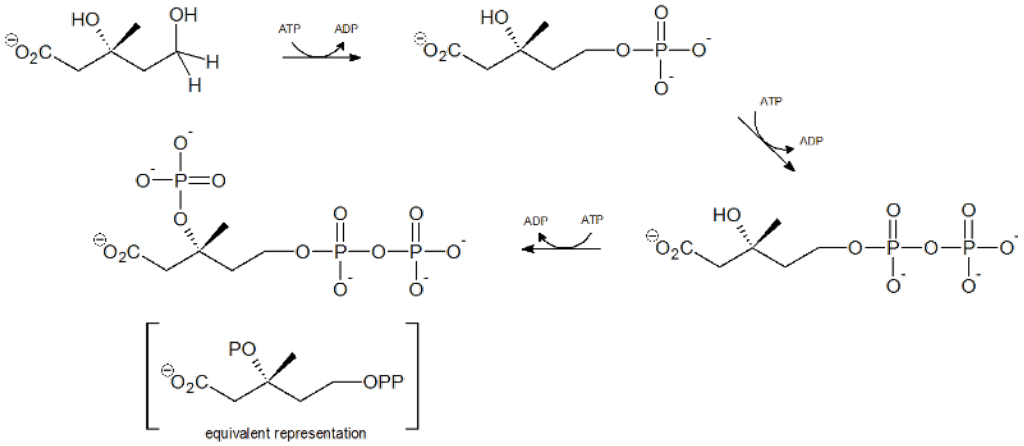
The thioester is reduced first to an aldehyde, then to a primary alcohol by two equivalents of NADPH producing (*R*)-mevalonate. The enzyme catalyzing this reaction is the target of the statin family of cholesterol-lowering drugs.



Generating (*R*)-Mevalonate

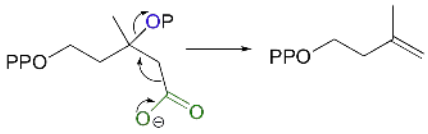
Step 4 - Mevalonate Phosphorylation

Two phsophorylations 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.



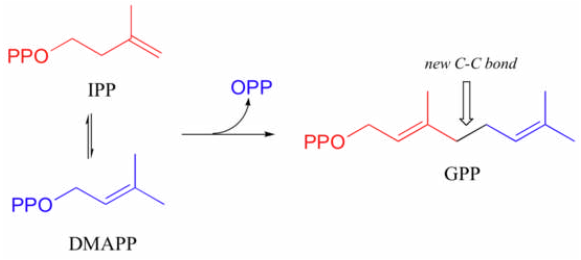
Step 5 - **Decarboxylation**

Finally isopentenyl diphosphate (IPP), the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.

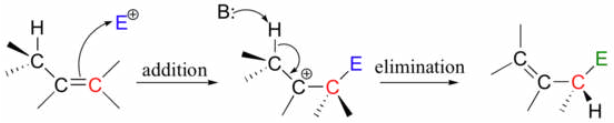


Conversion of IPP to Terpenoids

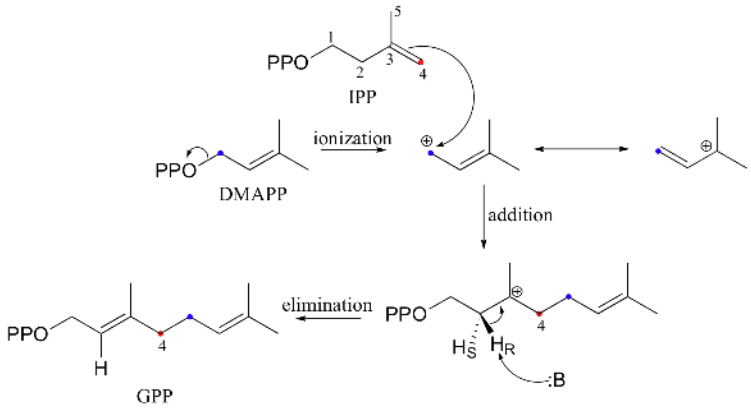
The electrophilic double bond isomerization catalyzed by IPP isomerase is a highly reversible reaction, with an equilibrium IPP:DMAPP ratio of about 6:1. In the next step of isoprenoid biosynthesis, the two five-carbon isomers condense to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP).



This is a nice example of an electrophilic addition/elimination mechanism:

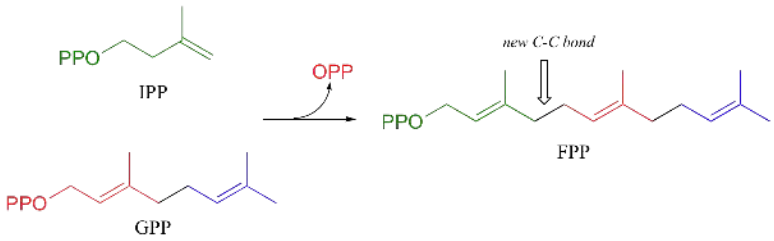


The first step is ionization of the electrophile - in other words, the leaving group departs and a carbocation intermediate is formed. In this case, the pyrophosphate group on DMAPP is the leaving group, and the electrophilic species is the resulting allylic carbocation.

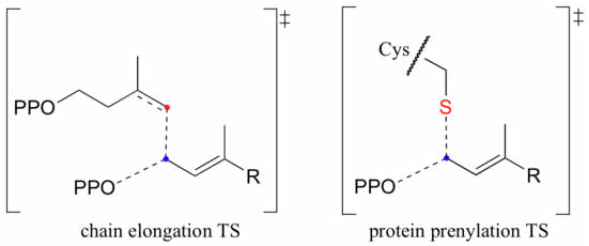


In the condensation (addition) step, the C_3-C_4 double bond in IPP attacks the positively-charged C_1 of DMAPP, resulting in a new carbon-carbon bond and a second carbocation intermediate, this time at a tertiary carbon. In the elimination phase, proton abstraction leads to re-establishment of a double bond in the GPP product. Notice that the enzyme specifically takes the *pro-R* proton in this step.

To continue the chain elongation process, another IPP molecule can then condense, in a very similar reaction, with C_1 of geranyl diphosphate to form a 15-carbon product called farnesyl diphosphate (FPP).

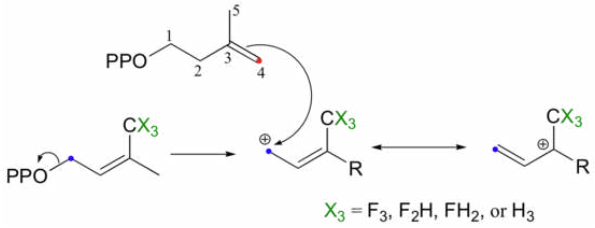


How do we know that these are indeed S_N1-like mechanisms with carbocation intermediates, rather than concerted S_N2-like mechanisms? First of all, recall that the question of whether a substitution is dissociative (S_N1-like) or associative (S_N2-like) is not always clear-cut - it could be somewhere in between, like the protein prenyltransferase reaction. The protein prenyltransferase reaction and the isoprenoid chain elongation reactions are very similar: the electrophile is the same, but in the former the nucleophile is a thiolate, while in the latter the nucleophile is a pi bond.



This difference in the identity of the nucleophilic species would lead one to predict that the chain elongation reaction has more S_N1-like character than the protein prenylation reaction. A thiolate is a very powerful nucleophile, and thus is able to *push* the pyrophosphate leaving group off, implying some degree of S_N2 character. The electrons in a pi bond, in contrast, are only weakly nucleophilic, and thus need to be *pulled* in by a powerful electrophile - *ie*. a carbocation.

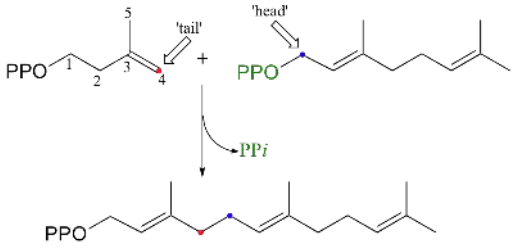
So it makes perfect sense that the chain elongation reaction should more S_N1-like than S_N2-like. Is this in fact the case? We know how to answer this question experimentally - just run the reaction with fluorinated DMAPP or GPP substrates and observe how much the fluorines slow things down.



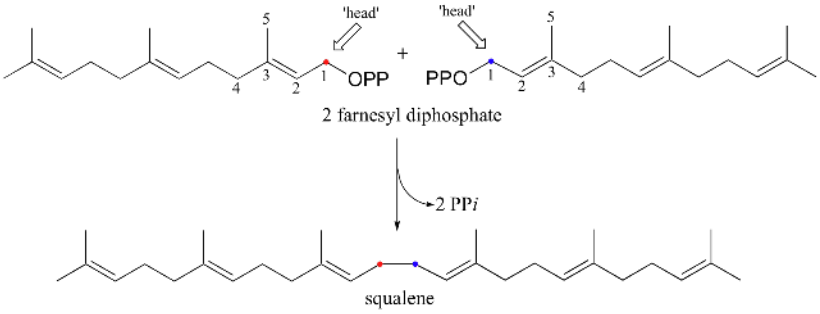
If the reaction is S_N1-like, the electron-withdrawing fluorines should destabilize the allylic carbocation intermediate and thus slow the reaction down considerably. If the mechanism is S_N2-like, the fluorine substitutions should not have a noticeable effect, because a carbocation intermediate would not be formed. When this experiment was performed with FPP synthase, the results were dramatic: the presence of a single fluorine slowed down the rate of the reaction by a factor of about 60, while two and three fluorines resulted in a reaction that was 500,000 and 3 million times slower, respectively (*J. Am. Chem. Soc*. **1981**, *103*, 3926.) These results strongly suggest indicate the formation of a carbocation intermediate in an S_N1-like displacement.

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.

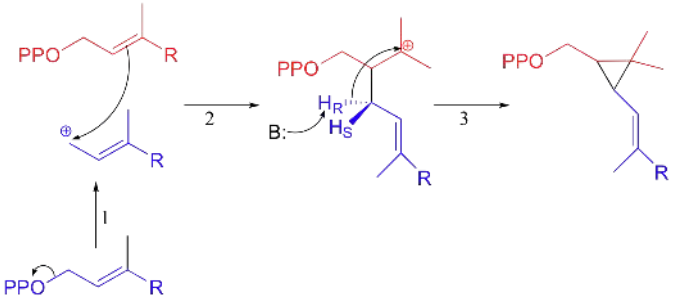
Cholesterol, as we discussed earlier in this chapter, is derived from a 30-carbon isoprenoid molecule called squalene. Squalene, in turn, is derived from the condensation of two molecules of farnesyl diphosphate (FPP), a 15-carbon isoprenoid. You may recall that FPP is the product of the C_4 to C_1, or 'head to tail' electrophilic condensation of isoprenoid chains:



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.



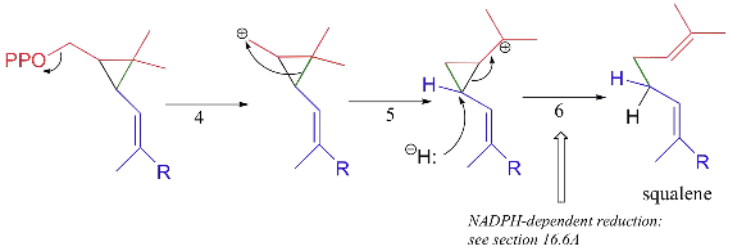
The first two steps are familiar: first, the pyrophosphate on one FPP molecule leaves (step 1), resulting in an allylic carbocation that is attacked by the C_2-C_3 π bond of the second molecule (step 2).



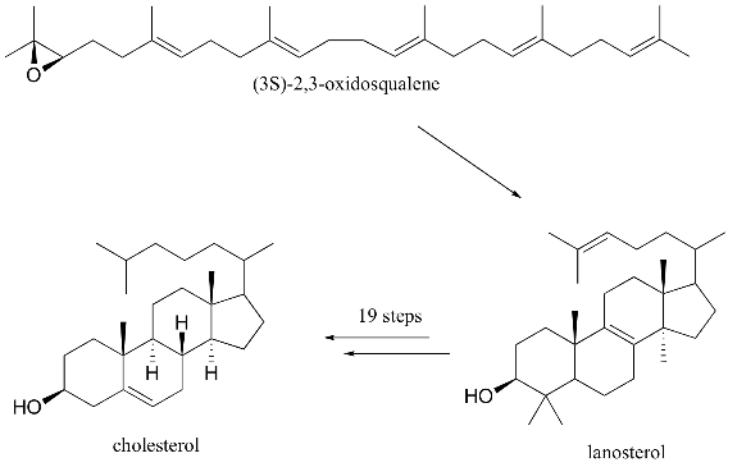
https://chem.libretexts.org/@go/page/396389

This results in a new carbon-carbon bond between the two FPP molecules, but with incorrect C_1 to C_2 connectivity (remember, the overall reaction is a C_1 to C_1 condensation). In step 3, a proton is abstracted and the electrons from the broken C-H bond bridge across a 2-carbon gap to form a cyclopropyl intermediate.

In the second stage of squalene synthesis, the second pyrophosphate group leaves, generating a cyclopropylcarbinyl cation (step 4). Because this is a primary carbocation, you probably are wondering about how stable it could be (and thus how likely an intermediate). As it turns out, such carbocations are remarkably stable, due to favorable interactions between the empty orbital and orbitals on the three-membered ring (the level of bonding theory needed to really understand this idea is beyond the scope of this text, but you may learn about it if you take a class in advanced organic chemistry). What occurs next is an alkyl shift leading to a tertiary carbocation (step 5).

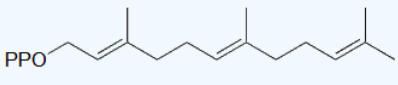


Discussion of the final step (step 6) will need to be put off - this is a reduction with a hydride nucleophile derived from a coenzyme called NADPH. Although this may seem like an extremely convoluted (and perhaps unlikely!) mechanism, there is much experimental evidence to back it up.



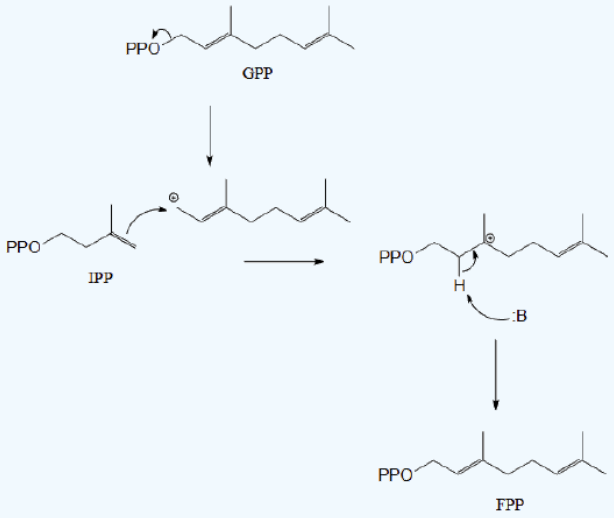
Exercise 8.5.1

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.



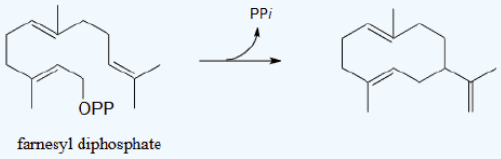
Answer

IPP is the five-carbon species added to geranyl diphosphate to make the 15-carbon farnesyl diphosphate.

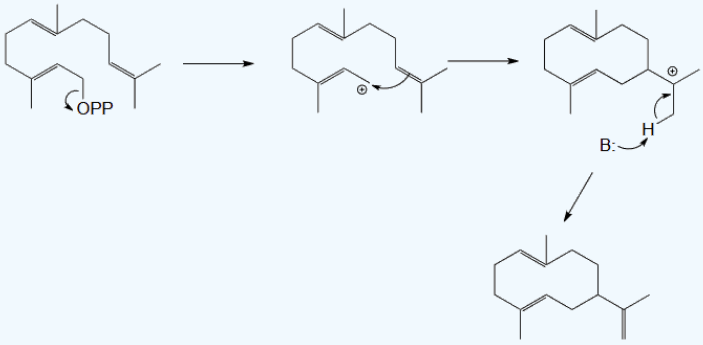


Exercise 8.5.2

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)

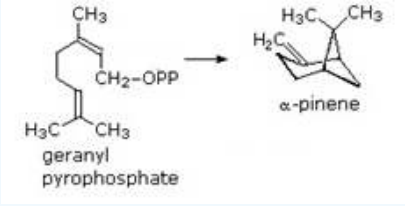


Answer

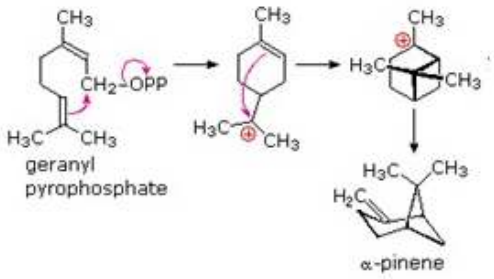


Exercise 8.5.3

Propose a likely mechanism for the following transformation.



Answers



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8.6: 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.

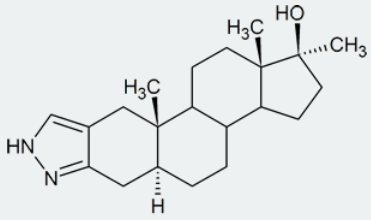
Key Terms

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

- steroid

Study Notes

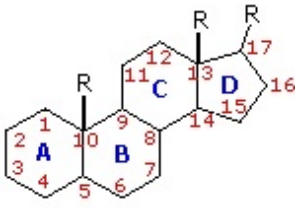
Since the 1988 Olympic Games in Seoul, even individuals who have no interest in chemistry or sport have heard the word “steroid” and are aware that some athletes use these substances to enhance their athletic abilities. Stanozolol, the substance which Canadian sprinter, Ben Johnson, was found to have used, has the structure shown below:



stanozolol

General Steroid Structure

The important class of lipids called **steroids** are actually metabolic derivatives 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, 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.

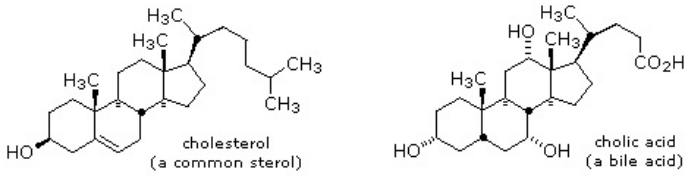


The Steroid
Carbon Skeleton

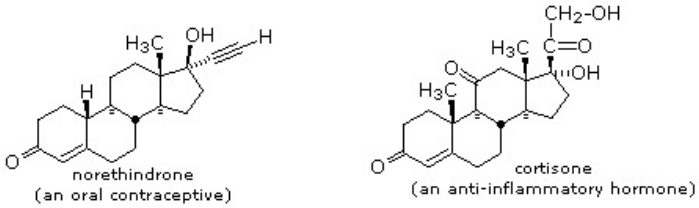
Common Steroids

Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally.

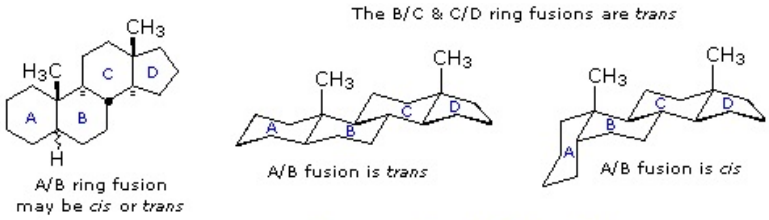
The generic steroid structure drawn above has seven chiral stereocenters (carbons 5, 8, 9, 10, 13, 14 & 17), which means that it may have as many as 128 stereoisomers. With the exception of C-5, natural steroids generally have a single common configuration.



Typical Animal Steroids



Medicinally Useful Steroids

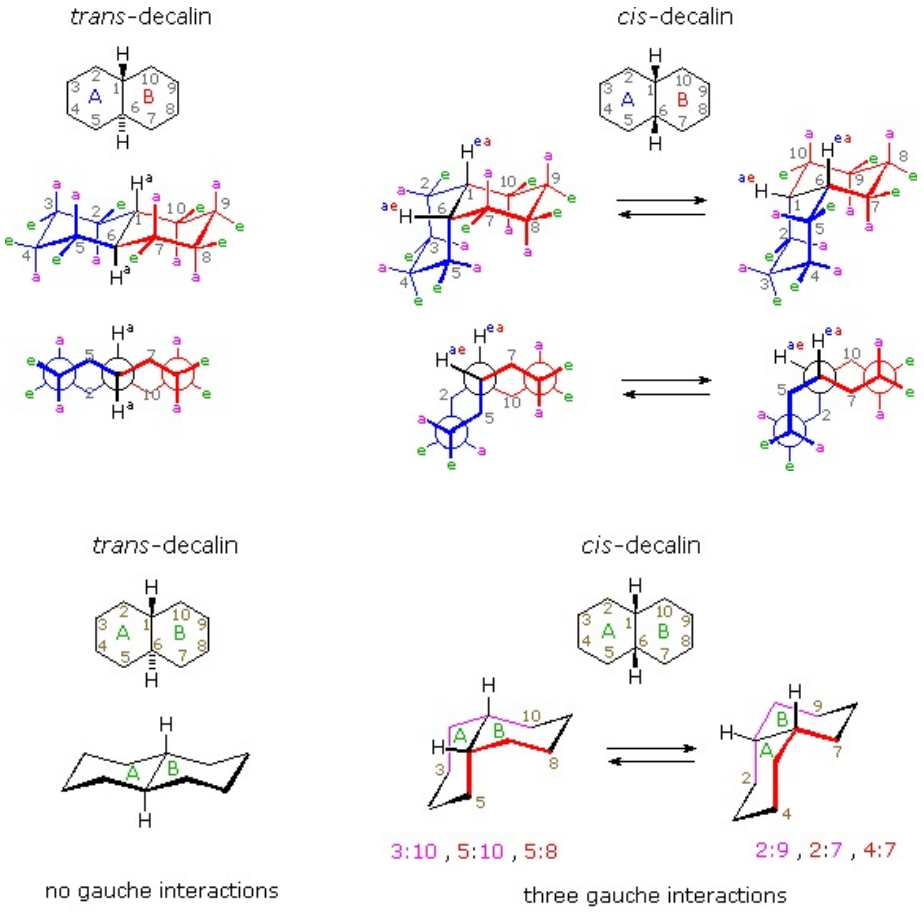


Common Steroid Conformations

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. Planar representations of these isomers are drawn at the top of the following diagram, with corresponding conformational formulas displayed underneath. The numbering shown for the ring carbons follows IUPAC rules, and is different from the unusual numbering used for steroids. 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 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.

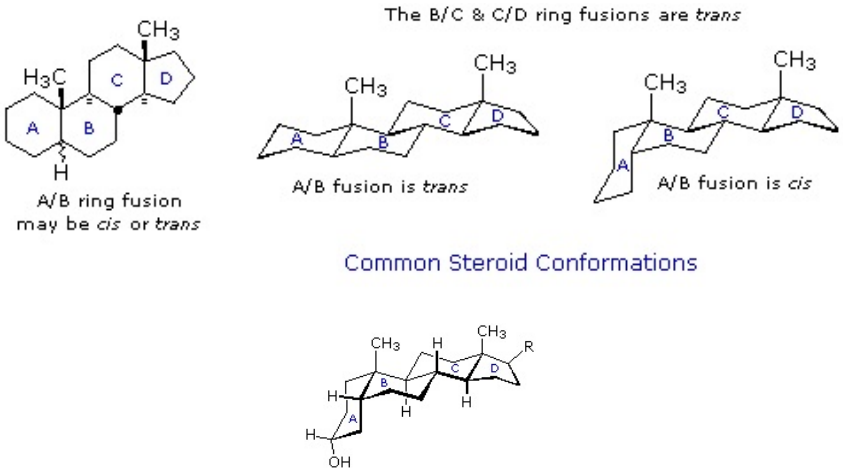
Conformational descriptions of cis- decalin are complicated by the fact that two energetically equivalent fusions of chair cyclohexanes are possible, and are in rapid equilibrium as the rings flip from one chair conformation to the other. In each of these all chair conformations the rings are fused by 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.

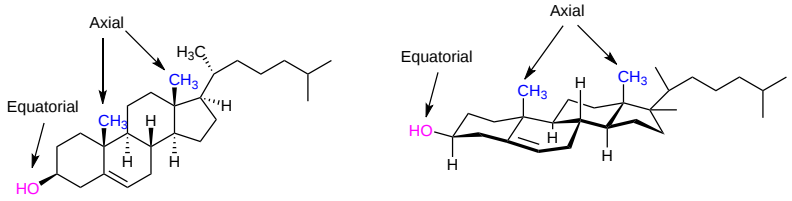
Steroid Conformations

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 cyclohexanes substituents (**Section 4-7**) on a steroid ring system can be either an axial or equatorial position. Fused rings makes steroids ridge and unable to undergo cyclohexane ring-flips Because of sterics, substituents in the equatorial posltion 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.

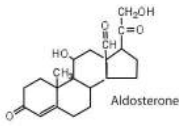


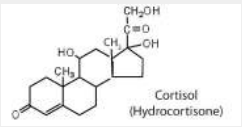
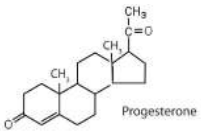
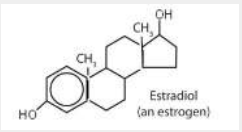
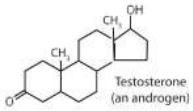
Steroid Hormones

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 27.6.1), 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 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.

Table 27.6.1 Representative Steroid Hormones and Their Physiological Effects

Hormone	Effect
 Aldosterone	regulates salt metabolism; stimulates kidneys to retain sodium and excrete potassium

Hormone	Effect
 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.

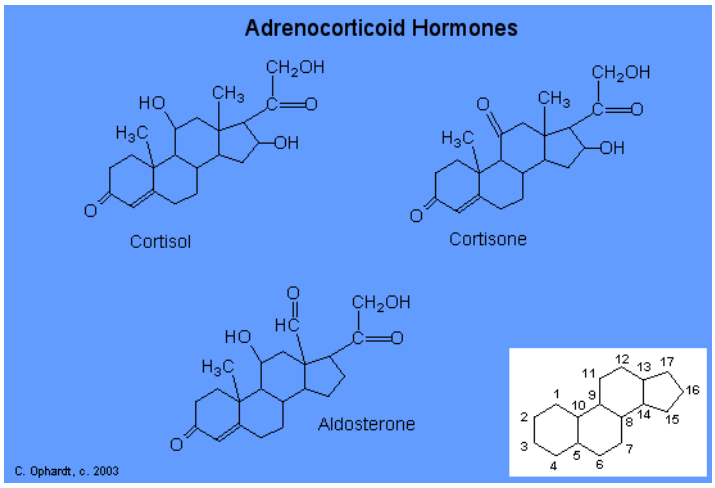
Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment 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.

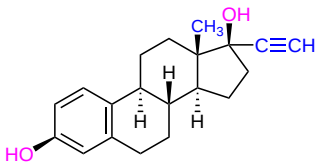
Cortisol, the most important glucocortinoid, has the function of increasing glucose and glycogen concentrations in the body. These reactions are completed in the liver by taking fatty acids from lipid storage cells and amino acids from body proteins to make glucose and glycogen.

In addition, cortisol and its ketone derivative, **cortisone**, have the ability to 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 with the use of cortisone drugs, so there use must be monitored carefully.

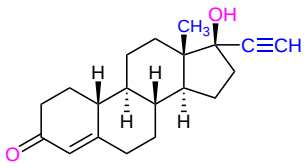


Synthetic Steroids

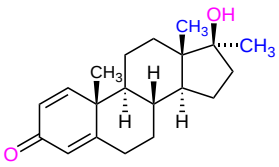
In the hope of producing new drugs, thousands of steroid derivatives have been synthesized and test by pharmaceutical companies. The two classes of synthetic steroids most commonly know by the public are oral contraceptives and anabolic steroids. Oral contraceptives contain synthetic versions of the 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.



Ethynylestradiol
(A synthetic estrogen)



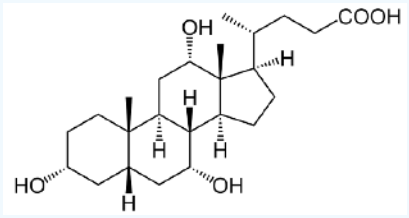
Norethindrone
(A synthetic progestin)



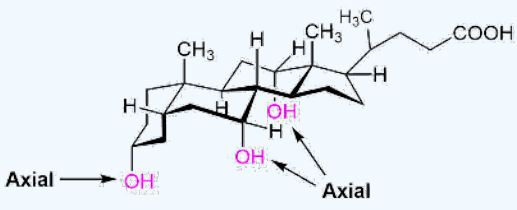
Methandrostenolone
(A synthetic androgen)

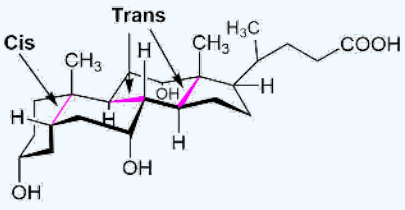
Exercise 8.6.1

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

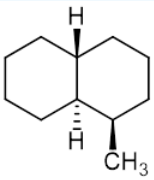




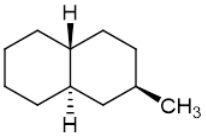
Exercise 8.6.2

Draw the following decalin molecules in chair conformations. Determine if the -CH_3 groups are axial or equatorial.

a)

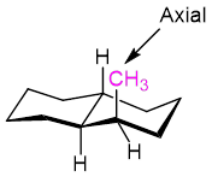


b)

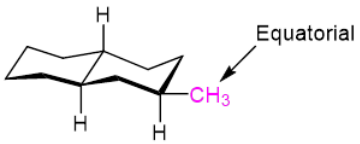


Answer

a)



b)



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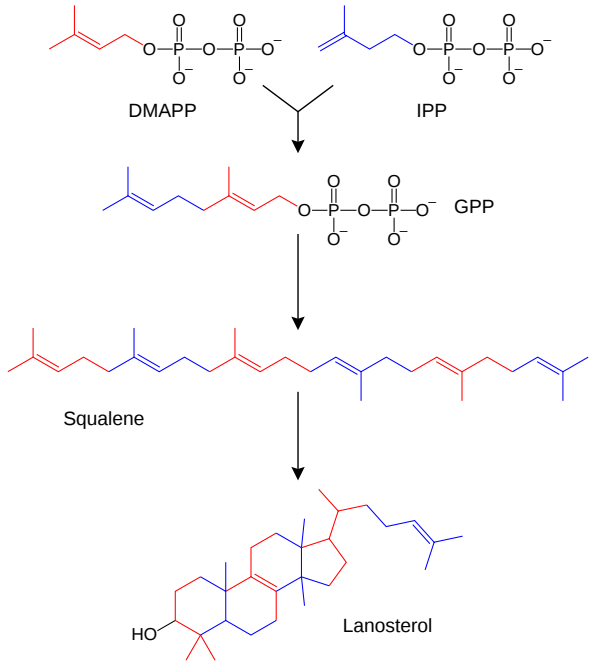
8.7: Biosynthesis of Steroids

Objectives

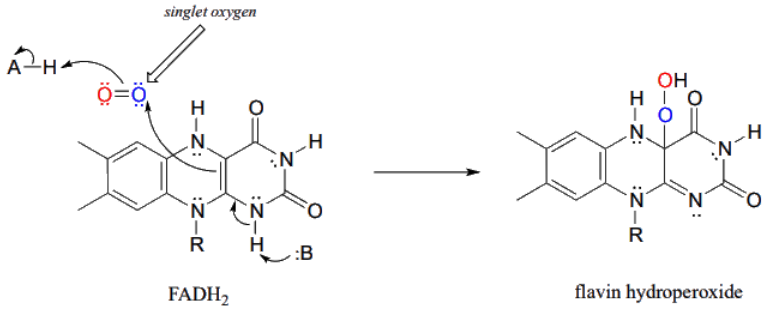
After completing this section, you should be able to

- 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.

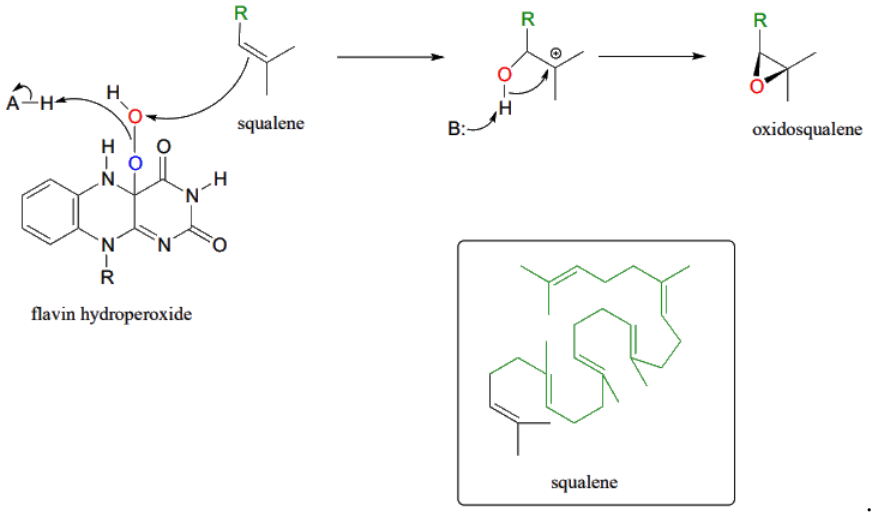


The key step in the biosynthesis of lanosterol is the regioselective epoxidation of squalene to give (3*S*)-2,3-oxidosqualene. This reaction is catalyzed by the monooxygenase enzyme squalene epoxidase. In this step, flavin hydroperoxide serves as the direct oxidizing agent. In flavin hydroperoxide, the 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.

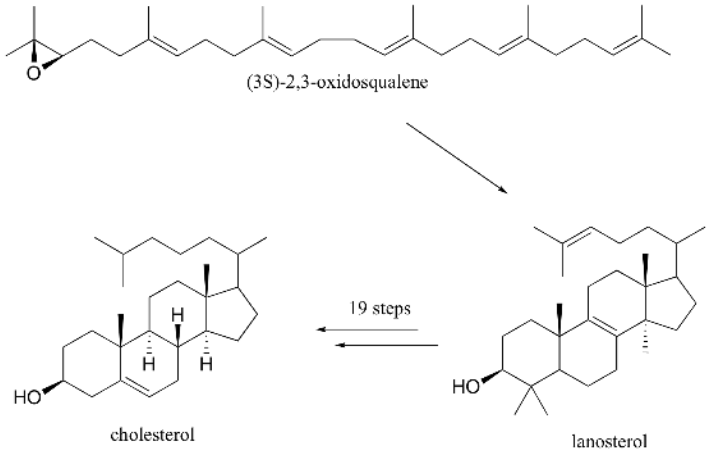


https://chem.libretexts.org/@go/page/396391

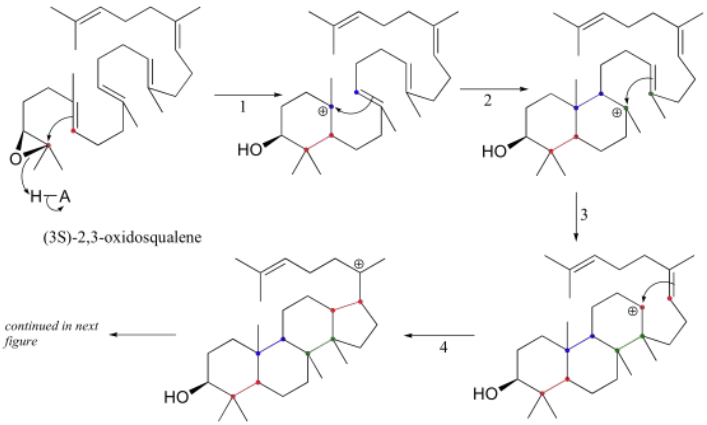
The mechanism for the flavin-hydroperoxide-dependent epoxidation of squalene is initiated by the nucleophilic attack of the pi electrons of a squalene double bond on the electrophilic terminal hydroperoxide oxygen.



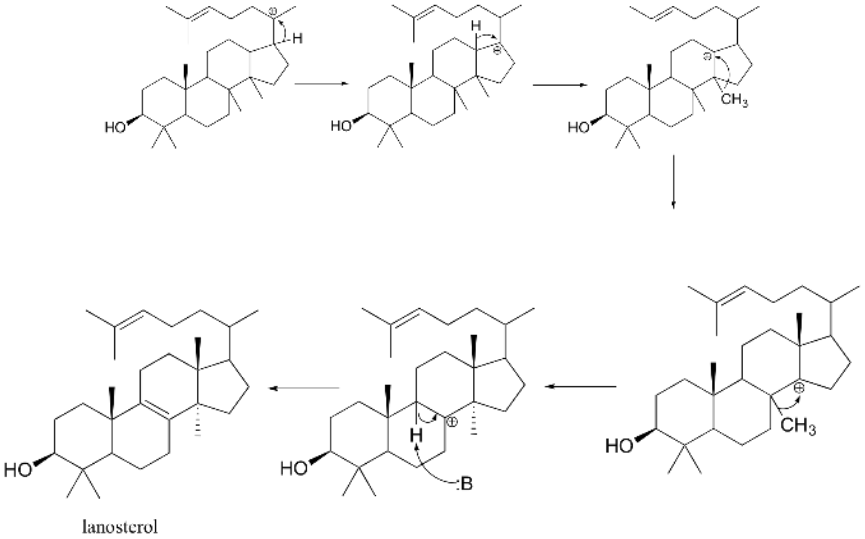
Oxidosqualene goes on to cyclize to lanosterol in a complex and fascinating electrophilic reaction which catalyzed by oxidosqualene-lanosterol cyclase. This reaction has two phases. The first phase, in which the actual cyclization takes place, is a series of electrophilic addition steps. The second phase 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.



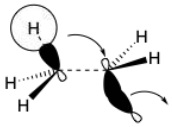
The cyclization phase begins with attack by pi electrons on an epoxide electrophile. The epoxide ring opens to form an alcohol after protonation. A relatively stable tertiary carbocation is also formed. Steps 2, 3, and 4 are simply successive attacks by pi electrons on the carbocation generated by the 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.

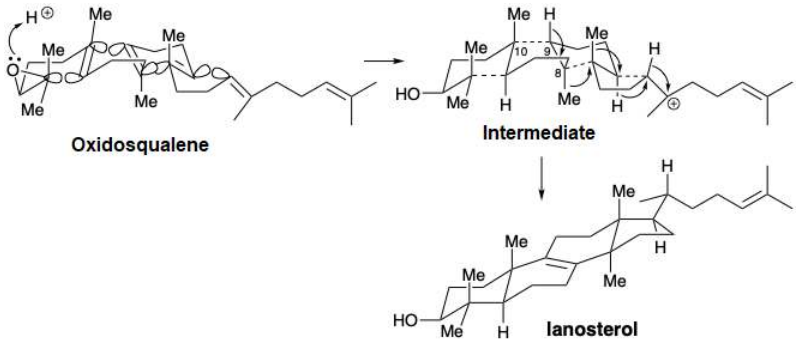


Next comes the rearrangement phase of the reaction in which a series of two 1,2-hydride and two 1,2-methyl shifts to give lanosterol after proton loss from the 9 position.



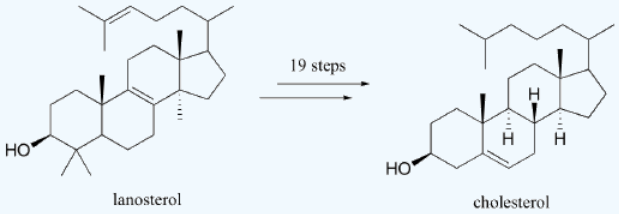
Especially interesting are the stereochemical details of the polyene cyclization and subsequent rearrangement. The polyene cyclization involves stereospecific **anti-periplanar** addition across three C=C bonds in oxidosqualene (see below). The folded conformation of oxidosqualene, required for cyclization 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 8.7.1

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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8.8: 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.

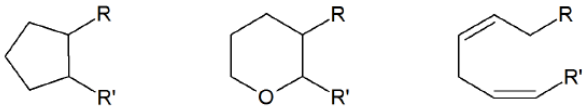
Key Terms

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

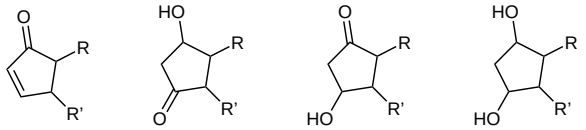
- eicosanoid
- prostaglandin

Eicosanoids

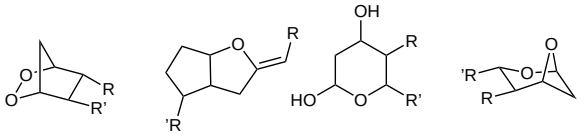
The members of this group of structurally related natural hormones have an extraordinary range of biological effects. They can lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses. Because their genesis in body 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.

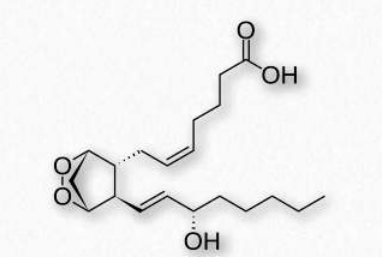


Prostaglandin structures for PGA, PGD, PGE and PGF



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.



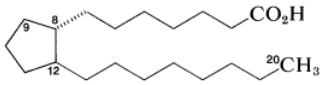
Prostaglandin PGH_2

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.

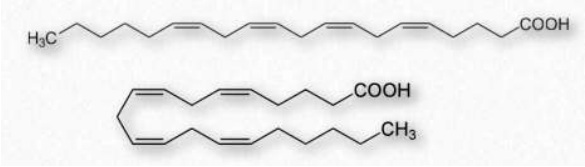
Prostaglandins are found in low concentrations distributed in a large number of organs, tissues, and body fluids of mammals. They exhibit a broad spectrum of physiological activity and are remarkably potent. Their precise biological role is not entirely clear, but they are known to induce strong contractions 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.



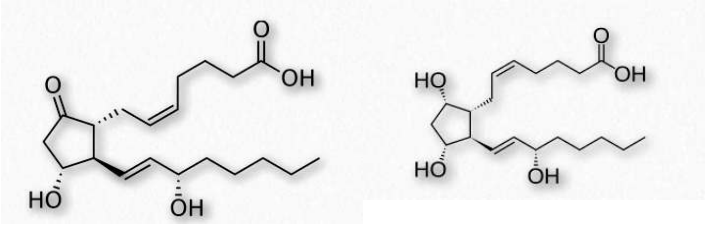
prostanoic acid

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.

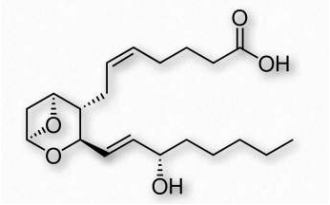


Prostaglandin E2 (left) and Prostaglandin $F_{2\alpha}$ (Right)

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

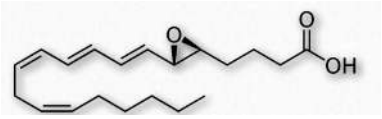
of synthesis of PGH2, which is the precursor of the thromboxanes. The most common thromboxanes are A2 (Figure 2.217) and B2.



Thromboxane $A2_2$

Leukotrienes

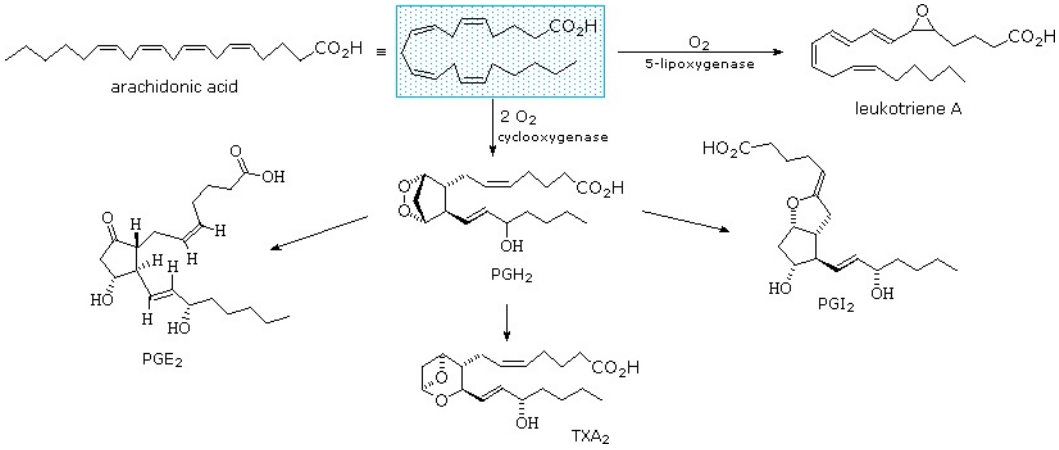
Another group of eicosanoid compounds are the leukotrienes (Figure 2.219). Like prostaglandins, leukotrienes are made from arachidonic acid. The enzyme catalyzing their formation is a dioxygenase known as arachidonate 5-lipoxygenase. Leukotrienes are involved in regulating immune responses. They are 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.



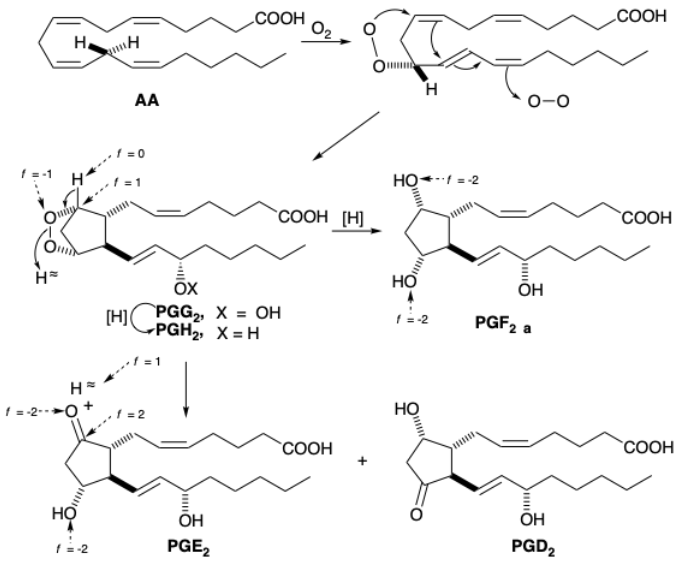
Leukotriene A_4 (LTA_4)

Eicosanoid Biosynthesis

The biosynthesis of eicosanoids begins with the reaction of arachidonic acid with 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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8.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.

25.1 Introduction

- Carbohydrates are composed of carbon, hydrog

25.2 Classification of Carbohydrates

- Carbohydrates originate as products from photosynt

25.3 Fischer Projections

- The Fischer projection is a type of notation often used when multip

25.4 D,L Sugars

- To determine absolute configuration for carbohydrates, Emil Fischer started with an arb

25.5 Configurations of Aldoses

- The aldos

25.6 Anomers

- The preferred structural form of mon

25.7 Reactions of Monosaccharides

- The -OH groups on a monosacc

25.8 The Eight Essential Monosaccharides

- The eight essential monos

25.9 Disaccharides

- Disaccharides are sugars com

25.10 Polysaccharides and Their Synthesis

- Polysaccharides are very large polymers co

25.11 Other Important Carbohydrates

- The backbone of DNA is based on a repeated

25.12 Cell-Surface Carbohydrates and Influenza Viruses

- Carbohydrates a

Skills to Master

- Skill 25.1 Determine which molecules can be classified as carbohydr
-

Summary of Reactions

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CHAPTER OVERVIEW

9: Biomolecules - Nucleic Acids

When you have completed Chapter 28, 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.

9.1: Nucleotides and Nucleic Acids
9.2: Base Pairing in DNA - The Watson-Crick Model
9.3: Replication of DNA
9.4: Transcription of DNA
9.5: Translation of RNA - Protein Biosynthesis
9.6: DNA Sequencing
9.7: DNA Synthesis
9.8: The Polymerase Chain Reaction

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 25) and simple heterocyclic systems. We have already discussed certain aspects of the structure of heterocyclic ring systems during our study of aromaticity (Sections 15.5–15.6). You may find it helpful to review this chapter.

Chapter 28 examines the structure and replication of DNA and then describes the structure and synthesis of RNA. The chapter closes with a brief study of the role played by RNA in the biosynthesis of proteins.

Contributors and Attributions

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9.1: Nucleotides and Nucleic Acids

Objectives

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)

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.

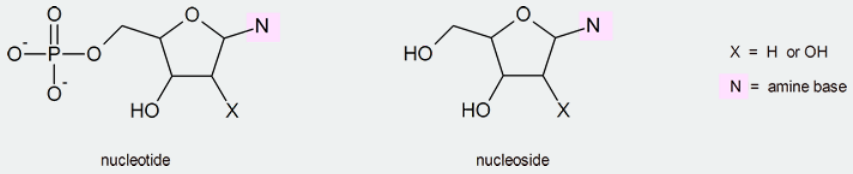


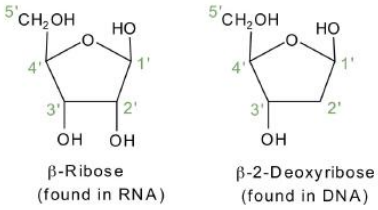
Figure 9.1.0 The Pyrimidine and Purine Nucleotides below.

The Learning Objective of this Module is to identify the different molecules that combine to form nucleotides.

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).

$$\text{nucleic acids} \xrightarrow[\text{down into}]{\text{can be broken}} \text{nucleotides} \xrightarrow[\text{down into}]{\text{can be broken}} H_3PO_4 + \text{nitrogen base} + \text{pentose sugar}$$

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 9.1.1). 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.

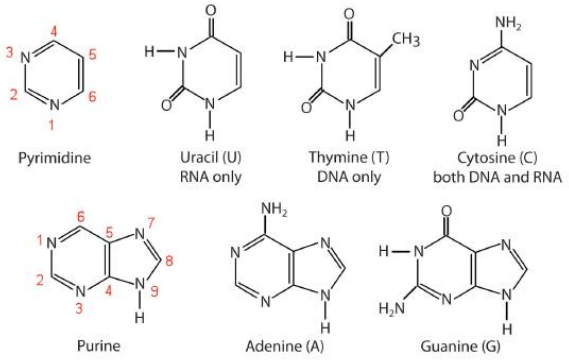
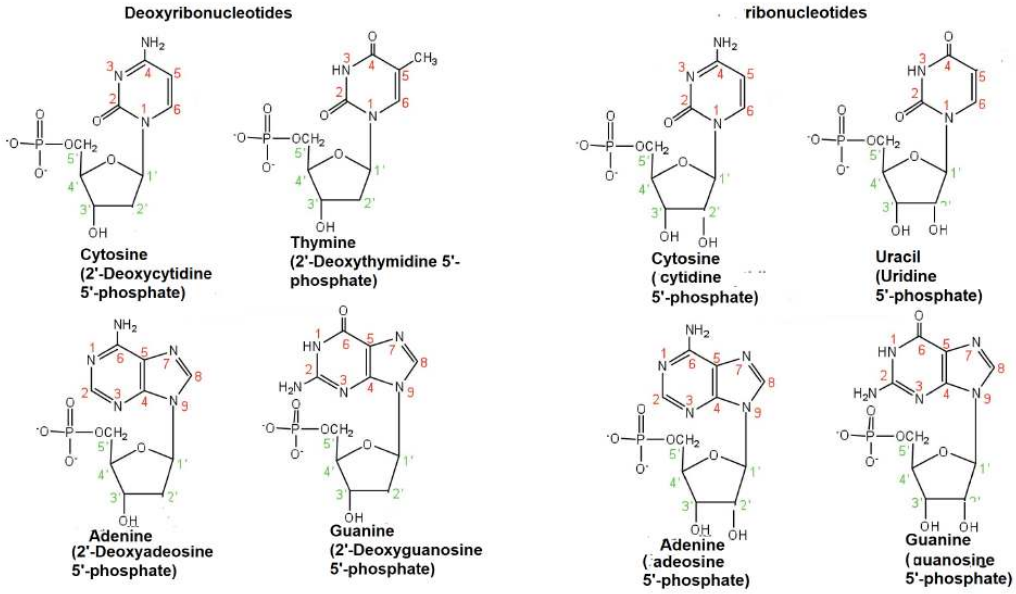


Figure 9.1.1: The Nitrogenous Bases Found in DNA and RNA

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 9.1.2.



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 9.1.3, 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.

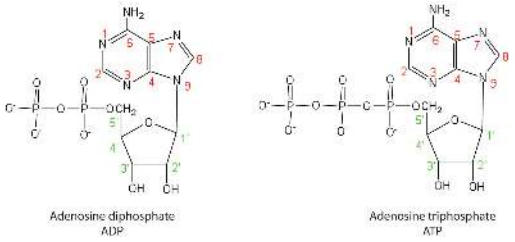


Figure 9.1.3: Structures of Two Important Adenine-Containing Nucleotides

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 28.1.4) 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 28.1.4 would be written 5′-dG-dT-dA-dC-3′, which is often further abbreviated to dGTAC or just GTAC.

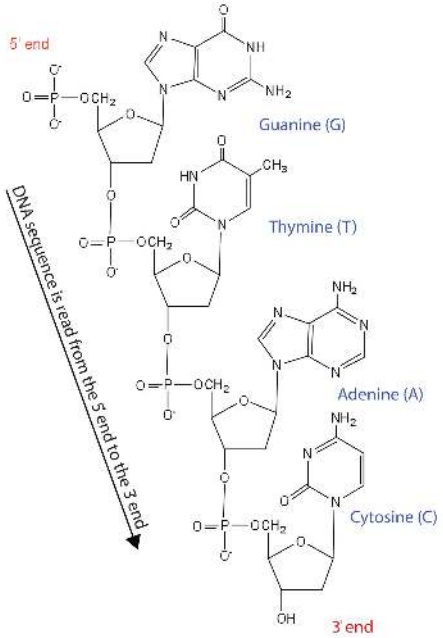


Figure 9.1.4: Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2′, and uracil would replace thymine.

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.

Exercise 9.1.1

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 9.1.2

Identify the three molecules needed to form the nucleotides in each nucleic acid.

a. DNA
b. RNA

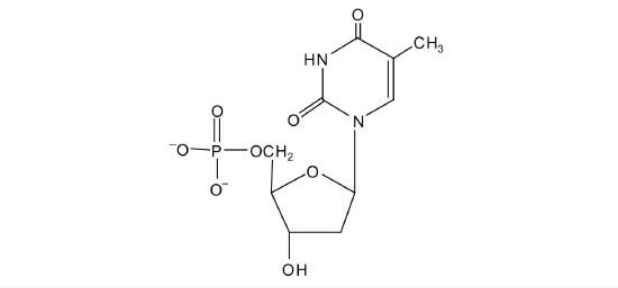
Answer

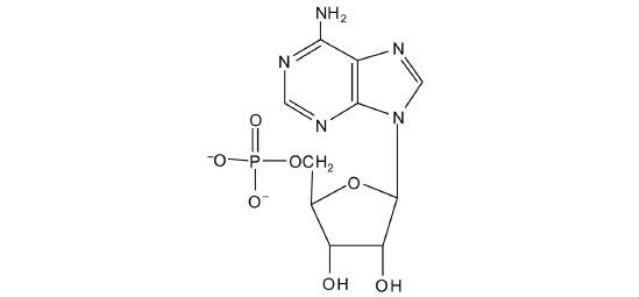
a. nitrogenous base (adenine, guanine, cytosine, and thymine), 2-deoxyribose, and H_3PO_4
b. nitrogenous base (adenine, guanine, cytosine, and uracil), ribose, and H_3PO_4

Exercise 9.1.3

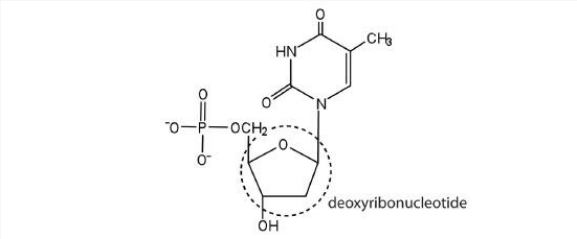
For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

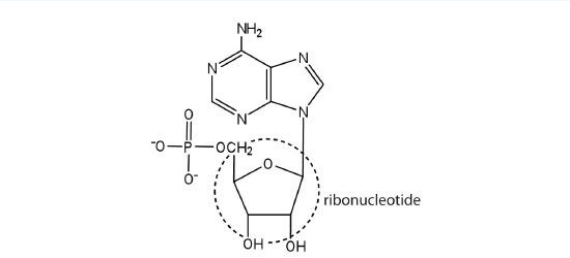
a.



- 

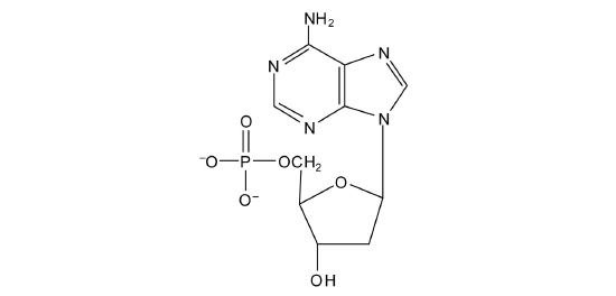
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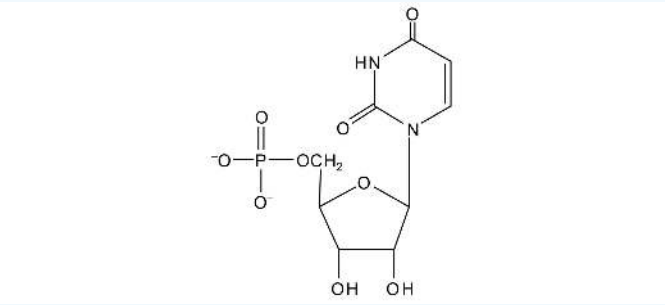
a. 

b. 

Exercise 9.1.4

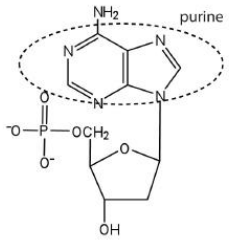
For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 

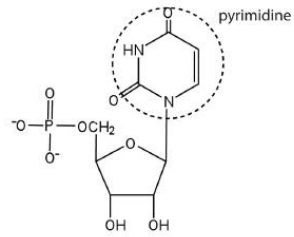
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Answer

a.



b.



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9.2: 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.

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.

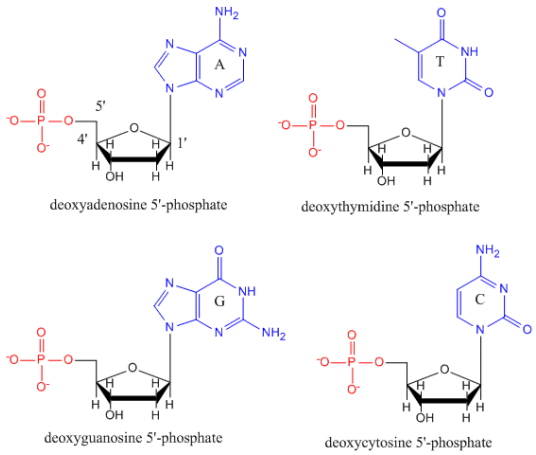
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Maddox, B. Rosalind Franklin: The Dark Lady of DNA. New York: HarperCollins, 2002.

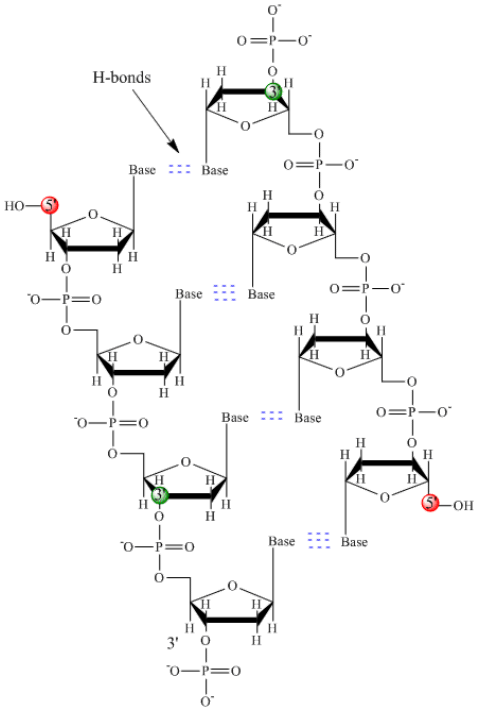
Intermolecular Forces in Nucleic Acids

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 which 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.



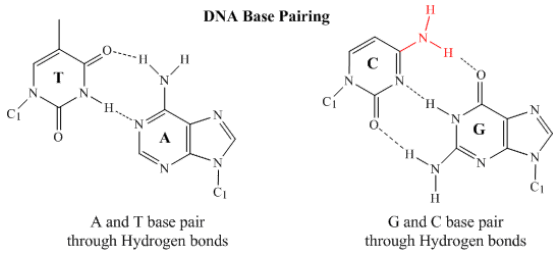
DNA

DNA is a polymer, consisting of monomers call 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 predominately 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 exists usually 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.



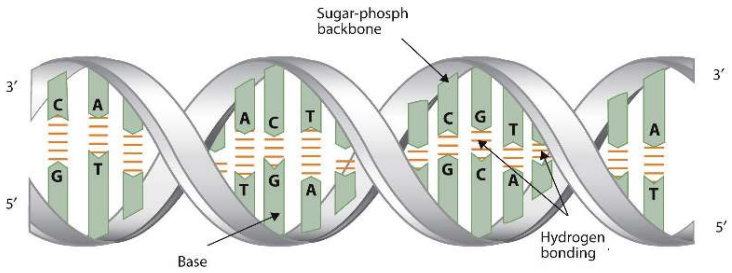
In 1950, Erwin Chargaff of Columbia University showed that the molar amount of adenine (A) in DNA was always equal to that of thymine (T). Similarly, he showed that the molar amount of guanine (G) was the same as that of cytosine (C). Chargaff's findings

clearly indicate that some type of 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 pairs to consists 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.

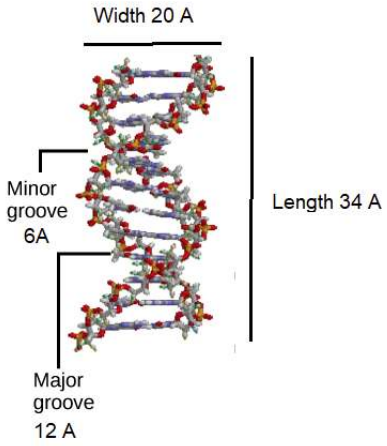


Secondary Structure of DNA

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).



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?

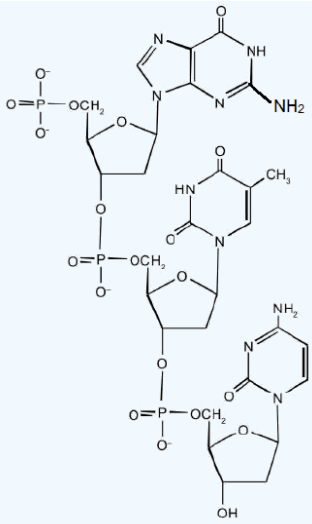
Three processes are required:

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.

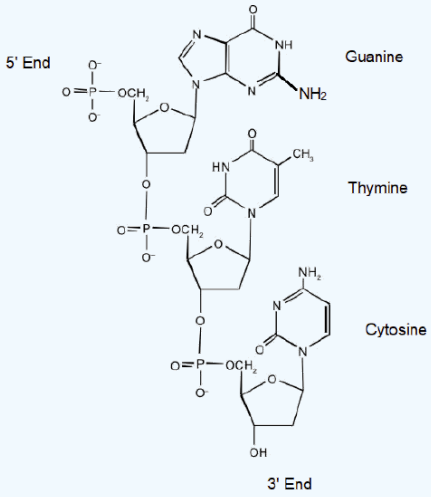
? Exercise 9.2.1

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 9.2.2

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

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Exercise 9.2.3

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 9.2.4

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).

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9.3: Replication of DNA

Objectives

After completing this section, you should be able to describe, very briefly, the replication of DNA.

Key Terms

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

- replication
- semiconservative replication

Study Notes

Notice that the objective for this section requires only that you be able to describe the replication process briefly.

According to the central dogma of molecular genetics, DNA is the genetically active component of the chromosomes of a cell. That is, DNA in the cell nucleus contains all the information necessary to control synthesis of the proteins, enzymes, and other molecules which are needed as that cell grows, carries on metabolism, and eventually reproduces. Thus when a cell divides, its DNA must pass on genetic information to both daughter cells. It must somehow be able to divide into duplicate copies. This process is called **replication**. Given the complementary double strands of DNA, it is relatively easy to see how DNA as a molecule is well structured for replication, as is show in Figure 9.3.1. Each strand serves as a template for a new strand. Thus, after DNA is replicated, each new DNA double helix will have one strand from the original DNA molecule, and one newly synthesized molecule. This is referred to as **semiconservative replication**.

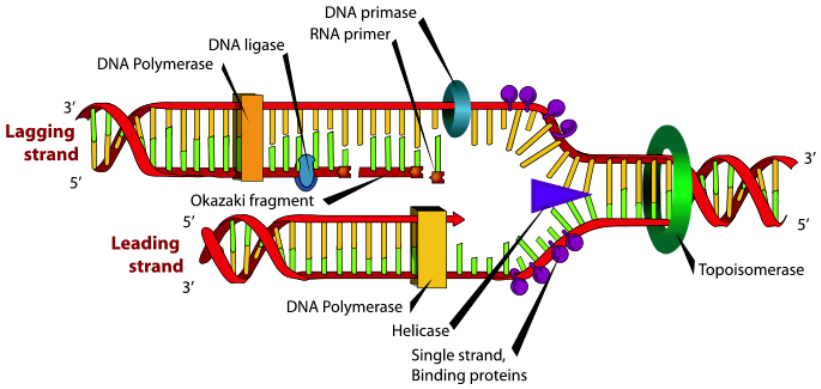


Figure 9.3.1: The replication of DNA. Replication occurs by means of partial unwinding of the two strands accompanied by synthesis of a new strand complementary to each of the originals. (CC BY 4.0; Aida Khakimova, Oleg Zolotarev, and Igor Zatsman via the Open Public Health Journal)

A rather complex mechanism exists for DNA replication, involving many different enzymes and protein factors. Let us consider some of the more important aspects of DNA replication. First, the double strand needs to be opened up to replicate each template strand. To do this, a set of proteins and enzymes bind to and open up the double helix at an origin point in the molecule. This forms **replication forks**, points where double stranded DNA opens up, allowing replication to occur. A helicase enzyme binds at the replication forks, with the function of further unwinding the DNA and allowing the replication fork to move along the double strand as DNA is replicated. Another enzyme, DNA gyrase, is also required to relieve stress on the duplex caused by unwinding the double strand. Further, single strand binding proteins are needed to prevent the single strands from reforming a double strand. Another essential enzyme in this initiation phase is primase, which creates an RNA primer on each single strand of DNA to begin replication from.

All of these initial functions are necessary to prepare the DNA for the main enzyme which builds then new strands, DNA polymerase. Multiple polymerase enzymes exist, but for the moment we will DNA polymerase III, the main DNA polymerase in *E. coli*. DNA polymerase III catalyzes the reaction by which a new nucleotide is added to a growing DNA strand. That reaction is

seen in Figure 9.3.2. The DNA polymerase enzymes need a free 3' OH group in order to begin synthesizing a new strand, which explains the necessity of the RNA primer, which gives a 3'OH group for DNA polymerase III to start from.

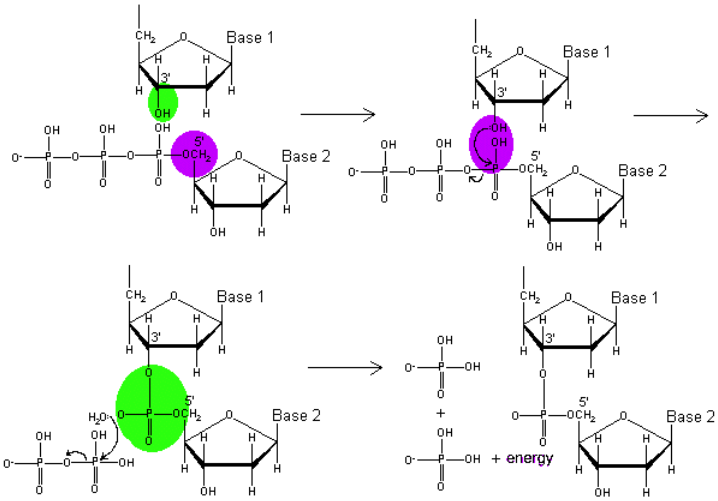


Figure 9.3.3: The polymerization of DNA nucleotides. The 3' hydroxyl group attacks the triphosphate group on the incoming nucleotide. A new phosphodiester bond is formed, and a pyrophosphate group leaves. This leaves two phosphates, the energy released from breaking down a the high energy phosphate group, and a elongated strand of DNA with a new 3' hydroxyl group to which another nucleotide may be added.
(Copyright; author via source)

This leads to another constraint on DNA polymerase III. One strand, the **leading strand** can be polymerized continuously since the new strand being created goes 5' to 3' from the replication fork, but since the original strands are anti-parallel, the other strand, the **lagging strand** is going in the wrong direction for polymerization. In this case, the polymerization reaction starts away from the replication fork and works back toward it. This means that the lagging strand is synthesized in disconnected segments, known as **Okazaki fragments**, instead of continuously. Later, another DNA polymerase, in the case of *E. coli*, DNA polymerase I, removes RNA primers and fills in the missing discontinuities. Then, *another* enzyme, DNA ligase, connects breaks between 3'OH groups and 5' phosphate groups in the newly synthesized strands that exist due to these discontinuities. While the enzymes of this process differ in eukaryotes, they fulfill similar mechanisms. Even with this complexity of this process, DNA polymerase III is able to add new nucleotides at a rate of 250-1,000 nucleotides per second.[3]

A number of advantages of the double-stranded structure held together by hydrogen bonds is evident in the process of replication. Complementary base pairing, A to T and G to C, insures that the two new DNA molecules will be the same as the original. The large number of hydrogen bonds, each of which is relatively weak, makes complete separation of the two strands unlikely, but one hydrogen bond, or even a few, can be broken rather easily. The helicase portion of the replication complex can therefore separate the two strands in much the same way that a zipper operates. Like the teeth of a zipper, hydrogen bonds provide great strength when all work together, but the proper tool can separate them one at a time.

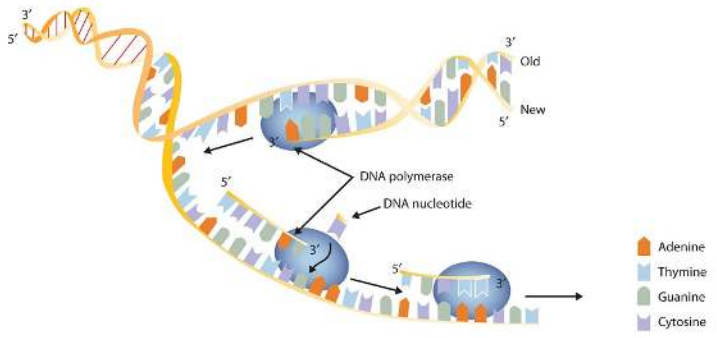


Figure 9.3.4: A Schematic Diagram of DNA Replication. DNA replication occurs by the sequential unzipping of segments of the double helix.

The Scope of the Problem of DNA Replication

The 46 chromosomes of the human genome consists of roughly 6.5 billion base pairs of DNA if one considers the full diploid genome (i.e. if you count the DNA inherited from both parents). Considering that this DNA can be copied in just a few hours shows that the rate of DNA replication is staggering.

Although DNA replication is typically a highly accurate process and proofreading DNA polymerases help to keep the error rate low (about one per 10 billion bases), mistakes still occur. In addition to errors of replication, environmental damage may also occur to the DNA. Such uncorrected errors of replication or environmental DNA damage may lead to serious consequences. Therefore, Nature has evolved several mechanisms for detecting and repairing damaged or incorrectly synthesized DNA.

✔ Example 9.3.1

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?

Solution

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).

? Exercise 28.3.1

A segment of one strand from a DNA molecule has the sequence 5′-CCAGTGAATTGCCTAT-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

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9.4: Transcription of DNA

Objectives

After completing this section, you should be able to

- describe, very briefly, how RNA is synthesized in the nucleus of the cell by transcription of DNA.
- identify the important structural differences between DNA and DNA.
- given the appropriate Kekulé structures, show how uracil can form strong hydrogen bonds to adenine.
- identify the base sequence in RNA that would be complementary to a given base sequence in DNA.

Key Terms

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

- messenger RNA
- RNA polymerase
- ribosomal RNA
- transcription
- transfer RNA

Study Notes

"Messenger RNA" (mRNA) carries the genetic information from the DNA in the nucleus to the cytoplasm where protein synthesis occurs. The code carried by mRNA is read by "transfer RNA" (tRNA) in a process called translation (see Section 28.5).

"Ribosomal RNA" (rRNA) is the term used to describe the RNA molecules which, together with proteins, make up the ribosomes on which proteins are synthesized.

Three types of RNA are formed during transcription: *messenger RNA* (mRNA), *ribosomal RNA* (rRNA), and *transfer RNA* (tRNA). These three types of RNA differ in function, size, and percentage of the total cell RNA (Table 9.4.1). mRNA makes up only a small percent of the total amount of RNA within the cell, primarily because each molecule of mRNA exists for a relatively short time; it is continuously being degraded and resynthesized. The molecular dimensions of the mRNA molecule vary according to the amount of genetic information a given molecule contains. After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Elsewhere, we shall see how mRNA directly determines the sequence of amino acids during protein synthesis.

Table 9.4.1: Properties of Cellular RNA in Escherichia coli

Type	Function	Approximate Number of Nucleotides	Percentage of Total Cell RNA
mRNA	codes for proteins	100–6,000	~3
rRNA	component of ribosomes	120–2900	83
tRNA	adapter molecule that brings the amino acid to the ribosome	75–90	14

For the hereditary information in DNA to be useful, it must be "expressed," that is, used to direct the growth and functioning of an organism. The flow of genetic information in cells goes from DNA to mRNA to protein, by genes which specify the sequences of mRNAs, which in turn specify the sequences of proteins.

The first step in the processes that constitute DNA expression is the synthesis of RNA, by a template mechanism that is in many ways analogous to DNA replication. Because the RNA that is synthesized is a complementary copy of information contained in DNA, RNA synthesis is referred to as transcription. Transcription requires the DNA double helix to partially unwind in the region

of mRNA synthesis. The region of unwinding is called a **transcription bubble**. The DNA sequence has patterns which indicate where RNA polymerase should start and end transcription. A DNA sequence at which the RNA polymerase binds to start transcription is called a **promoter**. The DNA sequence that indicates the endpoint of transcription, where the RNA polymerase should stop adding nucleotides and dissociate from the template is known as a **terminator** sequence. The promoter and terminator, thus, bracket the region of the DNA that is to be transcribed.

In bacteria, the promotor sequence contains two 6 bp region called **consensus** sequences. One sequence is centered about 10 bp upstream from the transcription start site. The second sequence at about 35 basepairs upstream from the start of transcription. The consensus sequences at -10 and -35 are necessary for recognition of the promoter region by RNA polymerase.

The DNA sequence that is transcribed to make RNA is called the antisense strand (also called template, anticoding, or transcribed strand), while the complementary sequence on the other DNA strand is called the sense strand (also called the coding or informational strand). To initiate RNA synthesis, the two DNA strands unwind at specific sites along the DNA molecule. Ribonucleotides are attracted to the uncoiling region of the DNA molecule, beginning at the 3′ end of the template strand, according to the rules of base pairing. Thymine in DNA calls for adenine in RNA, cytosine specifies guanine, guanine calls for cytosine, and adenine requires uracil. RNA polymerase—an enzyme—binds the complementary ribonucleotide and catalyzes the formation of the ester linkage between ribonucleotides, a reaction very similar to that catalyzed by DNA polymerase (Figure 9.4.1). Synthesis of the RNA strand takes place in the 5′ to 3′ direction, antiparallel to the template strand. Only a short segment of the RNA molecule is hydrogen-bonded to the template strand at any time during transcription. When transcription is completed, the RNA is released, and the DNA helix reforms. The nucleotide sequence of the RNA strand formed during transcription is identical to that of the corresponding coding strand of the DNA, except that U replaces T.

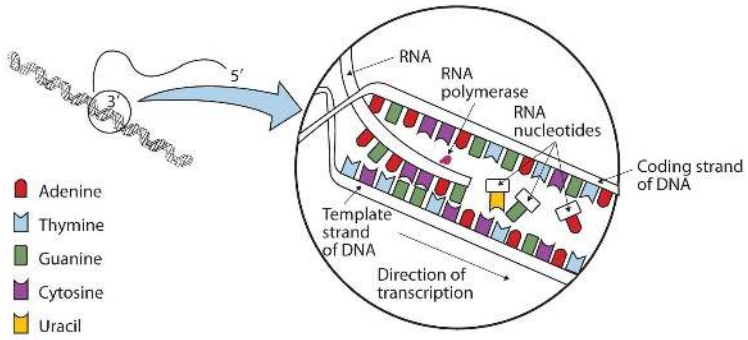


Figure 9.4.1: A Schematic Diagram of RNA Transcription from a DNA Template. The representation of RNA polymerase is proportionately much smaller than the actual molecule, which encompasses about 50 nucleotides at a time. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

The genes of eukaryotes (animals and plants) usually done have continuous segments of coding DNA. Rather they have intervening sequences of DNA (introns) within a given gene that separate coding fragments of DNA (exons). In a process called **splicing**, a primary transcript is made from the DNA, and then splicesomes cut out the introns and join the exons to form a contiguous stretch to form messenger RNA, mRNA. Once formed the mRNA leaves the nucleus is to be translated into a protein sequence..

New findings make it even more complicated to define a gene, especially if the transcripts of a "gene region" are studied. Cheng et al studied all transcripts from 10 different human chromosomes and 8 different cell lines. They found a large number of different transcripts, many of which overlapped. Splicing often occur between nonadjacent introns. Transcripts were found from both strands and were from regions containing introns and exons. Other studies found up to 5% of transcripts continued through the end of "gene" into other genes. 63% of the entire mouse genome, which is comprised of only 2% exons, is transcribed.

? Exercise 9.4.1

A portion of the template strand of a gene has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the RNA that is formed from this template?

Answer

Four things must be remembered in answering this question: (1) the DNA strand and the RNA strand being synthesized are antiparallel; (2) RNA is synthesized in a 5′ to 3′ direction, so transcription begins at the 3′ end of the template strand; (3) ribonucleotides are used in place of deoxyribonucleotides; and (4) thymine (T) base pairs with adenine (A), A base pairs

with uracil (U; in RNA), and cytosine (C) base pairs with guanine (G). The sequence is determined to be 3′-AGGUACUCAACU-5′ (can also be written as 5′-UCAACUCAUGGA-3′).

Exercise 9.4.2

What would be the DNA base sequence of the coding strand required to transcribe the following RNA sequence?

5′-AUGAGCGACUUUGCGGGAUUA-3′

Answer

5′-ATGAGCGACTTTGCGGGATTA-3′.

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9.5: Translation of RNA - Protein Biosynthesis

Objectives

After completing this section, you should be able to describe, very briefly, the roles of messenger RNA and transfer RNA in the biosynthesis of proteins.

Key Terms

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

- anticodon
- codon
- translation

Study Notes

As in the preceding section, you should not be too concerned about trying to memorize details. The objective requires you to have a general understanding of the roles played by mRNA and tRNA in the biosynthesis of proteins, and that you be able to describe this process.

After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Ribosomes are cellular substructures where proteins are synthesized. They contain about 65% rRNA and 35% protein, held together by numerous noncovalent interactions, such as hydrogen bonding, in an overall structure consisting of two globular particles of unequal size. We turn now to the question of how the sequence of nucleotides in a molecule of ribonucleic acid (RNA) is translated into an amino acid sequence.

How can a molecule containing just 4 different nucleotides specify the sequence of the 20 amino acids that occur in proteins? If each nucleotide coded for 1 amino acid, then obviously the nucleic acids could code for only 4 amino acids. What if amino acids were coded for by groups of 2 nucleotides? There are 4^2, or 16, different combinations of 2 nucleotides (AA, AU, AC, AG, UU, and so on). Such a code is more extensive but still not adequate to code for 20 amino acids. However, if the nucleotides are arranged in groups of 3, the number of different possible combinations is 4^3, or 64. Here we have a code that is extensive enough to direct the synthesis of the primary structure of a protein molecule.

The **genetic code** can therefore be described as the identification of each group of three nucleotides and its particular amino acid. The sequence of these triplet groups in the mRNA dictates the sequence of the amino acids in the protein. Each individual three-nucleotide coding unit, as we have seen, is called a **codon**.

First base	Second base: U	Second base: C	Second base: A	Second base: G	Third base
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Figure 9.5.1: The Genetic Code

Early experimenters were faced with the task of determining which of the 64 possible codons stood for each of the 20 amino acids. The cracking of the genetic code was the joint accomplishment of several well-known geneticists—notably Har Khorana, Marshall Nirenberg, Philip Leder, and Severo Ochoa—from 1961 to 1964. The genetic dictionary they compiled, summarized in Figure 9.5.3, shows that 61 codons code for amino acids, and 3 codons serve as signals for the termination of polypeptide synthesis (much like the period at the end of a sentence). Notice that only methionine (AUG) and tryptophan (UGG) have single codons. All other amino acids have two or more codons.

Protein synthesis is accomplished by orderly interactions between mRNA and the other ribonucleic acids (transfer RNA [tRNA] and ribosomal RNA [rRNA]), the ribosome, and more than 100 enzymes. The mRNA formed in the nucleus during transcription is transported across the nuclear membrane into the cytoplasm to the ribosomes—carrying with it the genetic instructions. The process in which the information encoded in the mRNA is used to direct the sequencing of amino acids and thus ultimately to synthesize a protein is referred to as *translation*.

Before an amino acid can be incorporated into a polypeptide chain, it must be attached to its unique tRNA. The carboxylic acid group of the amino acid forms an ester linkage with with the 3' hydroxyl group on the riboses bonded at the 3' end of the tRNA. This crucial process requires an enzyme known as aminoacyl-tRNA synthetase (Figure 9.5.1). There is a specific aminoacyl-tRNA synthetase for each amino acid. This high degree of specificity is vital to the incorporation of the correct amino acid into a protein. After the amino acid molecule has been bound to its tRNA carrier, protein synthesis can take place.

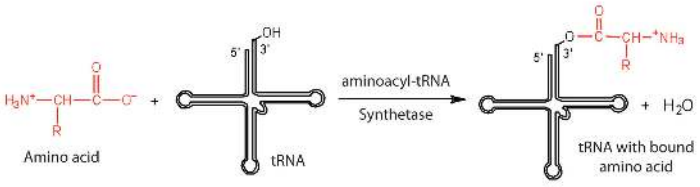


Figure 9.5.2 Binding of an Amino Acid to Its tRNA

The two-dimensional structure of a tRNA molecule is reminiscent of a cloverleaf. At one end of the tRNA molecule is the acceptor stem, where the amino acid is attached. The tRNA Molecule has three distinctive loops. One of these is called the anticodon loop which holds a sequence of three nucleotides called the **anticodon**. Each anticodon corresponds to the amino acid each is tRNA molecule is specifically designed to carry. For example, the amino acid lysine has the codon AAG, so the anticodon is UUC. Therefore, lysine would be carried by a tRNA molecule with the anticodon UUC. Each of the 20 amino acids found in proteins has at least one corresponding kind of tRNA, and most amino acids have more than one.

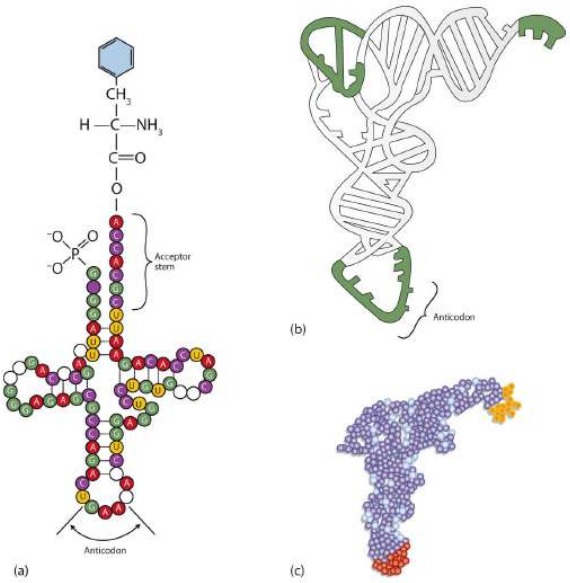
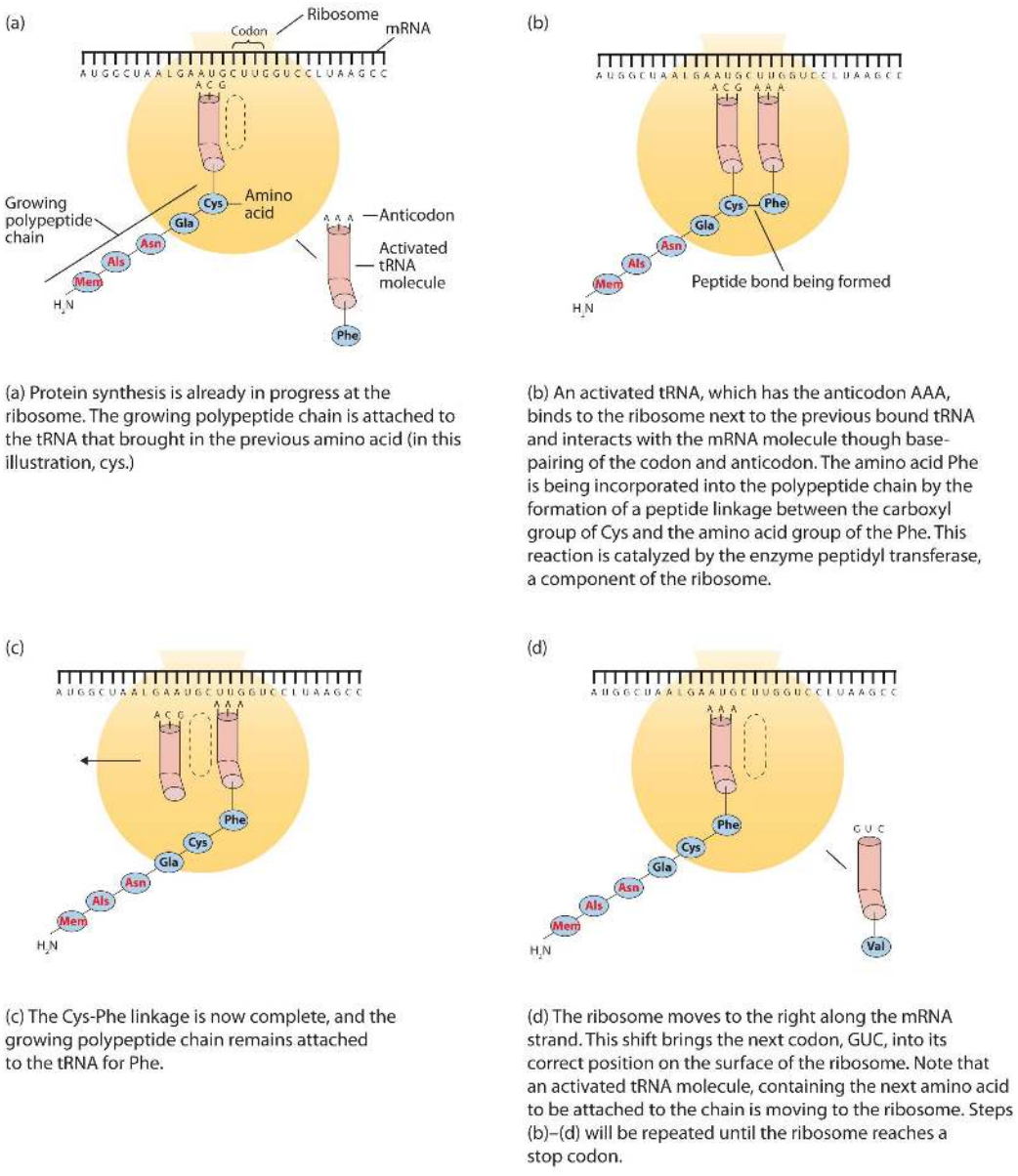


Figure 9.5.3: Transfer RNA (a) In the two-dimensional structure of a yeast tRNA molecule for phenylalanine, the amino acid binds to the acceptor stem located at the 3′ end of the tRNA primary sequence. (The nucleotides that are not specifically identified here are slightly altered analogs of the four common ribonucleotides A, U, C, and G.) (b) In the three-dimensional structure of yeast phenylalanine tRNA, note that the anticodon loop is at the bottom and the acceptor stem is at the top right. (c) This shows a space-filling model of the tRNA.

During protein synthesis the codon on the mRNA determines which kind of tRNA will add its amino acid to the growing chain. Wherever the codon AAG appears in mRNA, a UUC anticodon on a tRNA temporarily binds to the codon ect. As each different tRNA brings an amino acid into position an enzyme adds it to the growing protein chain. The protein is released from the ribosome once it is completed. Figure 9.5.2 depicts a schematic stepwise representation of this all-important process.



(a) Protein synthesis is already in progress at the ribosome. The growing polypeptide chain is attached to the tRNA that brought in the previous amino acid (in this illustration, cys.)

(b) An activated tRNA, which has the anticodon AAA, binds to the ribosome next to the previous bound tRNA and interacts with the mRNA molecule though base-pairing of the codon and anticodon. The amino acid Phe is being incorporated into the polypeptide chain by the formation of a peptide linkage between the carboxyl group of Cys and the amino acid group of the Phe. This reaction is catalyzed by the enzyme peptidyl transferase, a component of the ribosome.

(c) The Cys-Phe linkage is now complete, and the growing polypeptide chain remains attached to the tRNA for Phe.

(d) The ribosome moves to the right along the mRNA strand. This shift brings the next codon, GUC, into its correct position on the surface of the ribosome. Note that an activated tRNA molecule, containing the next amino acid to be attached to the chain is moving to the ribosome. Steps (b)–(d) will be repeated until the ribosome reaches a stop codon.

Figure 9.5.4: The Elongation Steps in Protein Synthesis

? Exercise 9.5.1

What are the roles of mRNA and tRNA in protein synthesis?

Answer

mRNA provides the code that determines the order of amino acids in the protein; tRNA transports the amino acids to the ribosome to incorporate into the growing protein chain.

? Exercise 9.5.2

A portion of an mRNA molecule has the sequence 5′-AUGCCACGAGUUGAC-3′. What amino acid sequence does this code for?

Answer

Use Figure 9.5.1 to determine what amino acid each set of three nucleotides (codon) codes for. Remember that the sequence is read starting from the 5′ end and that a protein is synthesized starting with the N-terminal amino acid. The sequence 5′-AUGCCACGAGUUGAC-3′ codes for met-pro-arg-val-asp.

Exercise 9.5.3

Write the anticodon on tRNA that would pair with each mRNA codon.

a. 5′-UUU-3′
b. 5′-CAU-3′
c. 5′-AGC-3′
d. 5′-CCG-3′

Answer

a. 3′-AAA-5′
b. 3′-GUA-5′
c. 3′-UCG-5′
d. 3′-GGC-5′

Exercise 9.5.4

The peptide hormone oxytocin contains 9 amino acid units. What is the minimum number of nucleotides needed to code for this peptide?

Answer

27 nucleotides (3 nucleotides/codon)

Exercise 9.5.5

Determine the amino acid sequence produced from this mRNA sequence: 5′-AUGAGCGACUUUGCGGGAUUA-3′.

Answer

met-ser-asp-phe-ala-gly-leu

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9.6: DNA Sequencing

Objectives

After completing this section, you should be able to

- Describe briefly how DNA sequencing is carried out.

DNA sequencing determines the order of nucleotide bases within a given fragment of DNA. This information can be used to infer the RNA or protein sequence encoded by the gene, from which further inferences may be made about the gene's function and its relationship to other genes and gene products. DNA sequence information is also useful in studying the regulation of gene expression. If DNA sequencing is applied to the study of many genes, or even a whole genome, it is considered an example of genomics.

While techniques to sequence proteins have been around since the 1950s, techniques to sequence DNA were not developed until the mid-1970s, when two distinct sequencing methods were developed almost simultaneously, one by Walter Gilbert's group at Harvard University, the other by Frederick Sanger's group at Cambridge University. However, until the 1990s, the sequencing of DNA was a relatively expensive and long process. Using radiolabeled nucleotides also compounded the problem through safety concerns. With currently-available technology and automated machines, the process is cheaper, safer, and can be completed in a matter of hours. The Sanger sequencing method was used for the human genome sequencing project, which was finished its sequencing phase in 2003, but today both it and the Gilbert method have been largely replaced by better methods.

Restriction Enzymes

To be able to sequence DNA, it is first necessary to cut it into smaller fragments. What is needed is a way to cleave the DNA molecule at a few precisely-located sites so that a small set of homogeneous fragments are produced. To cut DNA at known locations, researchers use **restriction endonucleases** enzymes that have been purified from various bacterial species, and which can be purchased from various commercial sources. REs occur naturally in bacteria, where they specifically recognize short stretches of nucleotides in DNA and catalyze double-strand breaks at or near the recognition site (also known as a restriction site). These enzymes are usually named after the bacterium from which they were first isolated. For example, ***EcoRI*** and *EcoRV* are both enzymes from *E. coli*.

Restriction enzymes like EcoRI are frequently called 6-cutters, because they recognize a 6-nucleotide sequence. Assuming a random distribution of A, C, G and Ts in DNA, probability predicts that a recognition site for a 6-cutter should occur about once for every 4096 bp (4^6) in DNA. Of course, the distribution of nucleotides in DNA is not random, so the actual sizes of DNA fragments produced by EcoRI range from hundreds to many thousands of base pairs, but the mean size is close to 4000 bp. DNA fragments of this length are useful in the lab, since they long enough to contain the coding sequence for proteins and are well-resolved on agarose gels.

EcoRI recognizes the sequence G A A T T C in double stranded DNA. This recognition sequence is a palindrome with a two-fold axis of symmetry, because reading from 5' to 3' on either strand of the helix gives the same sequence. The palindromic nature of the restriction site is more obvious in the figure below. The dot in the center of the restriction site denotes the axis of symmetry. EcoRI catalyzes the hydrolysis of the phosphodiester bonds between G and A on both DNA strands. The restriction fragments generated in the reaction have short single-stranded tails at the 5'-ends. These ends are often referred to as "sticky ends," because of their ability to form hydrogen bonds with complementary DNA sequences.



Figure 9.6.1: The recognition sequence for EcoRI (blue) is cleaved by the enzyme (grey). This particular enzyme cuts DNA at a position offset from the center of the restriction site. This creates an overhanging, sticky-end. (Original-Deyholos-CC:AN)

Reading DNA Sequences

We will discuss one method of reading the sequence of DNA. This method, developed by Sanger won him a second Nobel prize. Sanger sequencing, also known as chain-termination sequencing, requires a single-stranded DNA template, a DNA primer, a DNA polymerase, normal deoxynucleotidetriphosphates (dNTPs), and modified nucleotides (dideoxyNTPs - ddNTP) that terminate DNA strand elongation. These chain-terminating nucleotides lack a 3′-OH group required for the formation of a phosphodiester bond between two nucleotides, causing DNA polymerase to cease extension of DNA when a ddNTP is incorporated.

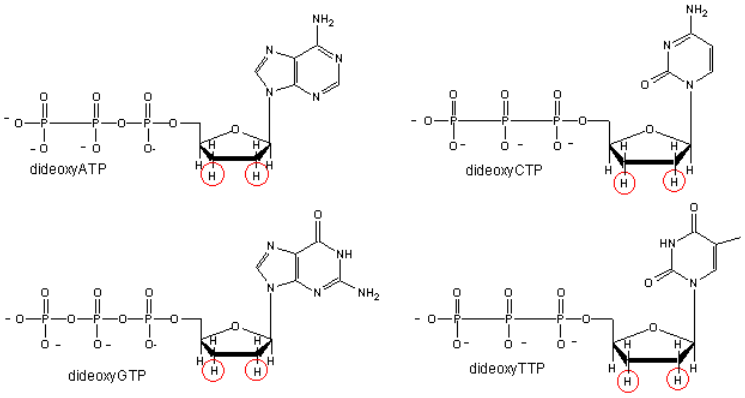


Figure 9.6.2: Didexoynucleotides

Four reaction tubes are set up, each containing the template DNA to be sequenced, a *primer* of known sequence, all four of the standard deoxynucleotides (dATP, dGTP, dCTP and dTTP), and the DNA polymerase. To each reaction is added only one of the four dideoxynucleotides (ddATP, ddGTP, ddCTP, or ddTTP) which has been fluorescently labeled. Most of the time in a Sanger sequencing reaction, DNA Polymerase will add a proper dNTP to the growing strand it is synthesizing in vitro. But at random locations, it will instead add a ddNTP. When it does, that strand will be terminated at the ddNTP just added. If enough template DNAs are included in the reaction mix, each one will have the labeled ddNTP inserted at a different random location, and there will be at least one DNA terminated at each different nucleotide along its length for as long as the in vitro reaction can take place (about 900 nucleotides under optimal conditions.)

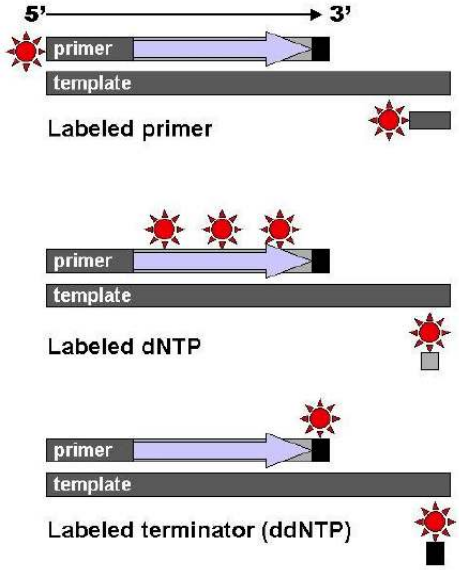


Figure 9.6.3: Sanger sequencing: Different types of Sanger sequencing, all of which depend on the sequence being stopped by a terminating dideoxynucleotide (black bars).

After the reactions are over, the newly synthesized strands can be denatured from the template, and then separated by capillary electrophoresis or other equivalent methods. Since each band differs in length by one nucleotide, and the identity of that nucleotide is known from its fluorescence, the DNA sequence can be read simply from the order of the colors in successive bands.

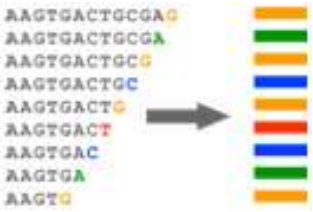


Figure 9.6.4: Fluorescently labeled products can be separated electrophoretically based on their length. (Original-Deyholos-CC:AN)

As each differently-sized fragment exits the capillary column, a laser excites the florescent tag on its terminal nucleotide. From the color of the resulting florescence, a computer can keep track of which nucleotide was present as the terminating nucleotide. The computer also keeps track of the order in which the terminating nucleotides appeared, which is the sequence of the DNA used in the original reaction. In practice, the maximum length of sequence that can be read from a single sequencing reaction is about 700 bp.

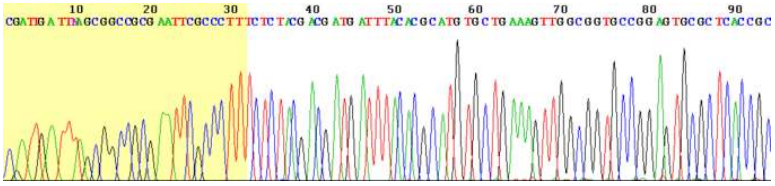


Figure 9.6.5: Chromatograph: This is an example of the output of a Sanger sequencing read using fluorescently labeled dye-terminators. The four DNA bases are represented by different colors which are interpreted by the software to give the DNA sequence above.

Scientists now know the sequence of all the 3 billion DNA base pairs in the entire human genome. This knowledge was attained by the **Human Genome Project (HGP),** a $3 billion, international scientific research project that was formally launched in 1990. The project was completed in 2003, two years ahead of its 15-year projected deadline. Determining the sequence of the billions of base pairs that make up human DNA was the main goal of the HGP. Another goal was mapping the location and determining the function of all the genes in the human genome. There are only about 20,500 genes in human beings. If modern methods were used it might bring the cost of sequencing the human genome down from the initial billion dollar range to $100.

Example 9.6.1

You will pretend to sequence a single stranded piece of DNA as shown below. The new nucleotides are added by the enzyme DNA polymerase to the primer, GACT, in the 5' to 3' direction. You will set up 4 reaction tubes, Each tube contains all the dXTP's. In addition, add ddATP to tube 1, ddTTP to tube 2, ddCTP to tube 3, and ddGTP to tube 4. For each separate reaction mixture, determine all the possible sequences made by writing the possible sequences on one of the unfinished complementary sequences below. Cut the completed sequences from the page, determine the size of the polynucleotide sequences made, and place them as they would migrate (based on size) in the appropriate lane of a imaginary gel which you have drawn on a piece of paper. Lane 1 will contain the nucleotides made in tube 1, etc. Then draw lines under the positions of the cutout nucleotides to represent DNA bands in the gel. Read the sequence of the complementary DNA synthesized. Then write the sequence of the ssDNA that was to be sequenced.

- 5' T C A A C G A T C T G A 3' (STAND TO SEQUENCE)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)

Since the DNA fragments have no detectable color, they can not be directly visualized in the gel. Alternative methods are used. In the one described above, radiolabeled ddXTP's where used. Once the sequencing gel is run, it can be dried and the bands visualized by radioautography (also called autoradiography). A place of x-ray film is placed over the dried gel in a dark environment. The radiolabeled bands will emit radiation which will expose the x-ray film directly over the bands. The film can be developed to detect the bands. In a newer technique, the primer can be labeled with a flourescent dye. If a different dye is used for each reaction mixture, all the reaction mixtures can be run in one lane of a gel. (Actually only one reaction mix containing all the ddXTP's together need be performed.) The gel can then be scanned by a laser, which detects fluorescence from the dyes, each at a different wavelength.

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9.7: DNA Synthesis

Objectives

After completing this section, you should be able to

- describe, briefly, the steps required for chemical synthesis of DNA segments.

DNA must be synthesized to study genes, the sequence of genomes, and many other studies. This occurs in two fashions, by polymerase chain reaction (PCR) and chemical synthesis. PCR is covered in Section 28.8. Here we will focus on chemical synthesis of short DNA segments, which which are called oligonucleotides. Oligonucleotide synthesis is the chemical synthesis of relatively short fragments of nucleic acids, both DNA and RNA with a defined chemical structure (sequence). The technique is extremely useful in current laboratory practice because it provides a rapid and inexpensive access to custom-made oligonucleotides of the desired sequence.

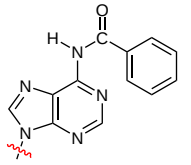
The synthesis of DNA is more difficult than peptide synthesis (Section 26-8) because of the complexity of nucleotide monomers. Commercial automated DNA synthesizers are available which allow for DNA segments to be made quickly and at a low cost. DNA synthesizers typically uses solid-phase techniques similar to the Merrifield solid-phase peptide synthesizer. Nucleotides are protected then covalently bonded to a solid support. Nucleotides are sequentially coupled to the growing oligonucleotide chain in the order required by the sequence of the product. Upon the completion of the chain assembly, the product is released from the solid phase to solution, it is then deprotected, and collected. The occurrence of side reactions sets practical limits for the length of synthetic oligonucleotides (up to about 200 nucleotide residues) because the number of errors accumulates with the length of the oligonucleotide being synthesized. Products are often isolated by HPLC to obtain the desired oligonucleotides in high purity. Typically, synthetic oligonucleotides are single-stranded DNA or RNA molecules around 15–25 bases in length.

DNA Chemical Synthesis

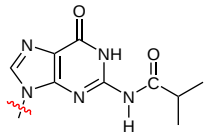
The synthesis of DNA involves five steps:

Step 1

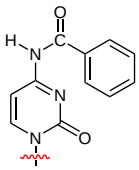
Nucleosides used for this synthesis are modified with a linking agent at the 3' hydroxyl group of deoxyribose. The 5' hydroxyl group of the nucleosides is protected with *p*-dimethoxytrityl (DMT) ether. The amine groups on the nucleoside's heterocyclic bases are also protected. The amines of adenine and cytosine bases are protected with benzoyl groups. Guanine's amine are protected by a isobutyryl group and thymine has no amine groups so protection is not required.



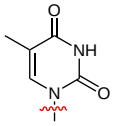
N-Protected Adenine



N-Protected Guanine

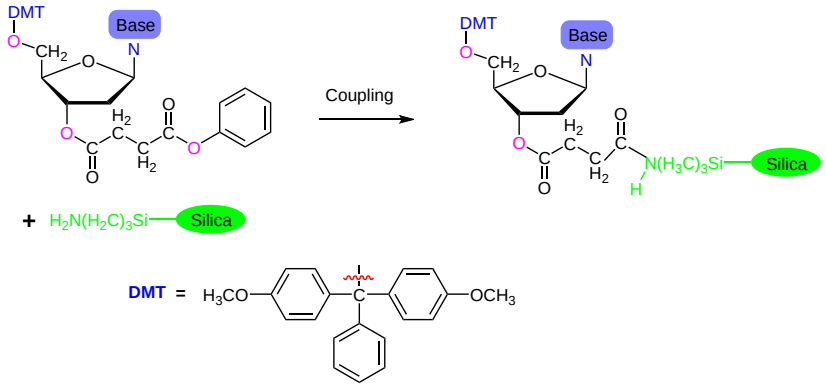


N-Protected Cytosine



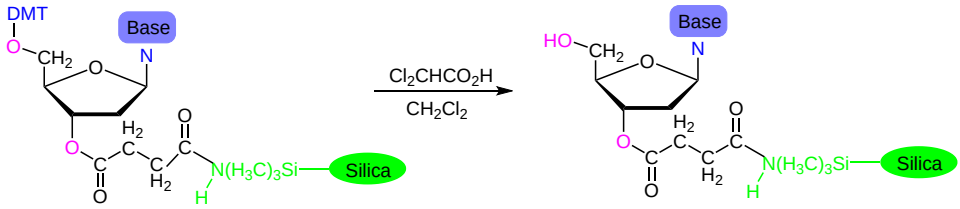
Thymine

The solid phase support used for DNA synthesis is commonly silica (SO_2) spheres which have been functionalized with (3-aminopropyl)triethoxysilane such that an amine group is available for reaction on the surface. A protected nucleoside is coupled to the solid phase support through an ester linkage with the 3' hydroxyl group of the nucleoside and an amide linkage with amine group from the silica surface.



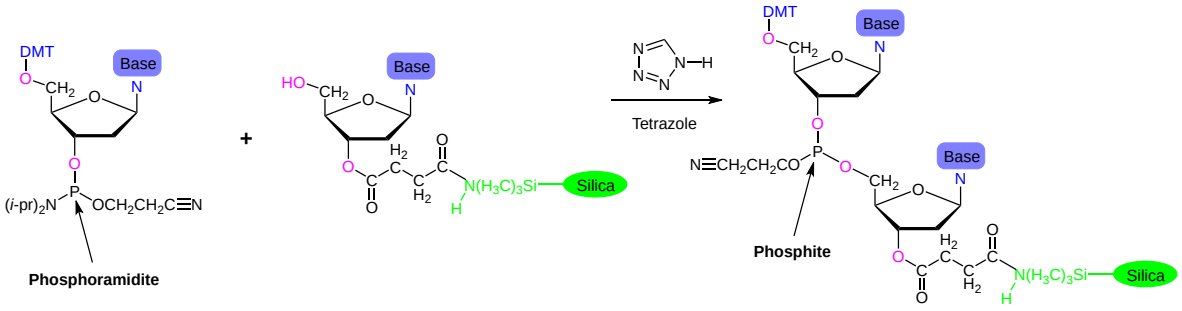
Step 2

Reaction with with dichloroacetic acid removes the DMT protecting group from the 5' hydroxyl of the nucleoside attached to the silica surface. The *p*-dimethoxytrityl leaving group forms a relatively stable dimethoxytrityl cation which is both tertiary and benzylic. The reaction proceeds rapidly through a S_N1 mechanism.



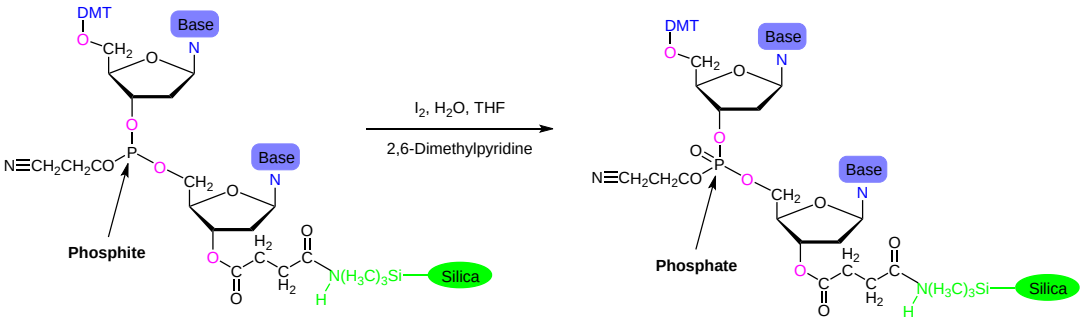
Step 3

The nucleoside attached to the silica surface is then reacted with a protected nucleoside which has a **phosphoramidite** functional group [$R_2NP(OR)_2$] attached to the 3' hydroxyl group of its deoxyribose moiety. In addition, one of the phosphorus oxygen atoms of the phosphoramidite group is protected with a beta-cyanoethyl group (-OCH_2CH_2CN). The two nucleosides are coupled in a reaction which uses acetonitrile as a polar aprotic solvent, tetrazole as a heterocyclic amine catalyst, and produces a product with a phosphite functional group [$P(OR)_3$].



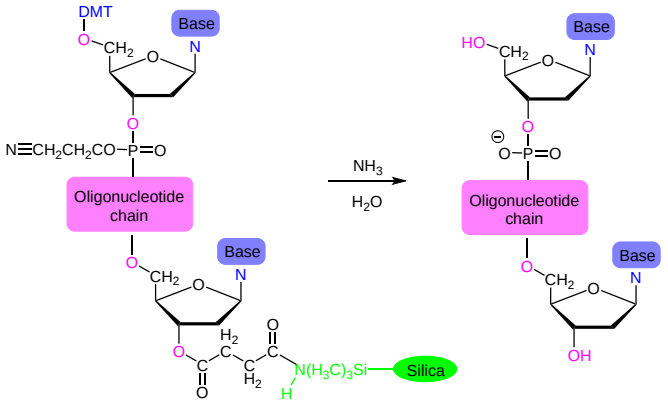
Step 4

Next the phosphite product of the previous step is oxidized to a phosphate by reaction with iodine (I_2) along with 2,6-dimethylpyridine in aqueous tetrahydrofuran (THF). Additional nucleosides can now be added by repeating the **phosphoramidite oligodeoxynucleotide synthesis cycle** of (1) DMT deprotection, (2) phosphoramidite coupling, and (3) oxidation to a phosphite.



Step 5

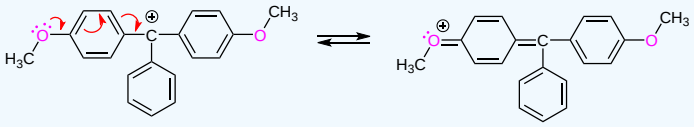
After the oligonucleotide chain of the desired sequence has been made, the final step is the removal of all the protecting groups and the linkage to silica by reaction with aqueous ammonia (NH_3).



Exercise 9.7.1

Draw a mechanism which shows why dimethoxytrityl cation produced by the cleavage of a *p*-dimethoxytrityl protecting group is exceptionally stable.

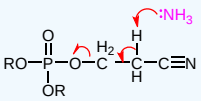
Answer



Exercise 9.7.2

When the beta-cyanoethyl protecting group is cleaved with aqueous ammonia, Acrylonitrile, H_2CCHCN , is also produced as a by-product. Draw a mechanism for the reaction.

Answer



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9.8: The Polymerase Chain Reaction

Objectives

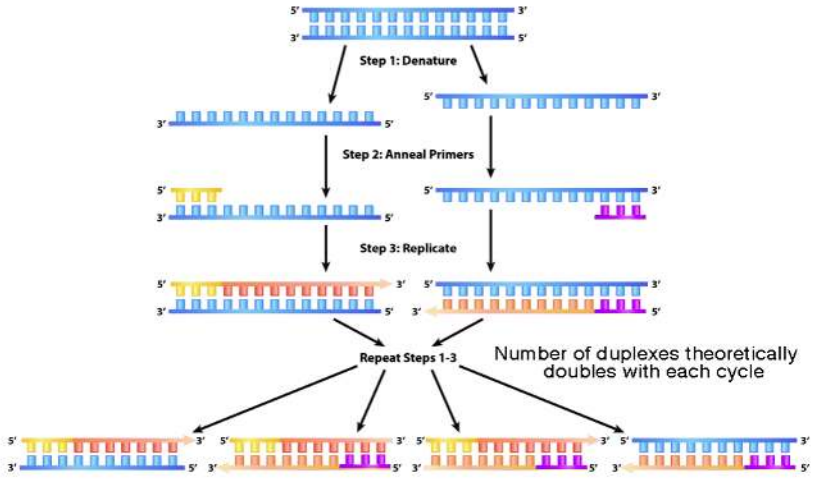
After completing this section, you should be able to

1. describe, briefly the three steps of PCR.

The polymerase chain reaction (PCR), allows one to use the power of DNA replication to amplify DNA enormously in a short period of time. As you know, cells replicate their DNA before they divide, and in doing so, double the amount of the cell's DNA. PCR essentially mimics cellular DNA replication in the test tube, repeatedly copying the target DNA over and over, to produce large quantities of the desired DNA. Kary B. Mullis was awarded a Nobel Prize in 1993 for his development of PCR, which is now the basis of innumerable research studies of gene structure, function and evolution as well as applications in criminal forensics, medical diagnostics and other commercial uses.

PCR requires a DNA fragment, some primers, which are short synthetic oligonucleotides whose sequence matches a region flanking the target sequence. All four deoxynucleotide triphosphates (dATP, dCTP, dGTP, dTTP), are added along with a heat stable DNA polymerase, **Taq**, from the organism *Thermophilus aquaticus* (which lives in hot springs).

PCR is run in a repeating cycle which involves three steps, template denaturing, primer annealing and primer extension.



Template Denaturing

This step is the first regular cycling event and consists of heating the reaction to 94-98°C. It causes denaturing of the DNA template by disrupting the hydrogen bonds between complementary bases, yielding single-stranded DNA molecules. The Taq polymerase is heat-stable so it is not denatured by the high temperature needed to separate the DNA template strands.

Primer Annealing

Next, the solution is cooled to 50-65°C, a temperature that favors complementary DNA sequences finding each other and making base pairs, a process called **annealing**. Since the primers are present in great excess, the complementary sequences they target are readily found and base-paired to the primers. These primers direct the synthesis of DNA. Only where primer anneals to a DNA strand will replication occur, since DNA polymerases require a primer to begin synthesis of a new strand.

Primer Extension

The temperature at this step depends on the DNA polymerase used; Taq polymerase has its optimum activity temperature at 75-80°C, and commonly a temperature of 72°C is used with this enzyme. At this step the DNA polymerase synthesizes a new DNA strand complementary to the DNA template strand by adding dNTPs that are complementary to the template in 5′ to 3′ direction, condensing the 5′-phosphate group of the dNTPs with the 3′-hydroxyl group at the end of the nascent (extending) DNA strand. On completion of this step there are two copies of the DNA template. The new DNA then be denatured to start the cycle again. Each

cycle doubles the amount of DNA. Using automated equipment, each cycle of replication can be completed in less than 5 minutes. After 30 cycles, what began as a single molecule of DNA has been amplified into more than a billion copies.

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CHAPTER OVERVIEW

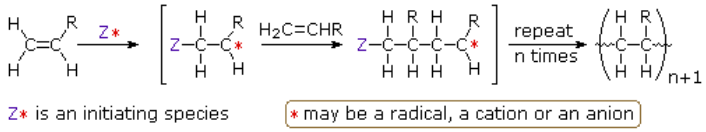
10: Synthetic Polymers

10.1: Chain-Growth Polymers
10.2: Stereochemistry of Polymerization- Ziegler-Natta Catalysts
10.3: Copolymers
10.4: Step-Growth Polymers
10.5: Olefin Metathesis Polymerization
10.6: Polymer Structure and Physical Properties
10.7: Plastics and the Environment
10.8: Biodegradable Plastics

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10.1: 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.

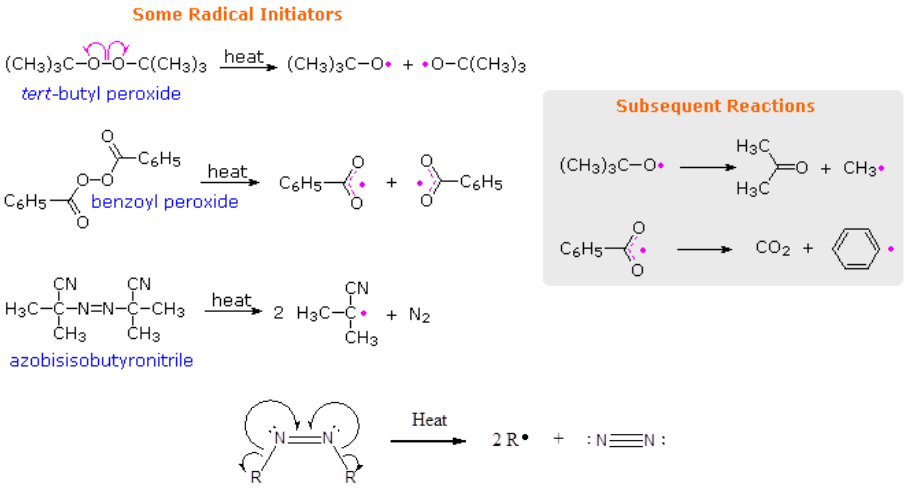


It is useful to distinguish four polymerization procedures fitting this general description.

• 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

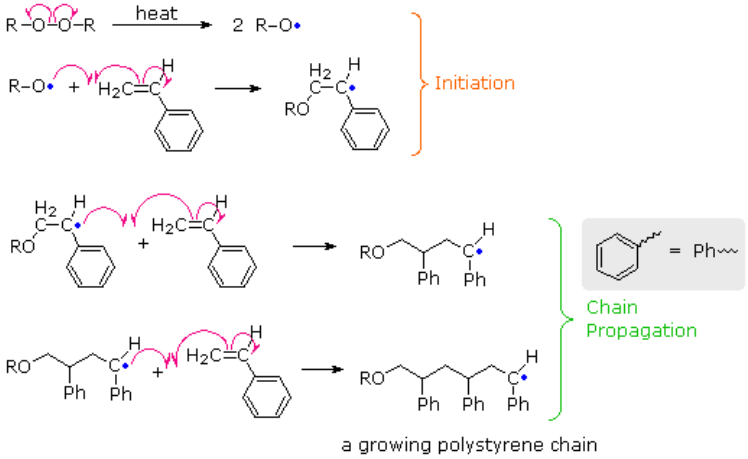
Virtually all of the monomers described above are subject to radical polymerization. Since this can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization 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.

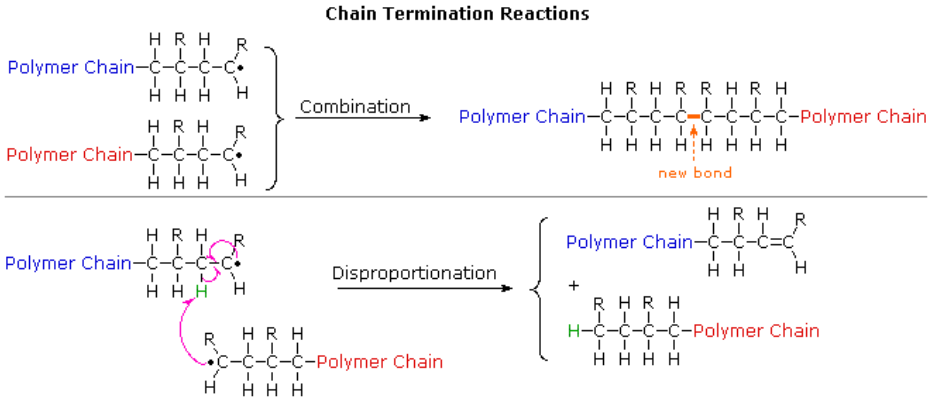
Each step in this polymer formation is an addition to an alkene. The mechanism is in most cases a *free radical* addition. In free radical reactions the pi pair of electrons separates. One of these electrons pairs with an electron from the attacking reagent to form a

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.



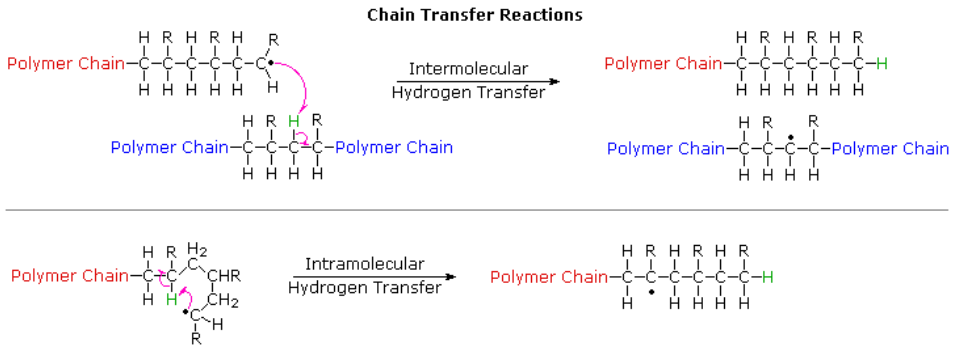
a growing polystyrene chain

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.

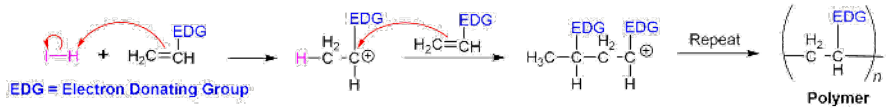
Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equations.



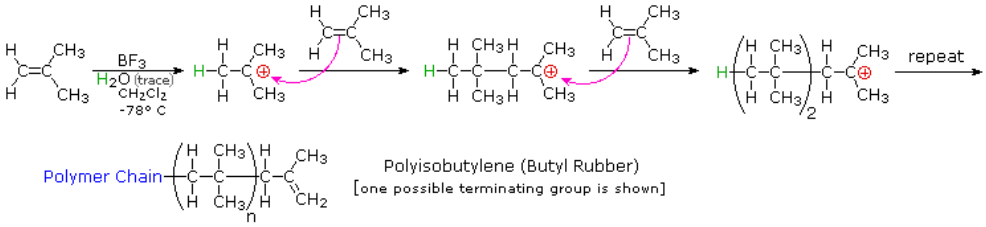
Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1º-radical at the end of a growing chain is converted to a more stable 2º-radical by hydrogen atom transfer. Further polymerization 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.

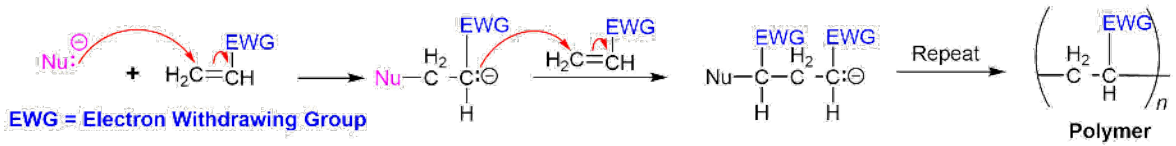


Polymerization of isobutylene (2-methylpropene) by traces of strong acids is an example of cationic polymerization. The initiation reagent cationic polymerization is commonly the Lewis acid, boron tribluoride (BF_3), along with traces of water to form the acidic $BF_3OH^-H^+$ catalyst. The polyisobutylene 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).

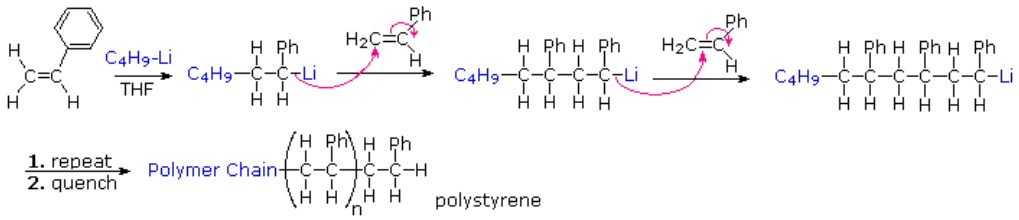


Anionic Chain-Growth Polymerization

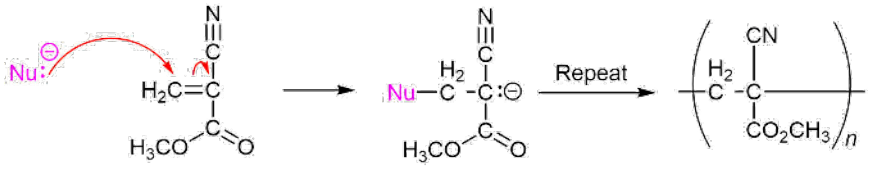
Only monomers having anion stabilizing electron-withdrawing groups (EWG) substituents, such as phenyl, cyano or carbonyl can undergo anionic polymerization.



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.

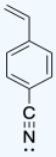


A practical application of anionic polymerization occurs in the use of superglue. This material is methyl 2-cyanoacrylate, CH_2=C(CN)CO_2CH_3. When exposed to water, amines or other nucleophiles, a rapid polymerization of this monomer takes place. Because the monomer has two electron withdrawing groups the polymerization particularly rapid.

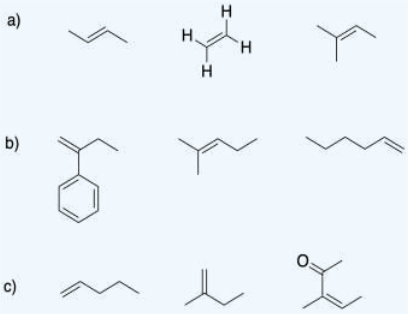


Exercise 10.1.1

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.

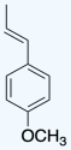


2) In each group, select the alkene monomer most suitable for cationic polymerization.



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:

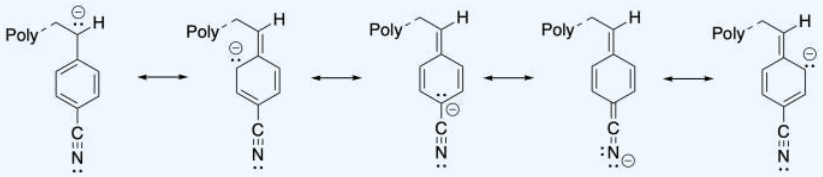
a) acrylonitrile, CH_2=CHCN

b) methyl acrylate, CH_2=$CHCO_2Me$

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Answer

1) The additional resonance stabilization of the anion by the nitrile group makes anionic polymerization proceed smoothly.



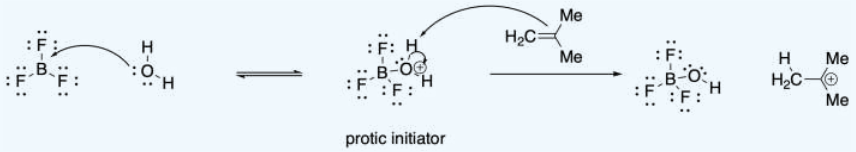
2)

a) tertiary cation

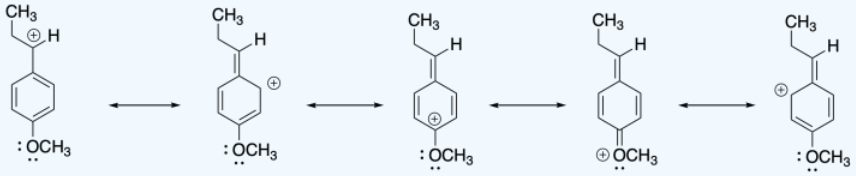
b) tertiary cation, resonance-stabilized

c) tertiary cation, without electron-withdrawing group

3)



4)

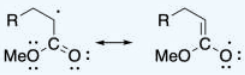


5)

a)



b)



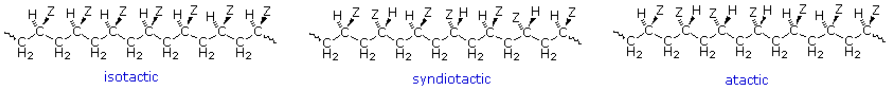
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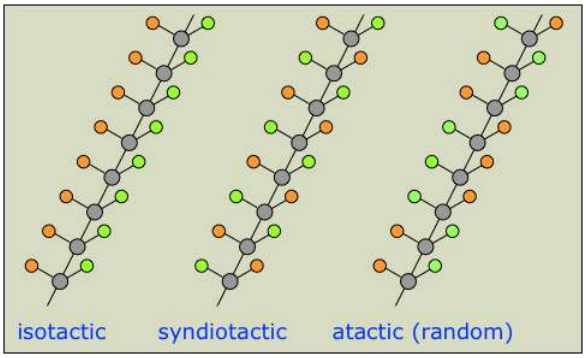
- **2.9: Radical Polymerization** by Chris Schaller is licensed CC BY-NC 3.0. Original source: https://employees.csbsju.edu/cschaller/Advanced/Polymers/Polycontents.htm.

10.2: Stereochemistry of Polymerization- Ziegler-Natta Catalysts

Ziegler-Natta Catalytic Polymerization

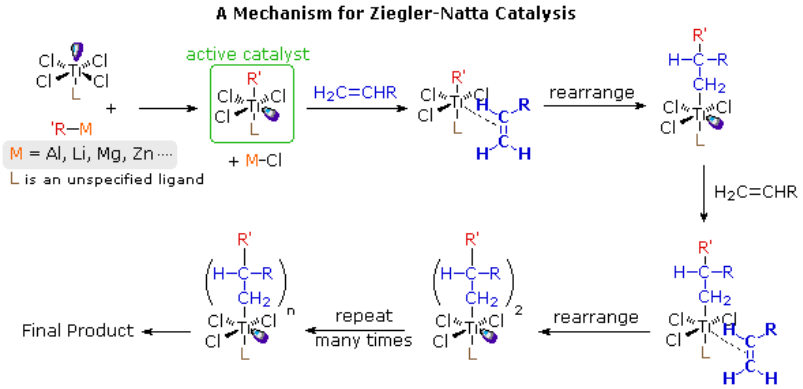
When propene is enchained into a polymer, a new chiral center is formed at every position where a methyl group branches from the backbone. Rather than trying to assign each of these chiral centers with stereochemical configurations (*R*) or (*S*), we instead describe the relative stereochemical relationships 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 10.2.1

When the monomer vinylidene fluoride, $H_2C{=}CF_2$, is polymerized it does not create isotactic, syndiotactic, and atactic forms. Please explain

Answer

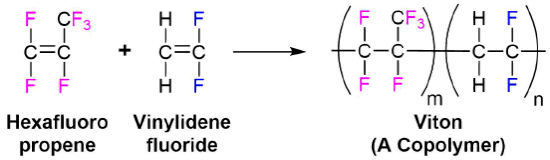
When vinylidene fluoride is polymerized it does not create a chiral center due to the symmetry created by the two fluorides. Chirality is necessary to create isotactic, syndiotactic, and atactic polymer forms.

10.2: Stereochemistry of Polymerization- Ziegler-Natta Catalysts is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

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10.3: 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.

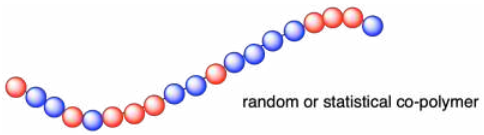


The synthesis of macromolecules composed of more than one repeating unit has been explored as a means of controlling the properties of the resulting material. In this respect, it is useful to distinguish several ways in which different monomeric units might be incorporated in a polymer. The following examples refer to a two component system, in which one monomer is designated A and the other B.

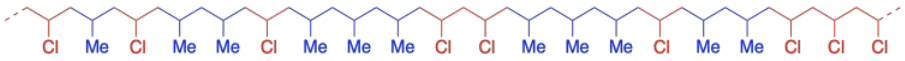
Statistical Copolymers

Also called random copolymers. Here the monomeric units are distributed randomly, and sometimes unevenly, in the polymer chain:

~ABBAAABAABBBABAABA~



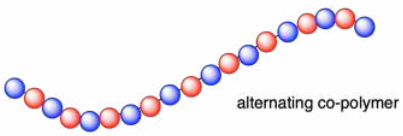
Most direct copolymerizations of equimolar mixtures of different monomers give statistical copolymers. If you take a mixture of alkenes that are capable of forming polymers and you polymerize them together, you may well get them randomly enchained into a growing polymer. For example, polymerizing propene and vinyl chloride together creates a polymer with random monmer unit.



Alternating Copolymers

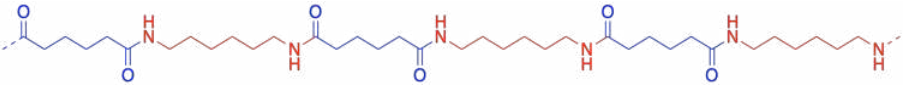
Here the monomeric units are distributed in a regular alternating fashion, with nearly equimolar amounts of each in the chain:

~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.

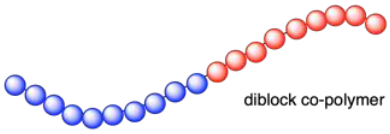
In some of the examples alternating copolymers, the chain is actually composed of two different monomers. This is the case in polyamides such as nylon-6,6, which is a chain is composed of difunctional amines alternating with difunctional carboxyloids (such as carboxylic acids or acid chlorides). Because 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.



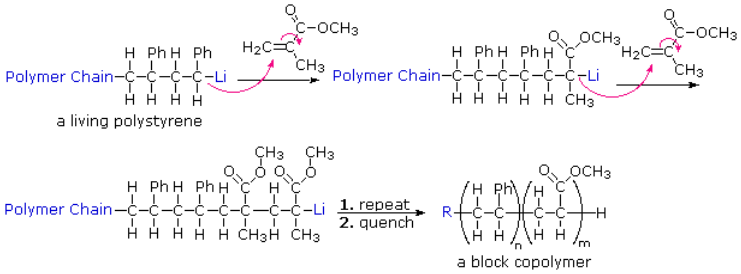
Block Copolymers

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~



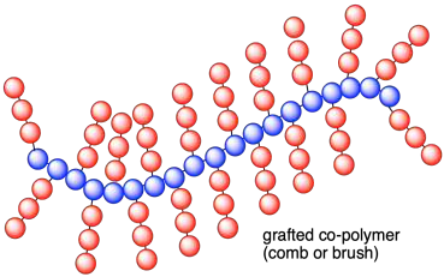
Several different techniques for preparing block copolymers have been developed, with a common example being anionic polymerization. In the anionic polymerization of styrene, a reactive site remains at the end of the chain until it is quenched. The unquenched polymer has been termed a living polymer 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

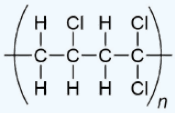
Monomer A	Monomer B	Copolymer	Uses
$H_2C=CHCl$	$H_2C=CCl_2$	Saran	films & fibers
$H_2C=CHC_6H_5$	$H_2C=C-CH=CH_2$	SBR styrene butadiene rubber	tires
$H_2C=CHCN$	$H_2C=C-CH=CH_2$	Nitrile Rubber	adhesives hoses
$H_2C=C(CH_3)_2$	$H_2C=C-CH=CH_2$	Butyl Rubber	inner tubes

Monomer A	Monomer B	Copolymer	Uses
$F_2C=CF(CF_3)$	$H_2C=CHF$	Viton	gaskets

? Exercise 10.3.1

Draw the structure of an alternating segment of Saran, a copolymer of vinyl chloride (chloroethene) and vinylidene chloride (1,1-dichloroethene).

Answer



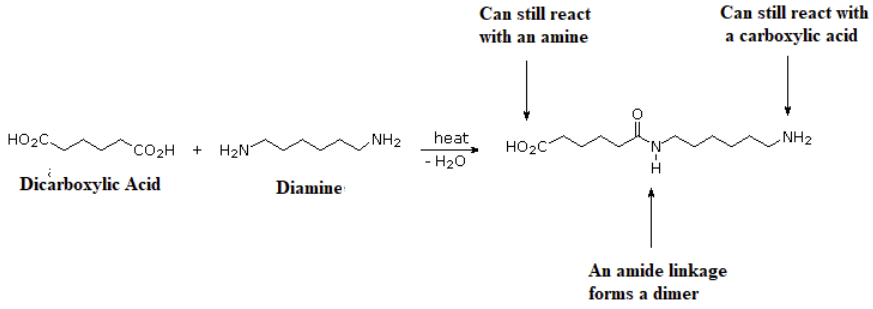
Saran

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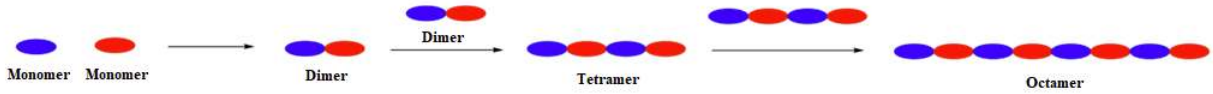
- **29.8: Block, Graft, and Ladder Polymers** by John D. Roberts and Marjorie C. Caserio is licensed CC BY-NC-SA 4.0.

10.4: 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.

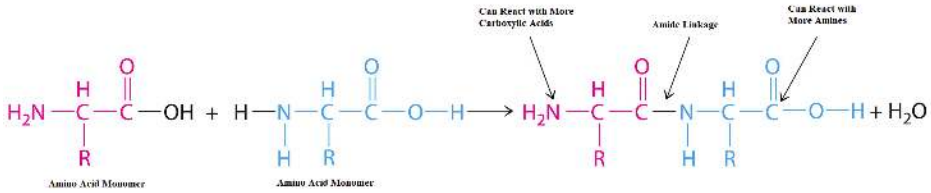


In fact the difuctionality of the monomers, allows step-growth polymers to grow in two directions at once. First, two complementary monomers react with each other to form a dimer. Assuming that monomers react at roughly similar rates, when one end of the dimer reacts again it will likely find another 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

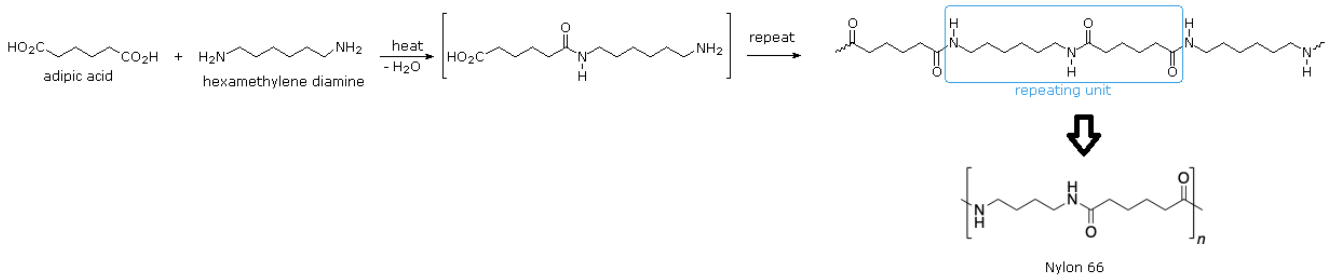
Virtually all fibers are made from some form of polymer. In particular, silk and wool are composed of a naturally occurring protein polymer. The monomers of proteins are called **amino acid residues**. These residues are connected by amide linkages which are also called **peptide bonds**. Many of the early efforts of polymer chemistry were to artificially create fibers which mimicked the properties of silk and wool.



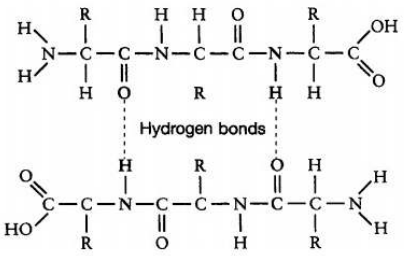
Polyamides

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

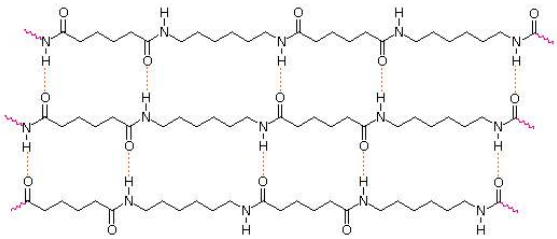
number indicated the number of carbons in the dicarboxylic acid. Simply by varying the number of carbons in each monomer, a wide variety of nylon polymers can be made.



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.



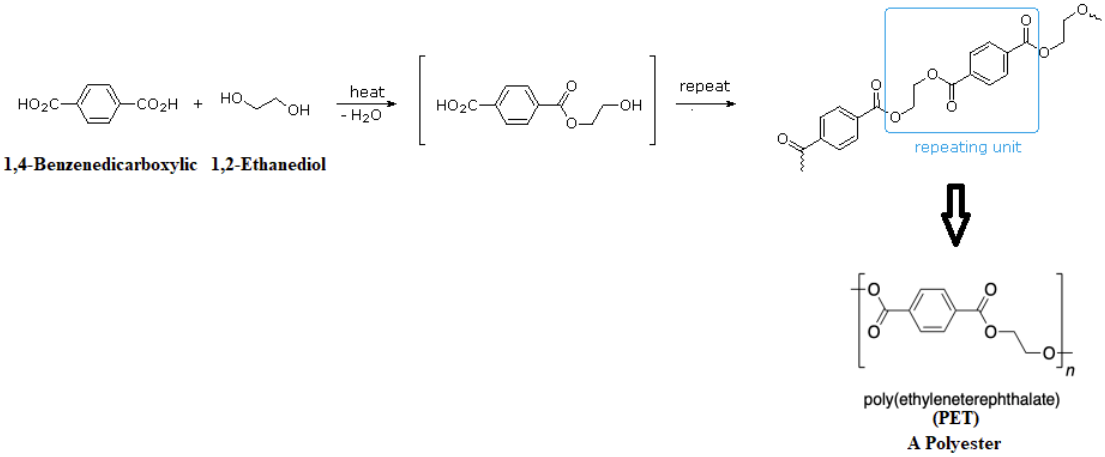
The Hydrogen Bonding between Proteins



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

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

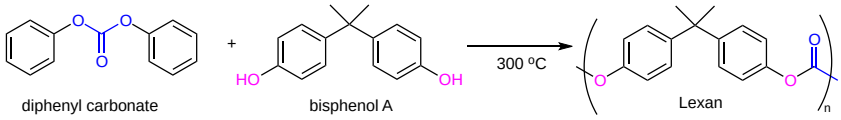
is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes.

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.



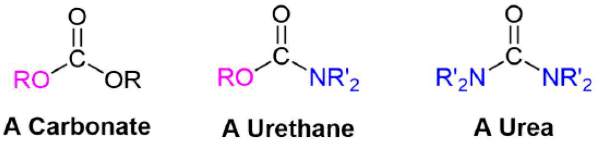
In effect, a carbonate is difunctional and can be reacted with a diol to form polymers containing repeated carbonate groups in their structure called polycarbonates. An example of a polycarbonate is the polymer, Lexan, which is created when diphenyl carbonate and bisphenol A (a diol) are reacted together.



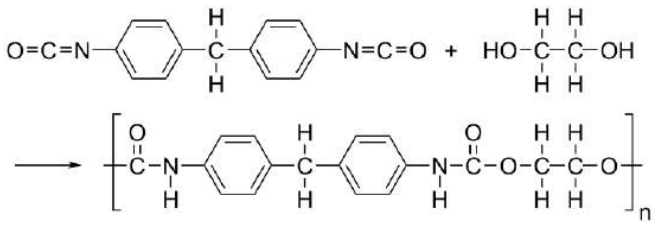
Bisphenol (BPA), primarily used to make polycarbonate, is one of the highest-volume chemicals produced in the world, with over six billion pounds made each year. Because polycarbonate is used to make plastic bottles, the lining for food cans, and the lining for beverage cans there has been much concern 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

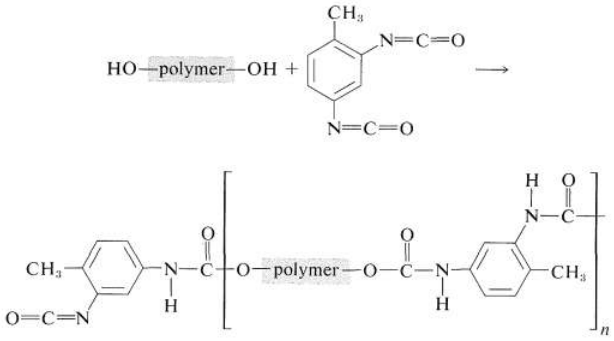
A urethane is a functional group similar to a carbonate and a urea. A urethane has an -OR and a -NR_2 group attached to the carbonyl carbon.



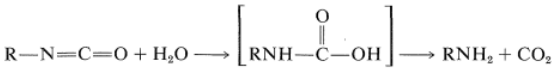
Polyurethane (**PUR** and **PU**) is a polymer composed of organic units joined by carbamate (urethane) links. Polyurethanes are produced by reacting an isocyanate containing two or more isocyanate groups per molecule ($R-(N=C=O)_n$) with a polyol containing on average two or more hydroxyl groups per molecule ($R'-(OH)_n$) in the presence of a catalyst or by activation with ultraviolet light.



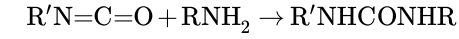
The very widely used polyurethane foams can be considered to be either block polymers or copolymers. The essential ingredients are a diisocyanate and a diol. The diisocyanate most used is 2,4-diisocyano-1-methylbenzene, and the diol can be a polyether or a polyester with hydroxyl end groups. The isocyano 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:

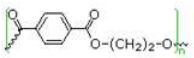
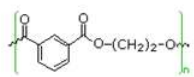
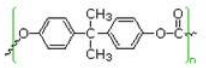
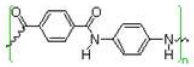
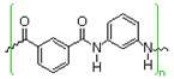


The carbon dioxide evolved is the foaming agent, and the amino groups formed at the same time extend the polymer chains by reacting with the residual isocyano end groups to form urea linkages:



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.

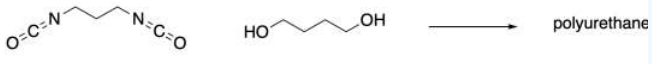
Common Step Growth Polymers

Formula	Type	Components	T_g °C	T_m °C
~[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

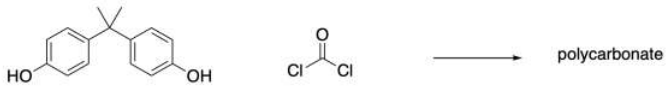
Exercise 10.4.1

1) The following difunctional monomers would undergo polymerization together. Show the product that results.

a)

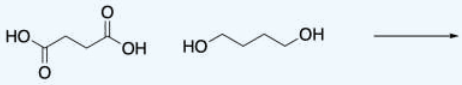


b)

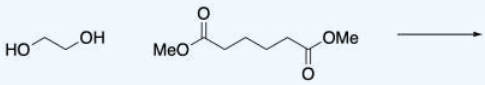


2) Provide structures of the polyesters made from the monomers as indicated.

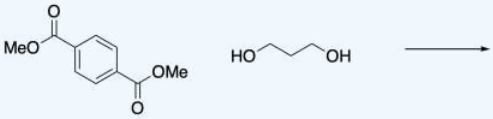
a)



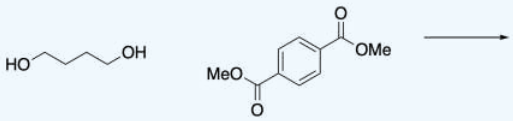
b)



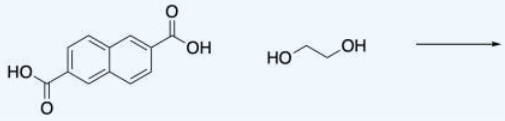
c)



d)



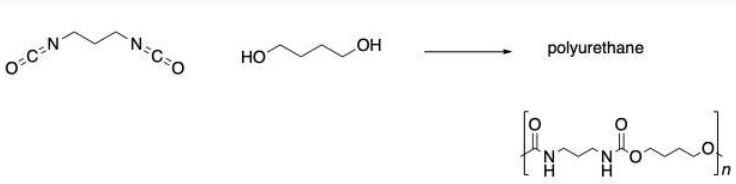
e)



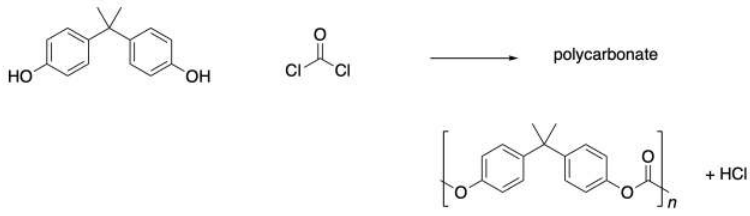
Answer

1)

a)

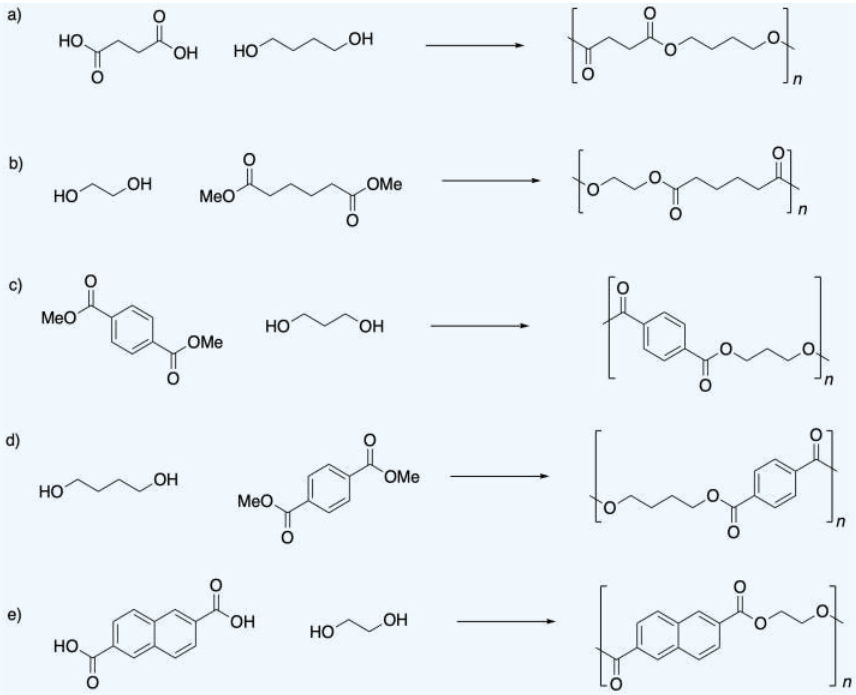


b)



2)

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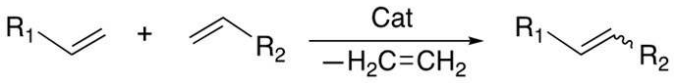
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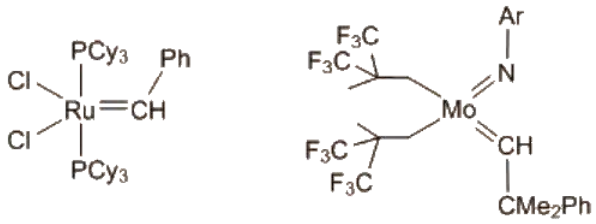
10.5: Olefin Metathesis Polymerization

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**.



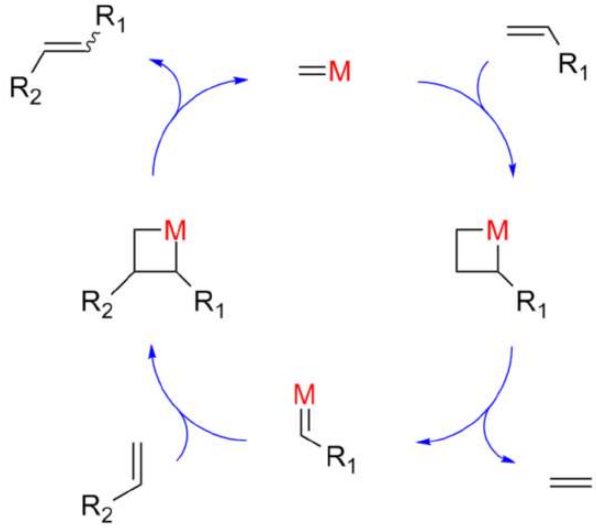
Grubbs catalyst

Schrock catalyst
(Ar = C_6H_3{2,6-*i*-Pr}$_2$)

The Grubb’s and the Schrock’s Catalyst

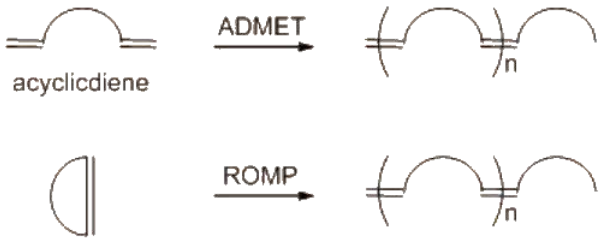
Mechanism Cross Metathesis

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.



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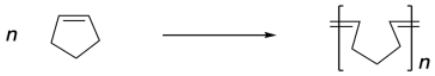
Olefin Metathesis Polymerization The variants of metathesis often used in producing polymers are: (*i*) the Acyclic Diene Metathesis (ADMET) and (*ii*) the Ring Opening Metathesis Polymerization (ROMP), both of which produce long chain polymers



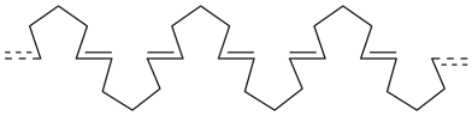
One method, called **ring-opening metathesis polymerization**, or ROMP, involves the use of a moderately strained cycloalkene, such as cyclopentene. The strain of the ring favors ring-opening, thereby driving formation of the open-chain product. The polymer that results has double bonds spaced regularly 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.

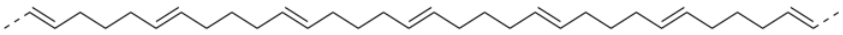
During a ROMP, a cyclopentene ring is opened up at the double bond and reaches out to join with other cyclopentene rings on either side of it.



The product polymer of a ROMP using cyclopentene rings would look something like this:

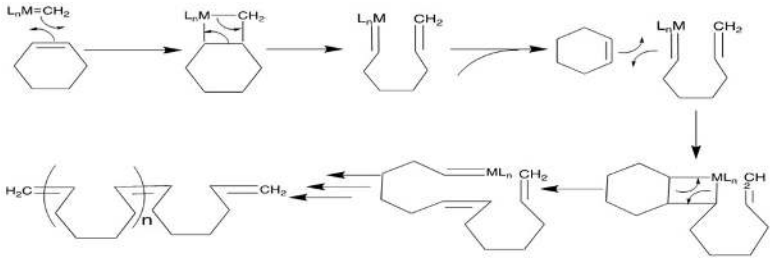


Which can draw it in an usual zig-zag conformation.

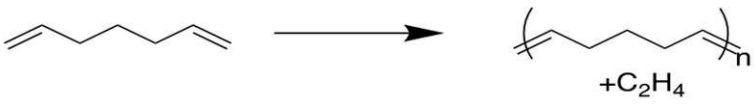


Mechanism

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.



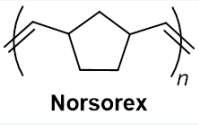
Exercise 10.5.1

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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10.6: 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.

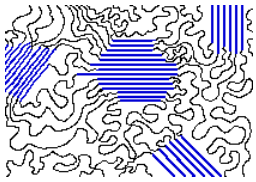


Figure 10.6.1: CSchematic diagram of crystallites (in blue) in a largely crystalline polymer.

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.

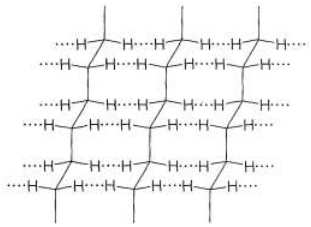


Figure 10.6.2: CRepresentation of attractive interactions between the hydrogens in a crystallite of polyethene

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.

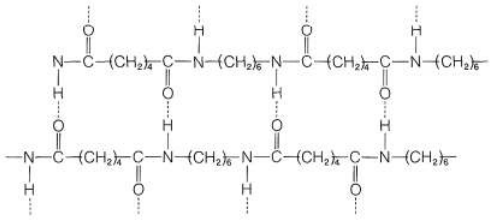


Figure 10.6.3: Possible hydrogen-bonded structure for crystallites of nylon 66, an amide-type polymer of hexanedioic acid and 1,6-hexanediamine.

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.

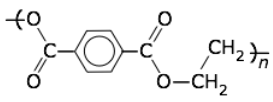
Polymer	LDPE	HDPE	PP	PVC	PS	PAN	PTFE	PMMA	Rubber
T_m (°C)	110	130	175	180	175	>200	330	180	30
T_g (°C)	−110	−100	−10	80	90	95	−110	105	−70

Polymer Categories

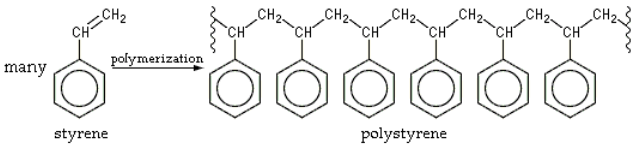
Thermoplastics

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.

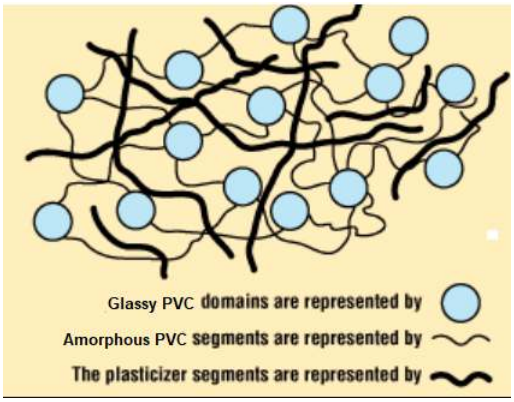


Polystyrene is also a common thermoplastic. The polymer is making it a solid but rather rather brittle at room temperature. Polystyrene is used to make hard clear plastic cups, foam cups, eating utensils, deli food containers, toy model kits, some packing popcorn.

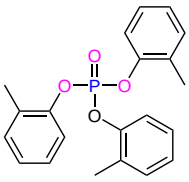


Plasticizers

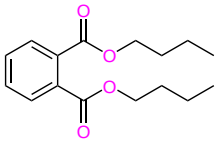
Plasticizers or **dispersants** are additives that increase the plasticity or decrease the viscosity of a material. These substances are compounded into certain types of plastics to render them more flexible by lowering the glass transition temperature. They accomplish this by taking up space between 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.



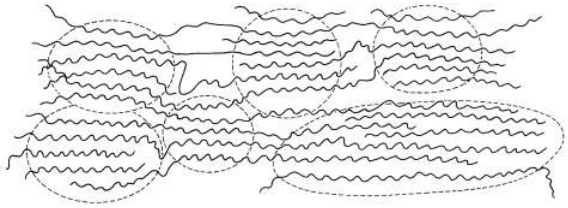
tris-(2-Methylphenyl) phosphate



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.

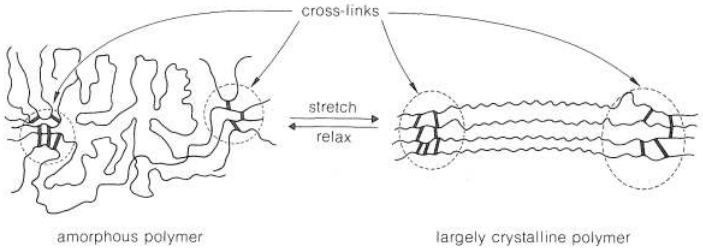
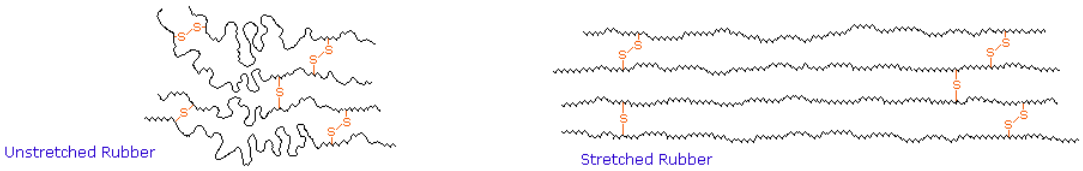
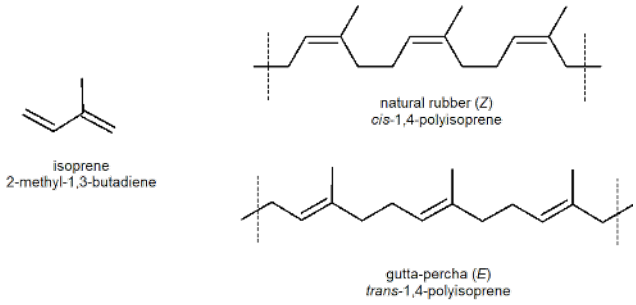


Figure 10.6.4: Schematic representation of an elastomer in relaxed and stretched configurations.

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.

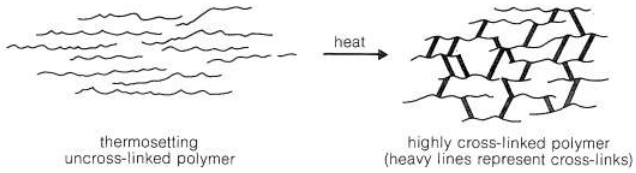
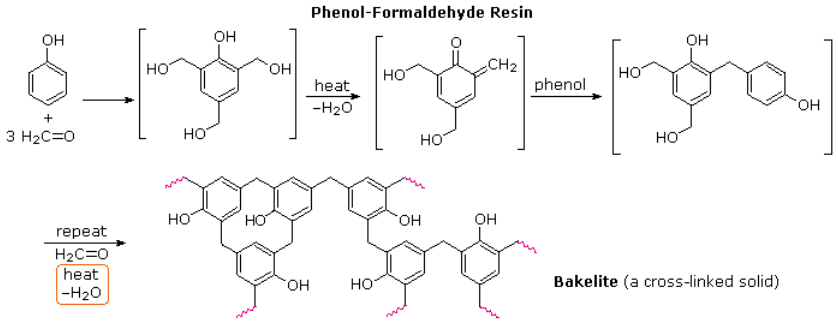


Figure 10.6.4: Schematic representation of the conversion of an uncross-linked thermosetting polymer to a highly cross-linked polymer. The cross-links are shown in a two-dimensional network, but in practice three-dimensional networks are formed.

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.

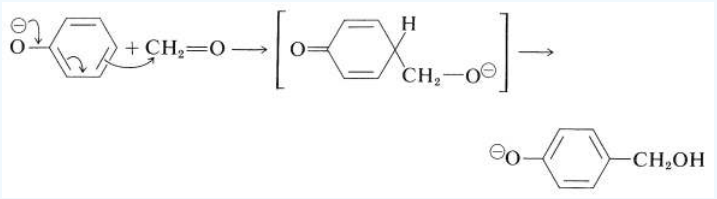


Exercise 10.6.1

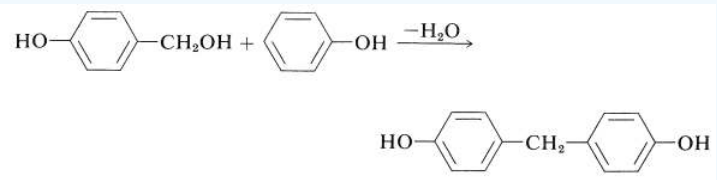
Propose a mechanism for the base-catalyzed polymerization of phenol and formaldehyde to form Bakelite.

Answer

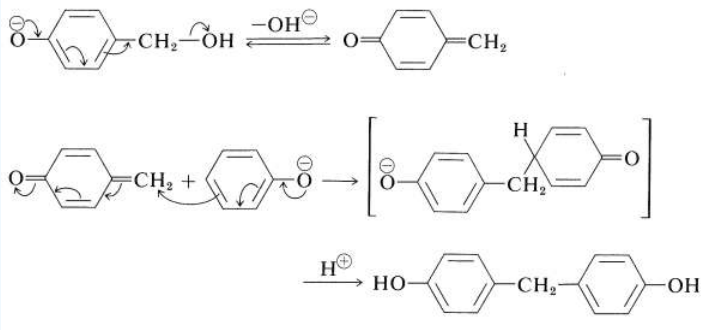
One of the oldest known thermosetting synthetic polymers is made by condensation of phenols with aldehydes using basic catalysts. The resins that are formed are known as **Bakelites**. The initial stage is the base-induced reaction of benzenol and methanal to give a (4-hydroxyphenyl)methanol, and this reaction closely resembles an aldol addition and can take place at either the 2- or the 4-position of the benzene ring:



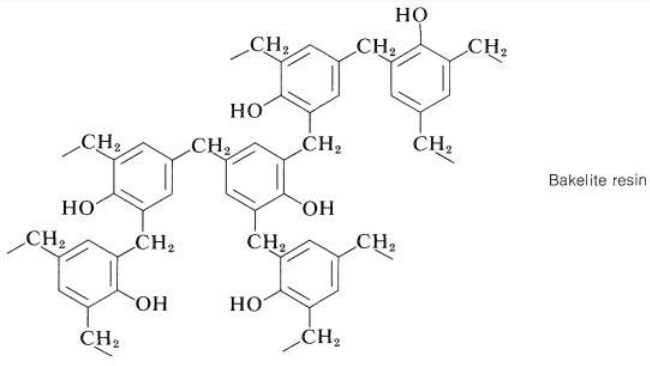
The next step in the condensation is formation of a bis(hydroxyphenyl)methane derivative, which for convenience is here taken to be the 4,4'-isomer:



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:



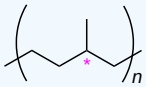
Bakelite resin

Exercise 10.6.2

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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10.7: Plastics and the Environment

Learning Objectives

- Know the problems associated with plastics.
- Identify the type of polymer associated with each recycling number.
- Know the different plastic recycling processes.

Problems with Plastics

Due to their low cost, ease of manufacture, versatility, and imperviousness to water, plastics are used in a multitude of products of different scale, including paper clips and spacecraft. They have prevailed over traditional materials, such as wood, stone, horn and bone, leather, metal, glass, and ceramic, in some products previously left to natural materials. However, there are numerous problems encountered with plastic use.

Small-molecule release

Many kinds of polymers contain small molecules — either unreacted monomers, or substances specifically added (plasticizers, uv absorbers, flame retardants, etc.) to modify their properties. Many of these smaller molecules are able to diffuse through the material and be released into any liquid or air in contact with the plastic — and eventually into the aquatic environment. Those that are used for building materials (in mobile homes, for example) can build up in closed environments and contribute to indoor air pollution.

Residual monomer

Formation of long polymer chains is a complicated and somewhat random process that is never perfectly stoichiometric. It is therefore not uncommon for some unreacted monomer to remain in the finished product. Some of these monomers, such as formaldehyde, styrene (from polystyrene, including polystyrene foam food take-out containers), vinyl chloride, and bisphenol-A (from polycarbonates) are known carcinogens. Although there is little evidence that the small quantities that diffuse into the air or leach out into fluids pose a quantifiable health risk, people are understandably reluctant to tolerate these exposures, and public policy is gradually beginning to regulate them.

Perfluorooctanoic acid (PFOA), the monomer from which Teflon is made, has been the subject of a 2004 lawsuit against a DuPont factory that contaminated groundwater. Small amounts of PFOA have been detected in gaseous emissions from hot fluorocarbon products.

Decomposition products

Most commonly-used polymers are not readily biodegradable, particularly under the anaerobic conditions of most landfills. And what decomposition does occur will combine with rainwater to form *leachates* that can contaminate nearby streams and groundwater supplies. Partial photodecomposition, initiated by exposure to sunlight, is a more likely long-term fate for exposed plastics, resulting in tiny broken-up fragments. Many of these materials are less dense than seawater, and once they enter the oceans through coastal sewage outfalls or from marine vessel wastes, they tend to remain there indefinitely.

Open burning of polymeric materials containing chlorine (polyvinyl chloride, for example) is known to release compounds such as dioxins that persist in the environment. Incineration under the right conditions can effectively eliminate this hazard. Disposed products containing **fluorocarbons** (Teflon-coated ware, some personal-care, waterproofing and anti-stick materials) break down into perfluorooctane sulfonate which has been shown to damage aquatic animals.

Hazards to animals

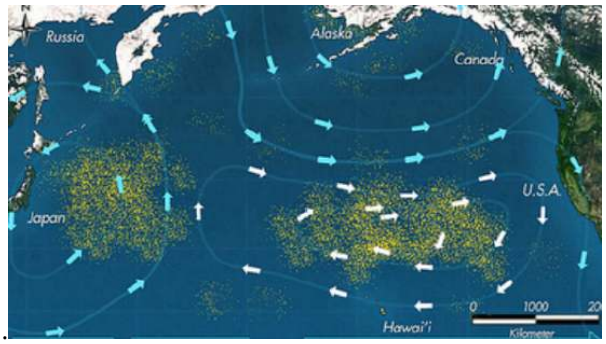
There are two general types of hazards that polymers can introduce into the aquatic environment. One of these relates to the release of small molecules that act as hormone disrupters as described above. It is well established that small aquatic animals such as fish are being seriously affected by such substances in many rivers and estuarine systems, but details of the sources and identities of these molecules have not been identified. One confounding factor is the release of sewage water containing human birth-control drugs (which have a feminizing effect on sexual development) into many waterways.

The other hazard relates to pieces of plastic waste that aquatic animals mistake for food or become entangled in (Figure 10.7.1) .



Figure 10.7.1 A p*lastic bag (probably mistaken for a jellyfish, the sea turtle's only food) cannot be regurgitated and leads to intestinal blockage and a slow death (left) remains of an albatross that mistook bits of plastic junk for food (right).*

These dangers occur throughout the ocean, but are greatly accentuated in regions known as gyres. These are regions of the ocean in which a combination of ocean currents drives permanent vortices that tend to collect and concentrate floating materials. The most notorious of these are the Great Pacific Gyres that have accumulated astounding quantities of plastic waste.



Recycling

The huge quantity (one estimate is 10^8 metric tons per year) of plastic materials produced for consumer and industrial use has created a gigantic problem of what to do with plastic waste which is difficult to incinerate safely and which, being largely non-biodegradable, threatens to overwhelm the capacity of landfills. An additional consideration is that *de novo* production most of the major polymers consumes non-renewable hydrocarbon resources.



Figure 10.7.2 Plastic water bottles present a special recycling problem because of their widespread use in away-from-home locations.

Plastics recycling has become a major industry, greatly aided by enlightened trash management policies in the major developed nations. However, it is plagued with some special problems of its own:

- Recycling is only profitable when there is a market for the regenerated material. Such markets vary with the economic cycle (they practically disappeared during the recession that commenced in 2008.)
- The energy-related costs of collecting and transporting plastic waste, and especially of processing it for re-use, are frequently the deciding factor in assessing the practicability of recycling.
- Collection of plastic wastes from diverse sources and locations and their transport to processing centers consumes energy and presents numerous operational problems.
- Most recycling processes are optimized for particular classes of polymers. The diversity of plastic types necessitates their separation into different waste streams — usually requiring manual (i.e., low-cost) labor. This in turn encourages shipment of these wastes to low-wage countries, thus reducing the availability of recycled materials in the countries in which the plastics originated.

Some of the major recycling processes include

- Thermal decomposition processes that can accommodate mixed kinds of plastics and render them into fuel oil, but the large inputs of energy they require have been a problem.
- A very small number of condensation polymers can be depolymerized so that the monomers can be recovered and re-used.
- Thermopolymers can be melted and pelletized, but those of widely differing types must be treated separately to avoid incompatability problems.
- Thermosets are usually shredded and used as filler material in recycled thermopolymers.

Other processes

A process has also been developed in which many kinds of plastic can be used as a carbon source in the recycling of

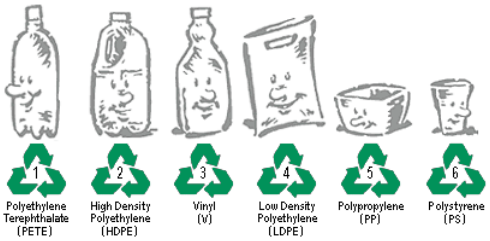
scrap steel. There is also a possibility of mixed recycling of different plastics, which does not require their separation. It is called compatibilization and requires use of special chemical bridging agents compatibilizers. It can help to keep the quality of recycled material and to skip often expensive and inefficient preliminary scanning of waste plastics streams and their separation/purification.

Figure 10.7.3 *Plastic or other polymer compatibilization.*

Recycled Plastics

Seven groups of plastic polymers, each with specific properties, are used worldwide for packaging applications (see Table 10.7.1). Each group of plastic polymer can be identified by its plastic identification code (PIC), usually a number or a letter abbreviation. For instance, low-density polyethylene can be identified by the number "4" or the letters "LDPE". The PIC appears inside a three-chasing-arrow recycling symbol. The symbol is used to indicate whether the plastic can be recycled into new products.

The PIC was introduced by the Society of the Plastics Industry, Inc., to provide a uniform system for the identification of various polymer types and to help recycling companies separate various plastics for reprocessing. Manufacturers of plastic products are required to use PIC labels in some countries/regions and can voluntarily mark their products with the PIC where there are no requirements. Consumers can identify the plastic types based on the codes usually found at the base or at the side of the plastic products, including food/chemical packaging and containers.



Not all categories are accepted by all local recycling authorities, so residents need to be informed about which kinds should be placed in recycling containers and which should be combined with ordinary trash.

Table 10.7.1 The Major Groups of Plastic Polymers. Source: Wikipedia

Plastic identification code	Type of plastic polymer	Properties	Common packaging applications	Melting temperatures (°C)
Symbol Resin Code 01 PET.svg	Polyethylene terephthalate(PET, PETE)	Clarity, strength, toughness, barrier to gas and moisture.	Soft drink, water and salad dressing bottles; peanut butter and jam jars; ice cream cone lids; small consumer electronics	Tm = 250
Symbol Resin Code 02 PE-HD.svg	High-density polyethylene(HDPE)	Stiffness, strength, toughness, resistance to moisture, permeability to gas	Water pipes, Gas & Fire Pipelines, Electrical & Communications conduit, hula hoop rings, five gallon buckets, milk, juice and water bottles; grocery bags, some shampoo/toiletry bottles	Tm = 130
Symbol Resin Code 03 PVC.svg	Polyvinyl chloride(PVC)	Versatility, ease of blending, strength, toughness.	Blister packaging for non-food items; cling films for non-food use. May be used for food packaging with the addition of the plasticisers needed to make natively rigid PVC flexible. Non-packaging uses are electrical cable insulation; rigid piping; vinyl records.	Tm = 240
Symbol Resin Code 04 PE-LD.svg	Low-density polyethylene(LDPE)	Ease of processing, strength, toughness, flexibility, ease of sealing, barrier to moisture	Frozen food bags; squeezable bottles, e.g. honey, mustard; cling films; flexible container lids	Tm = 120

Symbol Resin Code 05 PP.svg	Polypropylene(PP)	Strength, toughness, resistance to heat, chemicals, grease and oil, versatile, barrier to moisture.	Reusable microwaveable ware; kitchenware; yogurt containers; margarine tubs; microwaveable disposable take-away containers; disposable cups; soft drink bottle caps; plates.	Tm = 173
Symbol Resin Code 06 PS.svg	Polystyrene(PS)	Versatility, clarity, easily formed	Egg cartons; packing peanuts; disposable cups, plates, trays and cutlery; disposable take-away containers	Tm = 240
Symbol Resin Code 07 O.svg	Other (often polycarbonateor ABS)	Dependent on polymers or combination of polymers	Beverage bottles, baby milk bottles. Non-packaging uses for polycarbonate, compact discs, "unbreakable" glazing, electronic apparatus housing, lenses (including sunglasses), prescription glasses, automotive headlamps, riot shields, instrument panels.	Polycarbonate: Tm = 225

Tire Recycling

The large number of rubber tires that are disposed of, together with the increasing reluctance of landfills to accept them, has stimulated considerable innovation in the re-use of this material, especially in the construction industry.

Plastics and Fire Hazards

The term *fire (or flame)-retardant* as applied to organic (i.e., containing carbon) materials, is intended to refer to *reduced* fire hazard, as all will burn under certain circumstances. Fabric flammability is an important textile issue, especially for stage drapery that will be used in a public space such as a school, theatre or special event venue. In the United States, Federal regulations require that drapery fabrics used in such spaces be certified as flame or fire-retardant. For draperies and other fabrics used in public places, this is known as the NFPA 701 Test, which follows standards developed by the National Fire Protection Association (NFPA). Although all fabrics will burn, some are naturally more resistant to fire than others. Those that are more flammable can have their fire resistance drastically improved by treatment with fire-retardant chemicals. Inherently flame-retardant fabrics such as polyester are commonly used for flame retardant curtain fabrics.

The deaths in fiery crashes of race car drivers Fireball Roberts at Charlotte, and Eddie Sachs and Dave MacDonald at Indianapolis in 1964 led to the use of flame-resistant ics such as Nomex. Nomex and related aramid polymers are related to nylon, but have aromatic backbones, and hence are more rigid and more durable. Nomex is an example of a *meta* variant of the aramids (Kevlar is a *para* aramid). Unlike Kevlar, Nomex strands cannot align during filament polymerization and has less strength. However, it has excellent thermal, chemical, and radiation resistance for a polymer material.

A Nomex hood is a common piece of racing and firefighting equipment. It is placed on the head on top of a firefighter's face mask. The hood protects the portions of the head not covered by the helmet and face mask from the intense heat of the fire.

Figure 10.7.4 A firefighter in Toronto, Canada wears a Nomex hood in 2007.

Wildland firefighters wear Nomex shirts and trousers as part of their personal protective equipment during wildfire suppression activities.

Racing car drivers wear driving suits constructed of Nomex and or other fire retardant materials, along with Nomex gloves, long underwear, balaclavas, socks, helmet lining and shoes, to protect them in the event of a fire.

Military pilots and aircrew wear flight suits made of over 92 percent Nomex to protect them from the possibility of cockpit fires and other mishaps. Recently, troops riding in ground vehicles have also begun wearing Nomex. Kevlar thread is often used to hold the fabric together at seams.

Military tank drivers also typically use Nomex hoods as protection against fire.

Plasticizers and Pollution

Plasticizers (UK: **plasticisers**) 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.

Polyvinyl chloride polymers are one of the most widely-plasticized types, and the odors often associated with flexible vinyl materials such as garden hoses, waterbeds, cheap shower curtains, raincoats and upholstery are testament to their ability to migrate into the environment.

The well-known "new car smell" is largely due to plasticizer release from upholstery and internal trim.

According to 2014 data, the total global market for plasticizers was 8.4 million metric tonnes including 1.3 million metric tonnes in Europe.

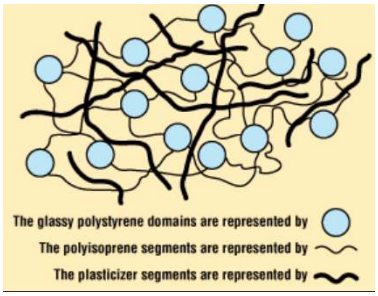


Figure 10.7.5 Shares of global plasticizer consumption in 2014 (8 million metric tons).

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.

Summary

- Plastics are found everywhere due to its low cost, versatility, ease of use etc.
- Plastics pose a threat to the environment due to residual or degradation products that contribute to air and water pollution.
- Plastics hazards to animals and marine life as these living creatures mistake them for food.
- Plastic polymers are classified into seven groups for recycling purposes.

Contributors and Attributions

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- Marisa Alviar-Agnew (Sacramento City College)
- Wikipedia

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10.8: Biodegradable Plastics

BIODEGRADABLE PLASTICS

Plastics have become a staple of modern life and are valued for their durability, strength, flexibility, light weight and low cost of production. They are versatile in that they carry our groceries home, hold our morning coffee, as well as control drug release and hold bones together. Plastics have become an environmentalists' nightmare, however, because of their durability and dependence on oil. Many types of plastics persist in landfills and in the environment where they are inadvertently ingested by animals and are making their way up the food chain. Although recycling would be a good way to reduce the plastics in the landfills, currently "only 5% out of 1 trillion plastic bags, annually produced in the US alone, are being recycled" (Sivan, 2011).

One way to mitigate the trash dilemma is to design new biodegradable plastics. Several biodegradable plastics are currently on the market today. Biodegradable plastics have many suitable applications. They can be used in plastic grocery bags, food service and single serve disposable containers, personal care products, razors, brushes, applicators, cell phones, pens, and office supplies, agricultural plastics, mulch film, netting, sod stakes, erosion control netting, plant posts, plant clips and medical devices.

Table 10.8.1 *Uses of Biodegradable Plastics*

Plastic Type	Use
Polylactic acid (PLA)	Packaging and paper coatings; other possible markets include sustained release systems for pesticides and fertilizers, mulch films, and compost bags
Polyglycolic acid (PGA)	Specialized applications; controlled drug releases; implantable composites; bone fixation parts
Polycaprolactone (PCL)	Long-term items; mulch and other agricultural films; fibers containing herbicides to control aquatic weeds; seedling containers; slow release systems for drugs
Polyhydroxybutyrate (PHB)	Products like bottles, bags, wrapping film and disposable diapers, as a material for tissue engineering scaffolds and for controlled drug release carriers
Polyhydroxyvalerate (PHBV)	Films and paper coatings; other possible markets include biomedical applications, therapeutic delivery of worm medicine for cattle, and sustained release systems for pharmaceutical drugs and insecticides
Polyvinyl alcohol (PHV)	Packaging and bagging applications which dissolve in water to release products such as laundry detergent, pesticides, and hospital washables
Polyvinyl acetate (PVAc)	Adhesives, the packaging applications include boxboard manufacture, paper bags, paper lamination

Table found in (Shah et al., 2008)
(www.envis-icpe.com, Plastics recycling-Economic and Ecological Options. ICPE 2006;4(4):1–12).
en.Wikipedia.org/w/index.php?title=Polyhydroxybutyrate&oldid=189442759. Accessed February 14, 2008.
www.chemquest.com/store/polyv...adhesives.html, 2006.

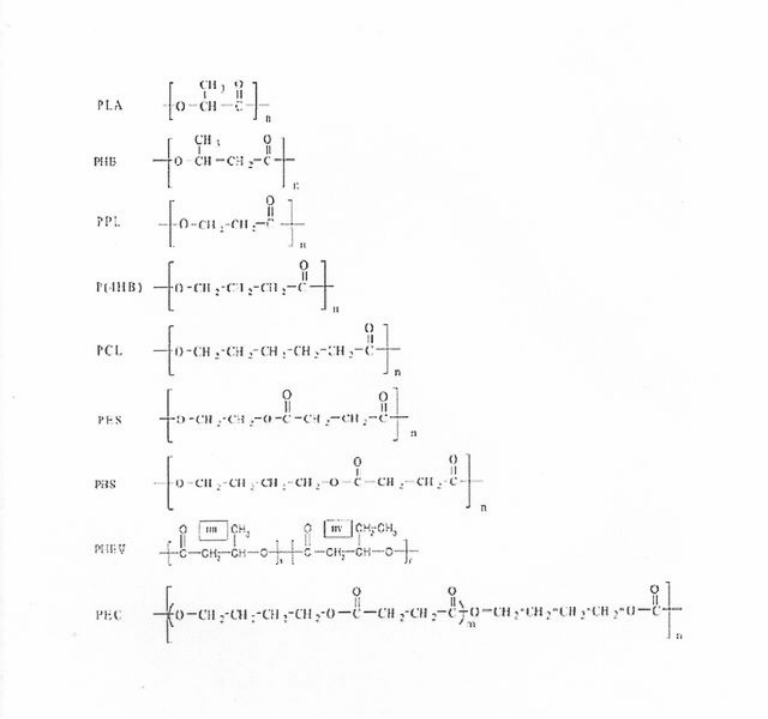


Figure 10.8.1 :*Types of Biodegradable Plastics in Use Today: Chemical structure of poly(lactide)(PLA), poly(3-hydroxybutyrate) (PHB), poly(propiolactone)(PPL), poly(ε-caprolactone)(PCL), poly(ethylene succinate(PES), poly(butylenes succinate)(PBS), poly(3-hydroxybutyrate-co-3-hydroxyvalerate)(PHBV) and poly(ester carbonate)(PEC) (Tokiwa and Calabia 2004)*

Polylactic acid (PLA) is a biodegradable plastic currently in use. Environmentalists like PLA because it is biodegradable and also made from waste products. Billions of pounds of potato peelings are wasted each year from french fries alone. Also, cheese manufactures toss away several billion pounds of cheese whey containing useable carbohydrates. Bacteria convert the carbohydrate rich waste into lactic acid. The lactic acid is then converted into PLA through condensation reactions. Another source of carbohydrates is corn, wheat and beets.

Polylactic acid is produced by poly-condensation of naturally produced lactic acid or by the catalytic ring opening of the lactide group.

Polylactic acid condensation reaction

$HO\text{-}(CH(CH_3)COO)n - H + HO(CH(CH_3)COO)m\text{-}H \rightarrow HO(CH(CH_3)COOn+m + H_2O$

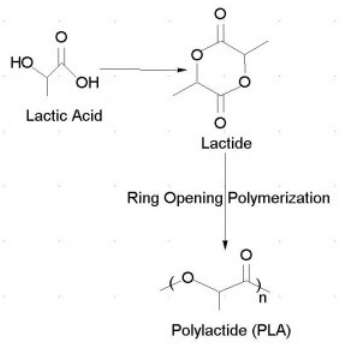


Figure 10.8.2 Catalytic ring opening of the lactide group downloaded from: bioplasticsonline.net/2010/06...on-of-lactide/

All plastics are polymers. Starch is made up of repeating glucose units held together by an α-(1→4) glycosidic bond. Starch can be formed in a condensation reaction in which water is removed when the monomers are added together. Enzymes present in plants and animals are responsible for condensation reactions. A picture of starch is shown below.

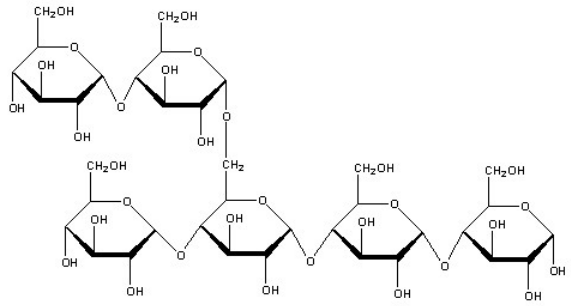


Figure 10.8.3 Starch Downloaded on June 15, 2011 from: www.cbu.edu/~seisen/OrganicChemistry.htm

How are plastics biodegraded? They are primarily degraded by bacteria. The long chains created in the polymerization are difficult for many bacteria to degrade. They can only attack the molecule at the ends. When starch is combined with the PLA, it can be degraded more easily by the bacteria. Plasticisers such as glycerol, sorbitol and triethyl citrate are also added to starch-PLA compounds to prevent brittleness. “PLA is fully biodegradable when composted in a large-scale operation with temperatures of 60 ºC and above. The first stage of degradation of PLA (two weeks) is via hydrolysis to water-soluble compounds and lactic acid” (Shah et al., 2008). Microorganisms then break down the lactic acid into CO_2, biomass and water.

From ChemPRIME: 8.24: Condensation Polymers

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Tokiwa Y.; Clabia BP. Degradation of microbial polyesters. Biotechnol Lett. 2004, 26, 1181-9.

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CHAPTER OVERVIEW

11: Introduction to Inorganic Chemistry

11.1: Hard and Soft Acids and Bases

11.2: Prelude to Redox Stability and Redox Reactions

11.3: Electrochemical Potentials

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11.1: Hard and Soft Acids and Bases

Lewis acids and bases can be classified by designating them as hard or soft.

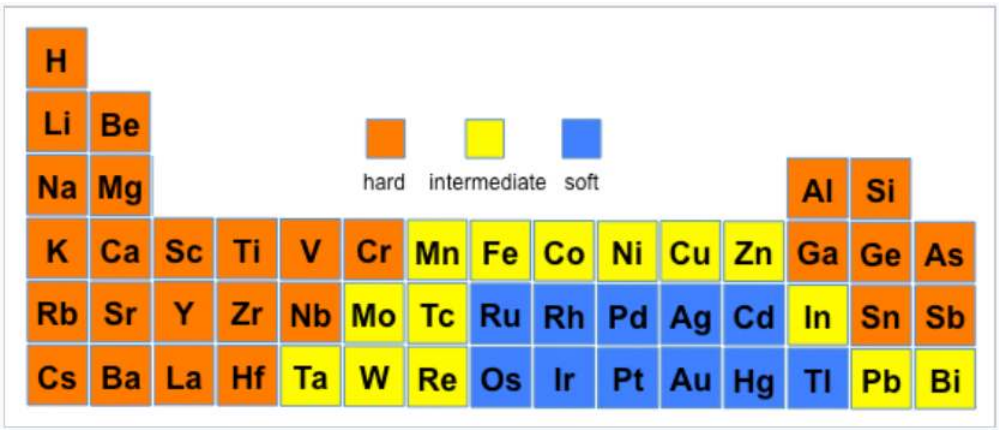
Hard Acids/Bases:

"Hard" acids and bases have a high charge (positive for acids, negative for bases) to ionic radius ratio along with higher oxidation states. Hard acids are not very polarizable and have high charge densities. Thus metal ions with high positive charges and smaller ionic sizes tend to be hard acids. Early transition metal ions in the 3d series tend to be hard Lewis acids. Hard bases are typically small anions and neutral molecules. Some examples of hard acids and bases include: H^+, O^{2-}, OH^-, F^-, Fe^{3+}, and Al^{3+}.

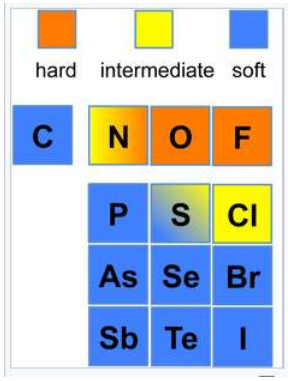
Soft Acids/Bases:

"Soft" acids or bases have a low charge to radius ratio, with low oxidation states. They are normally larger ions that are polarizable. For example, I^- and S^{2-} are soft bases and low charge density transition metals, such as Ag^+, are considered soft acids. Soft acids often include transition metals in the second and third row of the periodic table that have a +1 or +2 charge, as well as late transition metals (especially those in the 4d and 5d series) with filled or almost completely filled *d* orbitals.

Acids and bases are not strictly hard or soft, with many ions and compounds being classified as intermediate. For example, trimethylborane, Fe^{2+}, and Pb^{2+} cations are intermediate acids, and pyridine and aniline are examples of intermediate bases. An element can also change its hard/soft character depending on its oxidation state. The most extreme example is hydrogen, where H^+ is a hard acid and H^- is a soft base. Ni^{3+} (as in the layered compound NiOOH) is a hard acid, but Ni^0 (as in $Ni(CO)_4$) is a soft acid. The figures below show hard/soft trends for acids (left) and bases (right) in the periodic table. For bases, the major hard/soft discontinuity is between the 2nd row (N,O,F) and the rows below.



Hard-soft trends for acids



Hard-soft trends for bases

Like binds with Like

Hard acids interact more strongly with hard bases than they do with soft bases, and soft acids interact more strongly with soft bases than hard bases. Thus, the most stable complexes are those with hard-hard and soft-soft interactions. This tendency is illustrated in the table below, which shows the trend in formation constants for hard and soft acids. Hard acids bind halides in the order $F^- > Cl^- > Br^- > I^-$, whereas soft acids follow the opposite trend.

Log K_1	fluoride	chloride	bromide	iodide	acid classification
Fe^{3+}	6.0	1.4	0.5	-	Hard
Pb^{2+}	1.3	0.9	1.1	1.3	Intermediate
Ag^+	0.4	3.3	4.7	6.6	Soft
Hg^{2+}	1.0	6.7	8.9	12.9	Soft

The softest metal ion in the periodic table is $Au^+(aq)$. It forms stable complexes with soft bases such as phosphines and CN^-, but not with hard bases such as O^{2-} or F^-. The affinity of Au^+ for the soft base CN^- is high, and the resulting $[Au(CN)_2]^-$ complex is so stable that gold (which is normally very difficult to oxidize) can be oxidized by oxygen in the air:

$$4\,Au_{(s)} + 8\,CN^-_{(aq)} + O_{2(g)} + 2\,H_2O = 4\,[Au(CN)_2]^-_{(aq)} + 4\,OH^- \tag{11.1.1}$$

This reaction is used in gold mining to separate small flakes of Au from large volumes of sand and other oxides. Ag is similarly dissolved by air oxidation in cyanide solutions. The precious metals are then isolated from the solution using chemical reducing agents or by electroplating. The use of cyanide ion on a large scale in mining, however, creates a potentially serious environmental hazard. In 2000, a spill at Baia Mare, Romania resulted in the worst environmental disaster in Europe since Chernobyl. Cyanide, which is highly toxic, is gradually oxidized by air to the less toxic cyanate (OCN^-) ion. On the laboratory scale, cyanide plating solutions are typically disposed of by using bleach to oxidize CN^- to OCN^-, and the metal is recovered as an insoluble chloride salt.



Netted solution pond next to cyanide heap leaching of gold ore near Elko, Nevada (1992).

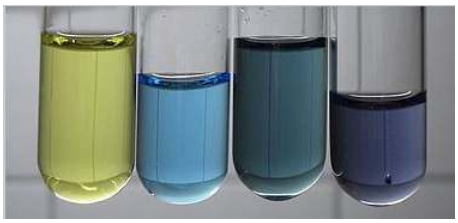
The Au^{3+} ion, because of its higher positive charge, is a harder acid than Au^+ and can form complexes with harder bases such as H_2O and amines. In keeping with the "like binds like" principle, the compound AuI (soft-soft) is stable, but AuI_3 (hard-soft) is unknown. Conversely, AuF has never been isolated but AuF_3 (hard-hard) is stable.

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11.2: Prelude to Redox Stability and Redox Reactions

In redox reactions, one element or compound is reduced (gains electrons) and another is oxidized (loses electrons). In terms of everyday life, redox reactions occur all of the time around us. For example, the metabolism of sugars to CO_2, which stores energy in the form of ATP, is a redox reaction. Another example of redox is fire or combustion, such as in a car engine. In a car engine, hydrocarbons in the fuel are oxidized to carbon dioxide and water, while oxygen is reduced to water. Corrosion (i.e. the formation of rust on iron) is a redox reaction involving oxidation of a metal.



Oxidation states of vanadium in acidic solution. From left to right the oxidation state goes from +5 to +2. These four oxidation states form the basis of the vanadium flow battery, a storage device for electricity generated from sunlight and wind.[1]

Oxidation-reduction reactions are important to understanding inorganic chemistry for several reasons:

- Transition metals can have multiple oxidation states
- Main group elements (N, halogens, O, S...) also have multiple oxidation states and important redox chemistry
- Many inorganic compounds catalyze redox reactions (which are especially useful in industrial and biological applications)
- Energy conversion and storage technologies (solar water splitting, batteries, electrolyzers, fuel cells) rely on inorganic redox reactions and catalysis
- Electrochemistry provides a way to measure equilibrium constants for dissolution/precipitation, complexation, and other reactions.
- Reaction mechanisms in organometallic chemistry (oxidative addition, reductive elimination) involve changes in the oxidation states of metals.

Not all oxidizers and reducers are created equal. The electrochemical series ranks substances according to their oxidizing and reducing power, i.e., their standard electrode potential. Strong oxidizing agents are typically compounds with elements in high oxidation states or with high electronegativity, which gain electrons in the redox reaction. Examples of strong oxidizers include hydrogen peroxide, permanganate, and osmium tetroxide. Reducing agents are typically electropositive elements such as hydrogen, lithium, sodium, iron, and aluminum, which lose electrons in redox reactions. Hydrides (compounds that contain hydrogen in the formal -1 oxidation state), such as sodium hydride, sodium borohydride and lithium aluminum hydride, are often used as reducing agents in organic and organometallic reactions.

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11.3: Electrochemical Potentials

In electrochemical cells, or in redox reactions that happen in solution, the thermodynamic driving force can be measured as the **cell potential**. Chemical reactions are spontaneous in the direction of -ΔG, which is also the direction in which the cell potential (defined as $E_{cathode}$ - E_{anode}) is positive. A cell operating in the **spontaneous** direction (for example, a battery that is discharging) is called a **galvanic cell**. A cell that is being driven in the **non-spontaneous** direction is called an **electrolytic cell**. For example, let us consider the reaction of hydrogen and oxygen to make water:

$$2\,H_{2(g)} + O_{2(g)} = 2\,H_2O_{(l)} \tag{11.3.1}$$

Thermodynamically, this reaction is spontaneous in the direction shown and has an overall standard free energy change (ΔG°) of -237 kJ per mole of water produced.

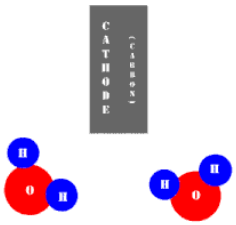
When this reaction occurs electrochemically in the spontaneous direction (e.g., in a hydrogen-air fuel cell), the two half cell reactions that occur are:

Anode: $H_{2(g)} \longrightarrow 2\,H^+_{(aq)} + 2\,e^-$

Cathode: $O_{2(g)} + 4\,H^+_{(aq)} + 4\,e^- \longrightarrow 2\,H_2O_{(l)}$

Here the anode is the negative electrode and the cathode is the positive electrode; under conditions of very low current density (where there are minimal resistive losses and kinetic overpotentials), the potential difference we would measure between the two electrodes would be 1.229 V.

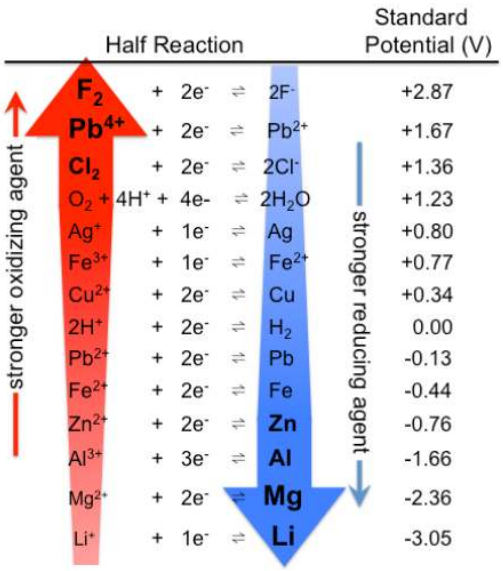
In an **electrolytic cell**, this reaction is run in reverse. That is, we put in electrical energy to split water into hydrogen and oxygen molecules. In this case, the half reactions (and their standard potentials) reverse. O_2(g) bubbles form at the anode and H_2(g) is formed at the cathode. Now the **anode** is the **positive** electrode and the **cathode** is **negative**. Electrons are extracted from the substance at the anode (water) and pumped into the solution at the cathode to make hydrogen. An animation of the cathode half reaction is shown below.



In both galvanic and electrolytic cells, **oxidation** occurs at the **anode** and **reduction** occurs at the **cathode**.

Half-cell potentials

As noted above, the equilibrium voltage of an electrochemical cell is proportional to the free energy change of the reaction. Because electrochemical reactions can be broken up into two half-reactions, it follows that the potentials of half reactions (like free energies) can be added and subtracted to give an overall value for the reaction. If we take the **standard hydrogen electrode** as our reference, i.e., if we assign it a value of zero volts, we can measure all the other half cells against it and thus obtain the voltage of each one. This allows us to rank redox couples according to their **standard reduction potentials** (or more simply their **standard potentials**), as shown in the table below.



Note that when we construct an electrochemical cell and calculate the voltage, we simply take the difference between the half cell potentials and do not worry about the number of electrons in the reaction. For example, for the displacement reaction in which silver ions are reduced by copper metal, the reaction is:

$$2\,\mathrm{Ag^{+}_{(aq)}} + \mathrm{Cu_{(s)}} = 2\,\mathrm{Ag_{(s)}} + \mathrm{Cu^{2+}_{(aq)}}$$

The two half-cell reactions are:

$$Ag^{+}_{(aq)} + e^{-} = Ag_{(s)} \quad +0.80V$$

$$Cu^{2+}_{(aq)} + 2e^{-} = Cu_{(s)} \quad +0.34V$$

and the standard potential $E^{o} = +0.80 - 0.34V = +0.46V$

The reason we don't need to multiply the Ag potential by 2 is that E^{o} is a measure of the free energy change **per electron**. Dividing the free energy change by the number of electrons (see below) makes E^{o} an **intensive property** (like pressure, temperature, etc.).

Relationship between E and ΔG. For systems that are in equilibrium, $\Delta G^{o} = -nFE^{o}_{cell}$, where *n* is number of moles of electrons per mole of products and *F* is the Faraday constant, ~96485 C/mol. Here the ^{o} symbol indicates that the substances involved in the reaction are in their standard states. For example, for the water electrolysis reaction, the standard states would be pure liquid water, H^{+} at 1M concentration (or more precisely, at unit activity), and O_2 and H_2(g) at 1 atmosphere pressure.

More generally (at any concentration or pressure), $\Delta G = -nFE$, where

$$E = E^{o} - \frac{RT}{nF} * lnQ \tag{11.3.2}$$

,

or at 298 K

$$E = E^{o} - \frac{0.0592}{n} * \log Q \tag{11.3.3}$$

where Q is the concentration ratio of products over reactants, raised to the powers of their coefficients in the reaction. This equation (in either form) is called the Nernst equation. The second term in the equation, when multiplied by -nF, is RT*lnQ. This is the free energy difference between ΔG and ΔG°. We can think of this as an entropic term that takes into account the positive entropy change of dilution, or the negative entropy change of concentrating a reactant or product, relative to its standard state.

Using the Nernst equation

Example 1:

For the half reaction $2\,\mathrm{H^{+}} + 2\,\mathrm{e^{-}} = \mathrm{H_2}$, $E^{\circ}_{1/2}$ = 0.000 V (by definition)

What is $E_{1/2}$ at pH 5 and P_{H_2} = 1 atm?
$pH = -\log[H^+] = 5$, so $[H^+] = 10^{-5}$ M

$$E = E^o - \frac{0.0592}{2} * \log \frac{P_{H2}}{(H^+)^2} = E^o - \frac{0.0592}{2} * \log(10^5)^2 = E^o - \frac{0.0592}{2}(10) = 0.000 - 0.296 = -0.296V \quad (11.3.4)$$

Example 2:

What is the potential of a fuel cell (a galvanic H_2/O_2 cell) operating at pH 5?

Overall reaction: $2\,H_{2(g)} + O_{2(g)} = 2\,H_2O_{(l)}$

In this reaction, H_2 is oxidized to H^+ and O_2 is reduced to H_2O. According to our convention, we write out and balance both half-cell reactions as reductions. For convenience, we do this in acid. (It is left as an exercise to the interested reader to try to work the problem in base)

Half cell reactions:

$2\,H_{2(g)} = 4\,H^+ + 4\,e^-$

$O_{2(g)} + 4\,H^+_{(aq)} + 4\,e^- = 2\,H_2O_{(l)}$



Toyota fuel cell hybrid bus. The bus runs on electrical energy obtained directly from the H_2/O_2 reaction. Individual fuel cells are connected in series to make a power train that charges a battery pack and drives an electric motor. Although the standard potential of the reaction is 1.23 V, because of kinetic overpotentials each fuel cell in the power train operates at a voltage of about 0.70 V. Despite this energy loss, the fuel cell system is still about twice as efficient as a combustion engine performing the same reaction.

To solve this problem we need to find the difference between the H_2/ H^+ and O_2/H_2O half cell potentials at pH 5.

$2\,H^+ + 2\,e^- \longrightarrow H_2$ $E°_{1/2}$ = 0.000 V

Like all standard potentials, this is written as a reduction. We need to reverse it and change the sign of E^o since H_2 is being oxidized:

$H_2 \longrightarrow 2\,H^+ + 2\,e^-$ $E°_{1/2}$ = -0.000 V

and add the standard potential of the substance being reduced at the cathode:

$O_2 + 4\,H^+ + 4\,e^- \longrightarrow 2\,H_2O$ $E°_{1/2}$ = +1.229 V

The difference between the two standard half cell potentials is +1.229 - 0.000 = +1.229 V

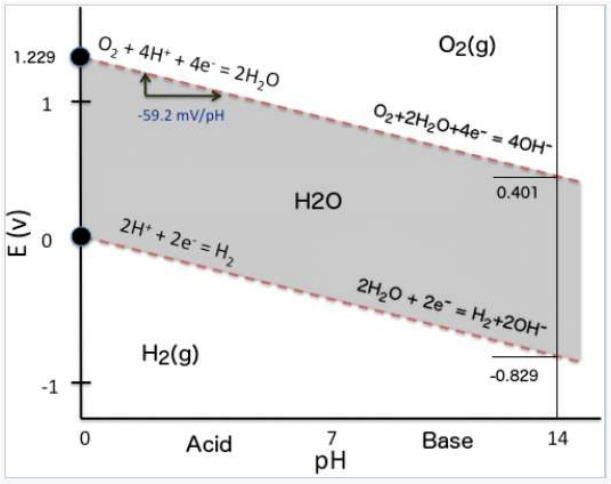
$E°_{cell}$ = +1.229 Volts

We now use the Nernst equation to account for the fact that H^+ is not in its standard state:

$$E_{cell} = E^o - \frac{0.0592}{4} * log \frac{[H^+]^4}{P_{O2}P_{H2}^2[H^+]^4} = E^o - \frac{0.0592}{4} * log(1) = E^o = +1.229V \quad (11.3.5)$$

Note that the value of E_{cell} **does not change** with pH since **both couples shift -59.2 mV/pH** according to the Nernst equation. This is the consequence of the fact that the number of electrons equals the number of protons in each of the half cell reactions. Another way to rationalize this result is to remember that the overall reaction ($2H_2 + O_2 = 2H_2O$) does not involve H^+ as a reactant or product, so ΔG and E should be independent of pH.

We can plot the shift in the H_2/H^+ and O_2/H_2O half-cell potentials with pH on a potential-pH diagram (also called a Pourbaix diagram) as shown below. The pH-dependent potentials of the H_2 and O_2 couples are shown as dotted lines. Notice that the potential difference between them is always 1.23 V. The dark circles represent the standard potentials.



Pourbaix diagram for water.

Pourbaix diagrams are essentially electrochemical **phase diagrams**, which plot regions of thermodynamic stability for redox-active substances. As in other kinds of phase diagrams, the lines represent conditions under which two phases coexist in equilibrium. The shaded area in the water Pourbaix diagram represents the conditions of potential and pH where liquid water is stable relative to hydrogen or oxygen. Outside the shaded region, water is thermodynamically unstable and is reduced to $H_2(g)$ or oxidized to $O_2(g)$. Although these processes are spontaneous in the thermodynamic sense (for example, water is unstable in the presence of Pb^{4+}, Cl_2, Fe, Zn, or Al), they are kinetically slow and require catalysis to proceed.

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CHAPTER OVERVIEW

12: Ionic and Covalent Solids - Structures

Learning Objectives

- Describe many crystal structures in terms of close-packed frameworks with systematic filling of octahedral and tetrahedral holes.
- Represent crystal structures by drawing them in sections.
- Rationalize, using chemical principles, why certain crystal structures are stable for certain compounds but not for others, as well as why certain structural and bonding motifs are preferred for certain compounds relative to others.
- Predict which crystal structures are most favorable for a given composition based on ionicity and periodic trends.
- Explain structure-dependent properties such as ferroelectricity and magnetic ordering based on crystal structures.
- Understand intercalation reactions in layered and open framework solids.
- Predict the preferred formation of normal or inverse spinels using arguments from transition metal chemistry (e.g. crystal field stabilization energies).

Inorganic solids often have simple crystal structures, and some of these structures are adopted by large families of ionic or covalent compounds. Examples of the most common structures include NaCl, CsCl, NiAs, zincblende, wurtzite, fluorite, perovskite, rutile, and spinel. We will develop these structures systematically from the close packed and non-close packed lattices shown below. Some layered structures, such as $CdCl_2$ and CdI_2, can be thought of as relatives of simple ionic lattices with some atoms "missing."

12.1: Prelude to Ionic and Covalent Solids - Structures
12.2: Close-packing and Interstitial Sites
12.3: Structures Related to NaCl and NiAs
12.4: Tetrahedral Structures
12.5: Layered Structures and Intercalation Reactions

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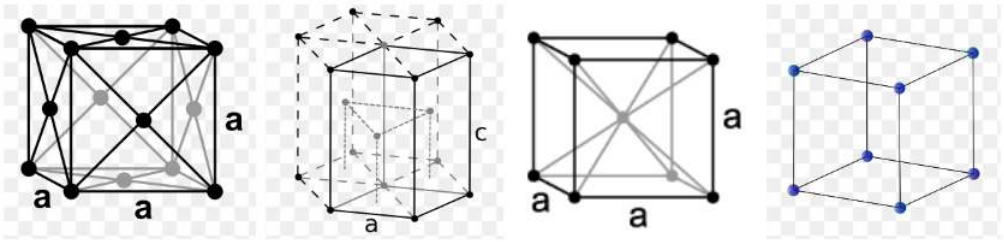
12.1: Prelude to Ionic and Covalent Solids - Structures

As we noted in our discussion of metal and alloy structures in Chapter 6, there is an intimate connection between the structures and the physical properties of materials. As we "graduate" from simple metal structures based on sphere packings to more complex structures, we find that this is still true. In this chapter we will try to systematize the structures of inorganic solids - metal oxides, halides, sulfides, and related compounds - and develop some rules for which structures to expect based on electronegativity differences, hard-soft acid-base rules, and other periodic trends. We will see that many of these structures are related to the sphere packings that we learned about in Chapter 6.



The morphology of twinned crystals of iron pyrite (FeS_2) is related to the underlying cubic symmetry of the unit cell. Like NaCl, the pyrite crystal structure can be thought of as a face-centered cubic array of anions (S_2^{2-}) with cations (Fe^{2+}) occupying all the octahedral holes.

Inorganic solids often have simple crystal structures, and some of these structures are adopted by large families of ionic or covalent compounds. Examples of the most common structures include NaCl, CsCl, NiAs, zincblende, wurtzite, fluorite, perovskite, rutile, and spinel. We will develop these structures systematically from the close packed and non-close packed lattices shown below. Some layered structures, such as $CdCl_2$ and CdI_2, can be thought of as relatives of simple ionic lattices with some atoms "missing."



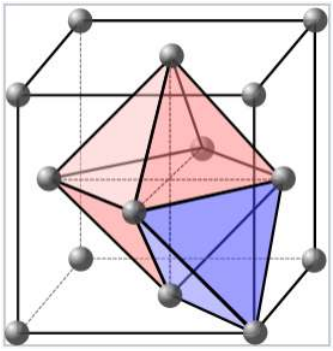
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12.2: Close-packing and Interstitial Sites

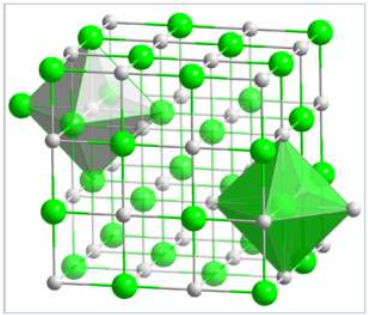
Many common inorganic crystals have structures that are related to cubic close packed (face-centered cubic) or hexagonal close packed sphere packings. These packing lattices contain two types of sites or "holes" that the interstitial atoms fill, and the coordination geometry of these sites is either **tetrahedral** or **octahedral**. An interstitial atom filling a tetrahedral hole is coordinated to four packing atoms, and an atom filling an octahedral hole is coordinated to six packing atoms. In both the hexagonal close packed and cubic close packed lattices, there is one octahedral hole and two tetrahedral holes per packing atom.

Question: Would anions or cations be better as packing atoms?
We might expect that anions, which are often larger than cations, would be better suited to the positions of packing atoms. While this is often true, there are many examples of structures in which cations are the packing atoms, and others in which the distinction is arbitrary. The NaCl structure is a good example of the latter.



One octahedral and one tetrahedral site in a face-centered cubic unit cell. Each cell contains four packing atoms (gray), four octahedral sites (pink), and eight tetrahedral sites (blue).

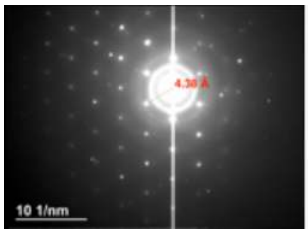
In the NaCl structure, shown on the right, the green spheres are the Cl^- ions and the gray spheres are the Na^+ ions. The octahedral holes in a face-centered cubic lattice can be found at fractional coordinates (1/2 1/2 1/2), (1/2 0 0), (0 1/2 0), and (0 0 1/2). There are four of these holes per cell, and they are filled by the chloride ions. The packing atoms (Na^+) have coordinates (0 0 0), (0 1/2 1/2), (1/2 1/2 0), and (1/2 0 1/2). Note that each of the Na^+ positions is related to a Cl^- position by a translation of (1/2 0 0). Another way of stating this is that the structure consists of **two interpenetrating fcc lattices**, which are related to each other by a translation of half the unit cell along any of the three Cartesian axes. We could have equivalently placed the Cl ions at the fcc lattice points and the Na ions in the octahedral holes by simply translating the origin of the unit cell by (1/2 0 0). Thus the distinction between packing and interstitial atoms in this case is arbitrary.



Crystal structure of NaCl. Both the Na^+ and Cl^- ions are octahedrally coordinated.

NaCl is interesting in that it is a three-dimensional checkerboard, and thus there are no NaCl "molecules" that exist in the structure. When this structure was originally solved (in 1913 by using X-ray diffraction) by W. L. Bragg, his interpretation met resistance by chemists who thought that precise integer stoichiometries were a consequence of the valency of atoms in molecules. The German chemist P. Pfeiffer noted in 1915 that ‘the ordinary notion of valency didn’t seem to apply’, and fourteen years later, the influential chemist H. E. Armstrong still found Bragg’s proposed structure of sodium chloride ‘more than repugnant to the common sense, not chemical cricket’! Nevertheless, Bragg and his father, W. H. Bragg, persevered and used the then-new technique of X-ray

diffraction to determine the structures of a number of other compounds, including diamond, zincblende, calcium fluoride, and other alkali halides. These experiments gave chemists their first real look at the atomic structure of solids, and laid the groundwork for X-ray diffraction experiments that later elucidated the structures of DNA, proteins, and many other compounds. For their work on X-ray diffraction the Braggs received the Nobel prize in Physics in 1915.

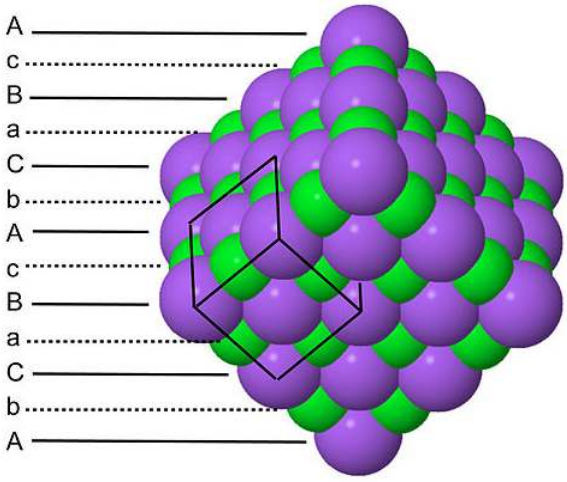


The lattice dimensions and positions of atoms in crystals such as NaCl are inferred from diffraction patterns.

Since each type of atom in the NaCl structure forms a face-centered cubic lattice, there are four Na and four Cl atoms per NaCl unit cell. It is because of this ratio that NaCl has a 1:1 stoichiometry. The shaded green and gray bipyramidal structures in the NaCl lattice show that the Na^+ ions are coordinated to six Cl^- ions, and vice versa. The NaCl structure can be alternatively drawn as a stacking of close-packed layer planes, AcBaCbAcBa... along the body diagonal of the unit cell. Here the uppercase letters represent the packing atoms, and the lower case letters are the interstitial atoms. This layered packing is illustrated below:

NaCl structure

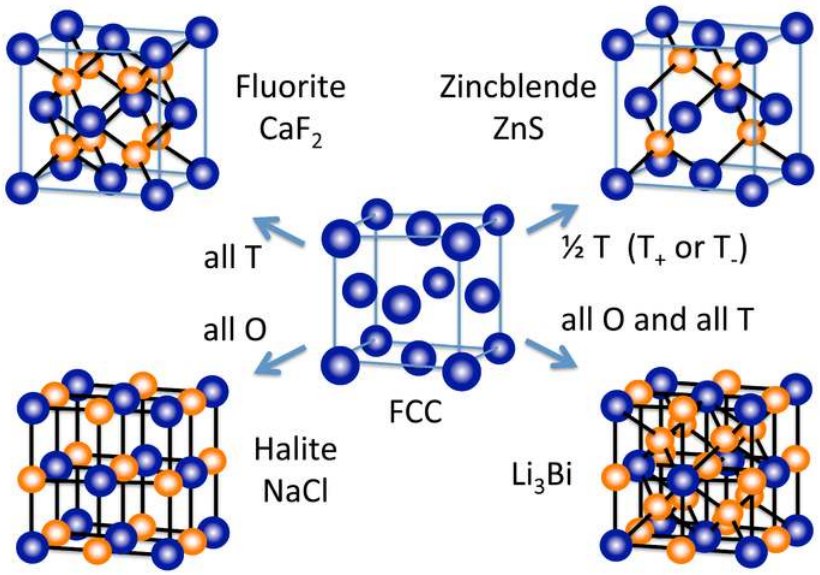
- ---------- A
- - - -c- - - -
- ---------- B
- - - -a- - - -
- ---------- C
- - - -b- - - -
- ---------- A
- - - -c- - - -
- ---------- B
- - - -a- - - -
- ---------- C
- - - -b- - - -
- ---------- A



Note that both the packing atoms and interstitials are stacked in the sequence A-B-C-A-B-C..., in keeping with the fact that each forms a cubic close-packed lattice.

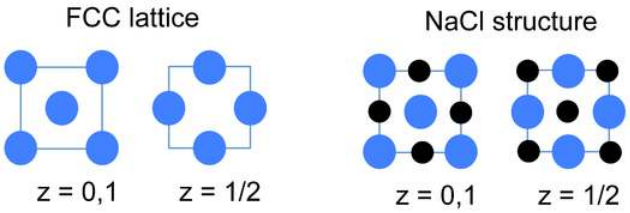
The NaCl structure is fairly common among ionic compounds:

- Alkali Halides (except CsCl, CsBr, and CsI)
- Transition Metal Monoxides (TiO, VO,..., NiO)
- Alkali Earth Oxides and Sulfides (MgO, CaO, BaS... except BeO and MgTe)
- Carbides and Nitrides (TiC, TiN, ZrC, NbC) -these are very stable refractory, interstitial alloys (metallic)



A number of other inorganic crystal structures are formed (at least conceptually) by filling octahedral and/or tetrahedral holes in close-packed lattices. The figure at the right shows some of the most common structures (fluorite, halite, zincblende) as well as a rather rare one (Li_3Bi) that derive from the fcc lattice. From the hcp lattice, we can make the NiAs and wurzite structures, which are the hexagonal relatives of NaCl and zincblende, respectively.

An alternative and very convenient way to represent inorganic crystal structures (especially complex structures such as Li_3Bi) is to draw the unit cell in slices along one of the unit cell axes. This kind of representation is shown at the left for the fcc lattice and the NaCl structure. Since all atoms in these structures have z-coordinates of either 0 or 1/2, only those sections need to be drawn in order to describe the contents of the unit cell. It is a useful exercise to draw some of the fcc compound structures (above) in sections.



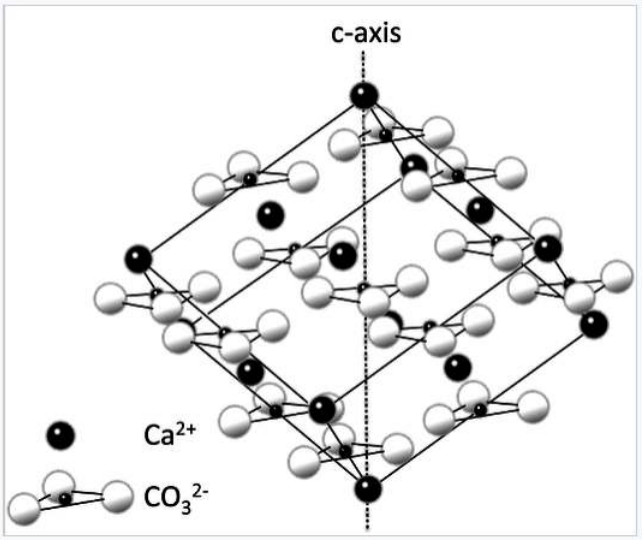
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12.3: Structures Related to NaCl and NiAs

There are a number of compounds that have structures similar to that of NaCl, but have a lower symmetry (usually imposed by the geometry of the anion) than NaCl itself. These compounds include:

- FeS_2 (pyrite, "fools gold"): S_2^{2-} (disulfide) and Fe^{2+}
- CaC_2 (a salt-like carbide): Ca^{2+} and linear C_2^{2-} anions
- $CaCO_3$ (calcite, limestone, marble): Ca^{2+} and triangular CO_3^{2-}.



The rhombohedral unit cell of the calcite crystal structure. The hexagonal c-axis is shown.

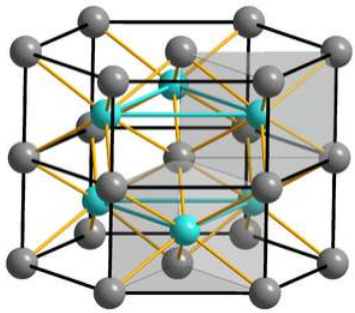
The **calcite** ($CaCO_3$) crystal structure is shown above. Triangular CO_3^{2-} ions fill octahedral holes between the Ca^{2+} ions (black spheres) in a distorted NaCl lattice. As in NaCl, each ion is coordinated by six of the other kind. From this image we can see why the $CaCO_3$ structure has a lower symmetry than that of NaCl. The fourfold rotation symmetry of the NaCl unit cell is lost when the spherical Cl^- ions are replaced by triangular CO_3^{2-} ions. Because of this symmetry lowering, transparent crystals calcite are birefringent, as illustrated below.



Calcite crystals are birefringent, meaning that their refractive indices are different along the two principal crystal directions. This gives rise to the phenomenon of double refraction.

NiAs structure

The NaCl structure can be described a face-centered cubic lattice with all of the octahedral holes filled. What if we start with a hexagonal-close packed lattice rather than a face-centered cubic lattice?



Nickel arsenide crystal structure. The Ni_6As trigonal prisms are shaded gray. One octahedron of six As atoms surrounding a Ni atom is shown in the center of the figure.

This is the structure adopted by **NiAs** and many other transition metal sulfides, phosphides, and arsenides. The cations are shown in gray while the anions are light blue in the figure at the right. The cations are in octahedral coordination, so each cation is coordinated to six anions. The anions are also coordinated to six cations, but they occupy trigonal prismatic sites. In terms of layer stacking, the NiAs structure is AcBcAcBc..., where the A and B sites (the hcp lattice) are occupied by the As atoms, and the c sites, which are eclipsed along the layer stacking axis, are occupied by Ni. Unlike the NaCl structure, where the anion and cation sites are interchangeable, NiAs has unique anion and cation sites. The layer stacking sequence for NiAs is shown below:

- ---------- A
- - - -c- - - -
- ---------- B
- - - -c- - - -
- ---------- A
- - - -c- - - -
- ---------- B
- - - -c- - - -

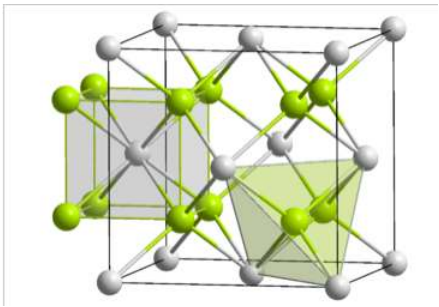
The NiAs structure cannot be adopted by ionic compounds because of the eclipsing cations, because the cation-cation repulsions would be internally destabilizing for an ionic compound. This structure is mainly adopted by covalent and polar covalent MX compounds, typically with "soft" X anions (S, Se, P, As,....) and low-valent transition metal cations. For example, some compounds with the NiAs structure are: MS, MSe, MTe (M=Ti, V, Fe, Co, Ni). Often these are nonstoichiometric or complex stoichiometries with ordered vacancies (Cr_7S_8, Fe_7S_8).

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12.4: Tetrahedral Structures

In ccp and hcp lattices, there are two tetrahedral holes per packing atom. A stoichiometry of either M_2X or MX_2 gives a structure that fills all tetrahedral sites, while an MX structure fills only half of the sites. An example of an MX_2 structure is **fluorite**, CaF_2, whose structure is shown in the figure at the left. The packing atom in fluorite is Ca^{2+} and the structure is composed of three interpenetrating fcc lattices. It should be noted that the Ca^{2+} ion (gray spheres) as a packing atom defies our "rule" that anions are larger than cations and therefore must be the packing atoms. The fluorite structure is common for ionic MX_2 (MgF_2, ZrO_2, etc.) and M_2X compounds (Li_2O). In contrast, the hcp relative of the fluorite structure is quite rare because of unfavorable close contacts between like-charged ions.

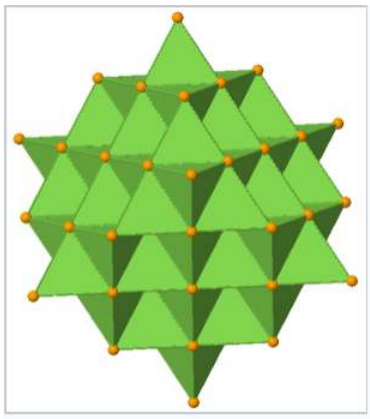


The fluorite (CaF_2) crystal structure showing the coordination environments of the Ca and F atoms

In terms of geometry, Ca^{2+} is in cubic coordination with eight F^- neighbors, and the fluoride ions are tetrahedrally coordinated by four Ca^{2+} ions. The 8:4 coordination geometry is consistent with the 1:2 Ca:F stoichiometry; in all crystal structures the ratio of the coordination numbers is the inverse of the stoichiometric ratio. The three interpenetrating fcc lattices have Ca at 0,0,0 , 1/2,1/2,0 , etc....F at 1/4,1/4,1/4 , 3/4,3/4,1/4 , etc... and F at 3/4,3/4,3/4 , 1/4,1/4/3/4 , etc.

Looking more closely at the tetrahedral sites in fluorite, we see that they fall into two distinct groups: T_+ and T_-. If a tetrahedron is oriented with a vertex pointing upwards along the stacking axis, the site is T_+. Likewise, a tetrahedron with a vertex oriented downward is T_-. The alternation of T_+ and T_- sites allows for efficient packing of ions in the structure. The layer stacking sequence in this structure (including fluoride ions in the T_+ and T_- sites) is:

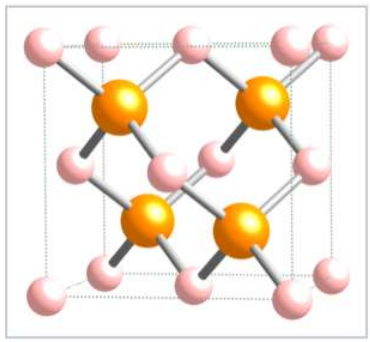
- ---------- A
- - - -b- - - T_+
- - - -a- - - T_-
- ---------- B
- - - -c- - - T_+
- - - -b- - - T_-
- ---------- C
- - - -a- - - T_+
- - - -c- - - T_-
- ---------- A
- - - -b- - - T_+
- - - -a- - - T_-



Polyhedral view of the fluorite crystal structure, showing T_+ and T_-. Ca_4F tetrahedra. The Ca^{2+} ions are stacked ABCABC... along the body diagonal of the unit cell, which is the vertical direction in this image.

Tetrahedrally bonded compounds with a 1:1 stoichiometry (MX compounds) have only **half** of the tetrahedral sites (either the T_+ or T_- sites) filled. In this case, both the M and the X atoms are tetrahedrally coordinated. The **zincblende** and **wurtzite** structures are 1:1 tetrahedral structures based on fcc and hcp lattices, respectively. Both structures are favored by p-block compounds that follow the octet rule, and these compounds are usually semiconductors or insulators. The zincblende structure, shown below, can be thought of as two interpenetrating fcc lattices, one of anions and one of cations, offset from each other by a translation of 1/4 along the body diagonal of the unit cell. Examples of compounds with the zincblende structure include CuCl, CuI, ZnSe, HgS, BeS, CdTe, AlP, GaP, SnSb, CSi, and diamond. Additionally, the compound $CuInSe_2$ is zincblende in an ordered, doubled unit cell (the chalcopyrite structure). The solid solution compounds $CuIn_{1-x}Ga_xSe_2$ with this structure are among the most widely studied materials for use in efficient thin film photovoltaic cells. Using ZnS as a representative of zincblende, the coordination of both Zn and S atoms is tetrahedral. The layer sequence, which is AbBcCaAbBcC..., results in six-membered ZnS rings that have the same geometry as the "chair" version of cyclohexane. The chair conformation allows for a relatively long distance between opposite atoms in the ring and, as a result, it is more sterically favorable than the boat form. The sequence of close-packed layers in zincblende, filling only the T_+ sites and leaving the T_- sites empty, is shown below:

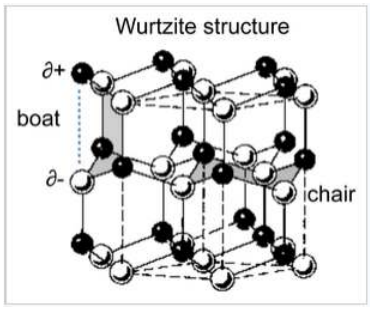
- ---------- A
- - - -b- - - T_+
- - - - - - - T_-
- ---------- B
- - - -c- - - T_+
- - - - - - - T_-
- ---------- C
- - - -a- - - T_+
- - - - - - - T_-



The zincblende unit cell

The wurtzite structure is a close relative of zinc blende, based on filling half the tetrahedral holes in the hcp lattice. Like zincblende, wurtzite contains planes of fused six-membered rings in the chair conformation. Unlike zincblende, however, the rings joining these planes contain six-membered "boat" rings. The boat aligns the anions so that they are directly above the cations in the structure, a less favorable situation sterically but a more favorable one in terms of electrostatics. As a result, the wurtzite structure tends to favor more polar or ionic compounds (e.g., ZnO, $NH_4^+F^-$) than the zincblende structure. As with zincblende, both ions are in tetrahedral (4:4) coordination and there are typically eight valence electrons in the MX compound. Examples of compounds with this structure include: BeO, ZnO, MnS, CdSe, MgTe, AlN, and NH_4F. The layered structure of wurtzite is AbBaAbB and the layer sequence with T_+ sites filled is illustrated below:

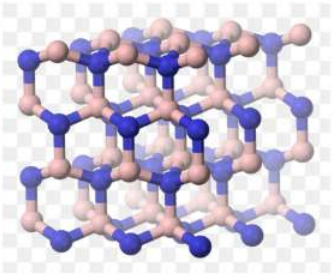
- ---------- A
- - - -b- - - T_+
- - - - - - - T_-
- ---------- B
- - - -a- - - T_+
- - - - - - - T_-
- ---------- A
- - - -b- - - T_+
- - - - - - - T_-
- ---------- B



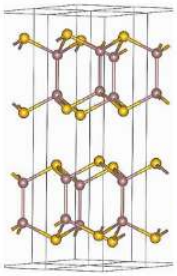
The chair and boat conformations of six-membered ZnS rings in the wurtzite structure.

An interesting consequence of the layer stacking in the wurtzite structure is that the crystals are polar. When cleaved along the c-axis (the stacking axis), crystals of ZnO, ZnS, and GaN have one negatively charged face and an opposite positively charged face. An applied electric field interacts with the crystal dipole, resulting in compression or elongation of the lattice along this direction. For this reason crystals of compounds in the wurtzite structure are typically piezoelectric.

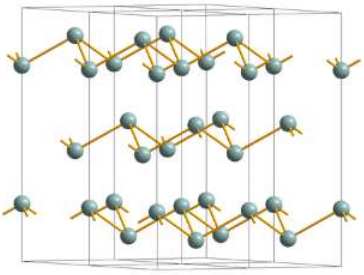
Some compounds are diamorphic and can have either the zincblende or wurtzite structure. Examples of these compounds that have intermediate polarities include CdS and ZnS. SiO_2 exists in polymorphs (crystobalite and tridymite) that resemble zincblende and wurtzite with O atoms midway between each of the Si atoms. The zincblende and wurtzite structures have efficient packing arrangements for tetrahedrally bonded networks and are commonly found in compounds that have tetrahedral bonding. Water, for example, has a tetrahedral hydrogen bonding network and is wurtzite-type. The undistorted wurtzite and zinc blende structures are typically found for AX compounds with eight valence electrons, which follow the octet rule. AX compounds with nine or ten electrons such as GaSe and GaAs crystallize in distorted variants of the wurtzite structure. In GaSe, the extra electrons form lone pairs and this creates layers in the structure, as can be seen in the figure below. To the right of GaSe, the structures of As, Sb, and SbAs show an ever further breakdown of the structure into layers as more valence electrons are added.



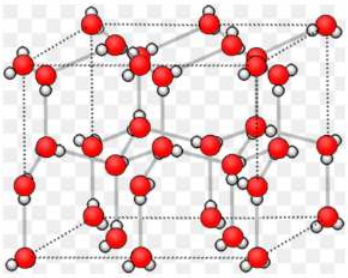
Wurtzite crystal structure



GaSe crystal structure



Crystal structure of Sb, SbAs, and gray As



Crystal structure of hexagonal ice

Hexagonal ice is the most stable polymorph of ice, which is obtained upon freezing at 1 atmosphere pressure. This polymorph (ice-I) has a hcp wurtzite-type structure. Looking at the structure shown at the right, we see that there are irregular arrangements of the O-H---O bonds. In the structure, hydrogen bonding enforces the tetrahedral coordination of each water molecule, resulting in a relatively open structure that is less dense than liquid water. For this reason, ice floats in water.

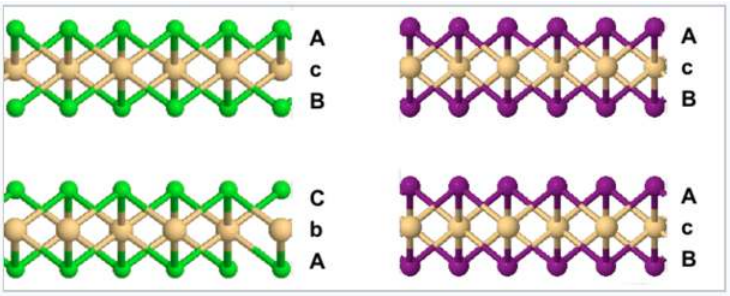
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12.5: Layered Structures and Intercalation Reactions

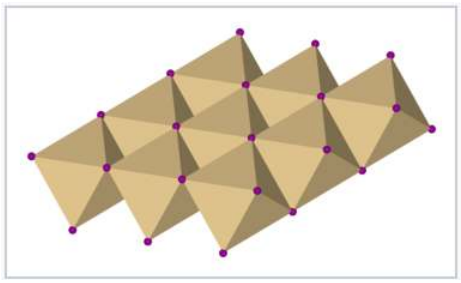
Layered structures are characterized by strong (and typically covalent) bonding between atoms in two dimensions and weaker bonding in the third. A broad range of compounds including metal halides, oxides, sulfides, selenides, borides, nitrides, carbides, and allotropes of some pure elements (B, C, P, As) exist in layered forms. Structurally, the simplest of these structures (for example binary metal halides and sulfides) can be described as having some fraction of the octahedral and/or tetrahedral sites are filled in the fcc and hcp lattices. For example, the $CdCl_2$ structure is formed by filling all the octahedral sites in alternate layers of the fcc lattice, and the CdI_2 structure is the relative of this structure in the hcp lattice.

In the **$CdCl_2$ structure**, the stacking sequence of anion layers is ABCABC...
In the **CdI_2 structure**, the anion stacking sequence is ABAB..., and all the cations are eclipsed along the stacking axis.



Comparison of the $CdCl_2$ (left) and CdI_2 (right) crystal structures

These are examples of **6-3 structures**, because the cations are coordinated by an octahedron of six anions, and the anions are coordinated by three cations to make a trigonal pyramid (like NH_3). Another way to describe these structures is to say that the MX_6 octahedra each share six edges in the MX_2 sheets.



Polyhedral drawing of one layer of the $CdCl_2$ or CdI_2 structure showing edge-sharing MX_6 octahedra

Because these structures place the packing atoms (the anions) in direct van der Waals contact, they are most stable for relatively **covalent** compounds. Otherwise, the electrostatic repulsion between contacting anions would destabilize the structure energetically. More ionic MX_2 compounds tend to adopt the fluorite (CaF_2) or rutile (TiO_2) structures, which are not layered.

Despite the fact that these two structure types are the same at the level of nearest and next-nearest neighbor ions, the CdI_2 structure is much more common than the $CdCl_2$ structure.

$CdCl_2$ structure:

MCl_2 (M = Mg, Mn, Fe, Co, Ni, Zn, Cd)

$NiBr_2$, NiI_2, $ZnBr_2$, ZnI_2

CdI_2 structure:

MCl_2 (M = Ti, V)

MBr_2 (M = Mg, Fe, Co, Cd)

MI_2 (M = Mg, Ca, Ti, V, Mn, Fe, Co, Cd, Ge, Pb, Th)

$M(OH)_2$ (M = Mg, Ca, Mn, Fe, Co, Ni, Cd)

MS_2 (M = Ti, Zr, Sn, Ta, Pt)

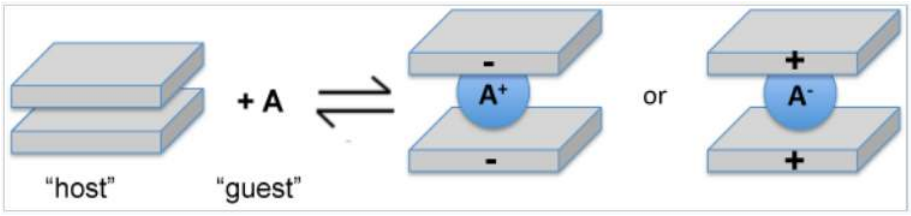
MSe_2 (M = Ti, Zr, Sn, V, Pt)

MTe_2 (M = Ti, Co, Ni, Rh, Pd, Pt)

Physically, layered compounds are **soft** and **slippery**, because the layer planes slide past each other easily. For example, graphite, MoS_2, and talc (a silicate) are layered compounds that are used widely as **lubricants** and lubricant additives.

An important reaction of layered compounds is **intercalation**. In intercalation reactions, guest molecules and ions enter the galleries that separate the sheets, usually with expansion of the lattice along the stacking axis. This reaction is typically reversible if it does not perturb the bonding within the sheets. Often the **driving force for intercalation is a redox reaction**, i.e., electron transfer between the host and guest. For example, lithium metal reacts with TiS_2, MoS_2, and graphite to produce $LiTiS_2$, Li_xMoS_2 ($x < 1$), and LiC_6. In these compounds, lithium is ionized to Li^+ and the sheets are negatively charged. Oxidizing agents such as Br_2, $FeCl_3$, and AsF_5 also react with graphite. In the resulting intercalation compounds, the sheets are positively charged and the intercalated species are anionic.

Intercalation reactions are especially important for electrochemical energy storage in **secondary batteries**, such as **lithium ion** batteries, **nickel-metal hydride** batteries, and **nickel-cadmium** batteries. The reversible nature of the intercalation reaction allows the electrodes to be charged and discharged up to several thousand times without losing their mechanical integrity. In lithium ion batteries, the negative electrode material is typically graphite, which is intercalated by lithium to make LiC_6. Several different oxides and phosphates containing redox active transition metal ions (Mn, Fe, Co, Ni) are used as the positive electrode materials.



Oxidative or reductive intercalation involves the placement of anions or cations between sheets.

Lithium ion batteries based on CoO_2 were first described in 1980[1] by John B. Goodenough's research group at Oxford. In batteries based on CoO_2, which has the CdI_2 structure, the positive electrode half-reaction is:

$$LiCoO_2 \leftrightharpoons Li_{1-x}CoO_2 + xLi^+ + xe^- \tag{12.5.1}$$

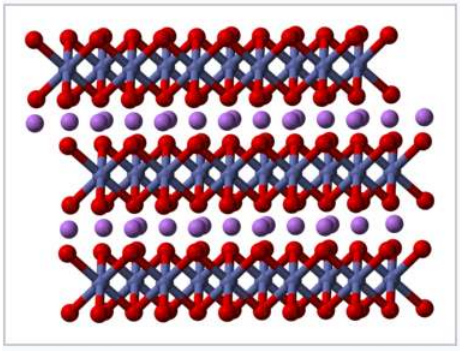
The negative electrode half reaction is:

$$xLi^+ + xe^- + xC_6 \leftrightharpoons xLiC_6 \tag{12.5.2}$$

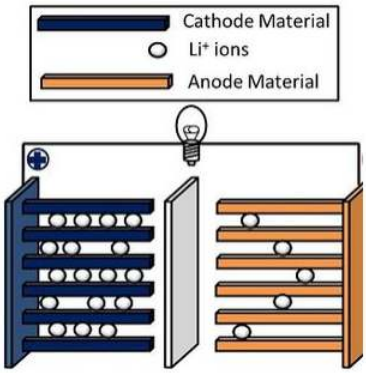
The battery is fully charged when the positive electrode is in the CoO_2 form and the negative electrode is in the LiC_6 form. Discharge involves the motion of Li^+ ions through the electrolyte, forming Li_xCoO_2 and graphite at the two electrodes.



Blue plaque erected by the Royal Society of Chemistry commemorating the development of cathode materials for the lithium-ion battery



Crystal structure of $LiCoO_2$[2]



The lithium ion battery is a "rocking chair" battery, so named because charging and discharging involve moving Li^+ ions from one side to the other. CoO_2 is one example of a positive electrode material that has been used in lithium ion batteries. It has a high energy density, but batteries based on CoO_2 have poor thermal stability. Safer materials include lithium iron phosphate ($LiFePO_4$), and $LiMO_2$ (M = a mixture of Co, Mn, and Ni). These batteries are used widely in laptop computers, portable electronics, cellular telephones, cordless tools, and electric and hybrid vehicles.

A similar intercalation reaction occurs in nickel-cadmium batteries and nickel-metal hydride batteries, except in this case the reaction involves the movement of protons in and out of the $Ni(OH)_2$ lattice, which has the CdI_2 structure:

$$NiO(OH) + H_2O + e^- \longrightarrow Ni(OH)_2 + OH^- \tag{12.5.3}$$

There are many layered compounds that cannot be intercalated by redox reactions, typically because some other stable product is formed. For example, the reaction of layered CdI_2 with Li produces LiI (NaCl structure) and Cd metal.

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CHAPTER OVERVIEW

13: Crystallography

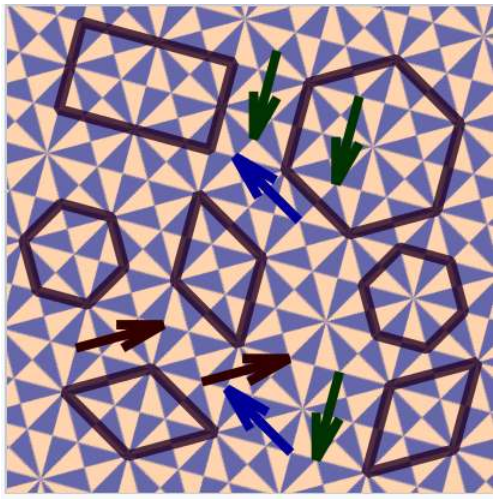
13.1: Unit Cells and Crystal Structures
13.2: Crystal Structures of Metals
13.3: Bragg's Law
13.4: X-ray Diffraction

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13.1: Unit Cells and Crystal Structures

Crystals can be thought of as repeating patterns, much like wallpaper or bathroom tiles, but in three dimensions. The fundamental repeating unit of the crystal is called the **unit cell**. It is a three dimensional shape that can be repeated over and over by unit translations to fill space (and leave minimal gaps) in the structure. Some possible unit cells are shown in the tiling pattern at the right, along with arrows that indicate **unit translation vectors**. In three dimensions, the hexagonal or rhombic unit cells of this pattern would be replaced by three dimensional boxes that would stack together to fill all space. As shown in the figure, the origin of the unit cell is arbitrary. The same set of boxes will fill all space no matter where we define the origin of the lattice. We will see that pure metals typically have very simple crystal structures with cubic or hexagonal unit cells. However the crystal structures of alloys can be quite complicated.

When considering the crystal structures of metals and alloys, it is not sufficient to think of each atom and its neighboring ligands as an isolated system. Instead, think of the entire metallic crystal as a network of atoms connected by a sea of shared valence electrons. The **electrons are delocalized** because there are **not enough of them** to fill each "bond" between atoms with an electron pair. For example, in the crystal structures of s-block and p-block metals, each atom has either 8 or 12 nearest neighbors, but the maximum number of s + p electrons is 8. Thus, there are not enough to put two electrons between each pair of atoms. Transition metals can also use their d-orbitals in bonding, but again there are never enough electrons to completely fill all the "bonds."



Possible unit cells in a periodic tile pattern. The arrows connect translationally equivalent points (lattice points) in the pattern.

The atoms in a metal lattice arrange themselves in a certain pattern which can be represented as a 3D box structure known as the **unit cell** which repeats across the entire metal.

Simple Cubic	Body Centered Cubic	Face Centered Cubic	Hexagonal Close Packed
Simple cubic.svg	Lattice body centered cubic.svg	Lattice face centered cubic.svg	Hexagonal close packed.png
1 atom/cell	2 atoms/cell	4 atoms/cell	2 atoms/cell

Metal atoms can be approximated as spheres, and therefore are not 100 % efficient in packing, the same way a stack of cannonballs has some empty spaces between the balls. Different unit cells have different packing efficiencies. The number of atoms that is included in the unit cell only includes the fractions of atoms *inside* of the box. Atoms on the corners of the unit cell count as ⅛ of an atom, atoms on a face count as ½, an atom in the center counts as a full atom. Using this, let's calculate the number of atoms in a simple cubic unit cell, a face centered cubic (fcc) unit cell, and a body centered cubic (bcc) unit cell.

Simple Cubic:

8 corner atoms × ⅛ = 1 atom/cell. The packing in this structure is not efficient (52%) and so this structure type is very rare for metals.

Body Centered Cubic, bcc:

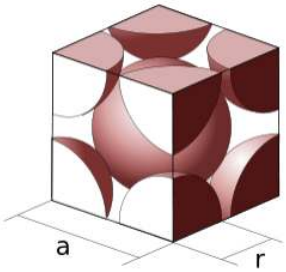
(8 corner atoms × ⅛) + (1 center atom × 1)= 2 atoms/cell. The packing is more efficient (68%) and the structure is a common one for alkali metals and early transition metals. Alloys such as brass (CuZn) also adopt these structures.

Face Centered Cubic, fcc (also called Cubic Close Packed, ccp):

(8 corner atoms × ⅛)+ (6 face atoms × ½)= 4 atoms/cell. This structure, along with its hexagonal relative (hcp), has the most efficient packing (74%). Many metals adopt either the fcc or hcp structure.

Hexagonal Close Packed, hcp:

Like the fcc structure, the packing density of hcp is 74%.

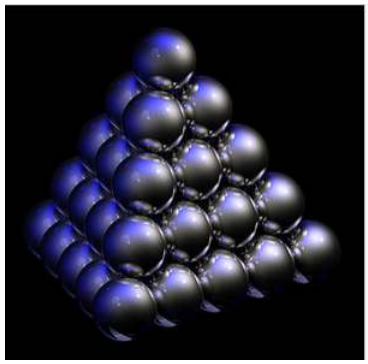


The unit cell of a bcc metal contains two atoms.

Calculating the packing fraction. The packing fractions of the crystal structures shown above can be calculated by dividing the volume of the atoms in the cell by the volume of the cell itself. The volume of the atoms in the cell is equal to the number of atoms/cell times the volume of a sphere, (4/3)πr^3. The volume of the cubic cells is found by cubing the side length. As an example, let's calculate the packing efficiency of a simple cubic unit cell. As we saw earlier in the section, a simple cubic unit cell contains one atom. The side length of the simple cubic unit cell is 2r, since the centers of each atom occupy the corners of the unit cell.

$$\text{Packing efficiency} = \frac{(1\ atom) \times (\frac{4}{3})\pi r^3}{(2r)^3} = 0.523 \tag{13.1.1}$$

The same method can be applied to bcc and fcc structures.



Face-centered cubic stack of cannonballs.

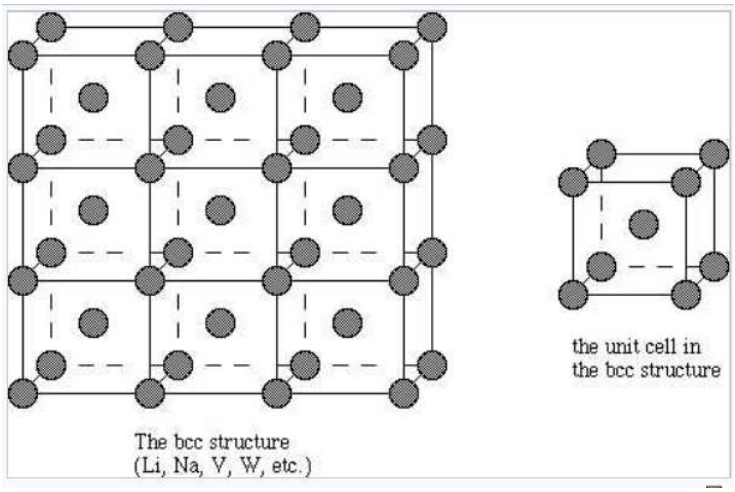
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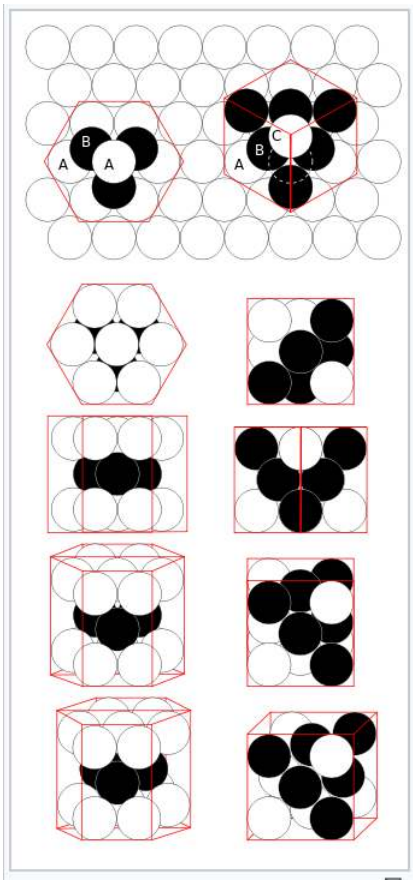
13.2: Crystal Structures of Metals

The Crystalline Nature of Metals

All metallic elements (except Cs, Ga, and Hg) are crystalline solids at room temperature. Like ionic solids, metals and alloys have a very strong tendency to crystallize, whether they are made by thermal processing or by other techniques such as solution reduction or electroplating. Metals crystallize readily and it is difficult to form a glassy metal even with very rapid cooling. Molten metals have low viscosity, and the identical (essentially spherical) atoms can pack into a crystal very easily. Glassy metals can be made, however, by rapidly cooling alloys, particularly if the constituent atoms have different sizes. The different atoms cannot pack in a simple unit cell, sometimes making crystallization slow enough to form a glass.



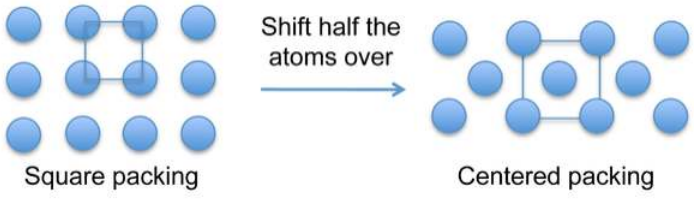
Body-centered cubic



hcp (left) and fcc (right) close-packing of spheres

Crystal structures

Most metals and alloys crystallize in one of three very common structures: body-centered cubic (bcc), hexagonal close packed (hcp), or cubic close packed (ccp, also called face centered cubic, fcc). In all three structures the coordination number of the metal atoms (i.e., the number of equidistant nearest neighbors) is rather high: 8 for bcc, and 12 for hcp and ccp. We can contrast this with the low coordination numbers (i.e., low valences - like 2 for O, 3 for N, or 4 for C) found in nonmetals. In the bcc structure, the nearest neighbors are at the corners of a cube surrounding the metal atom in the center. In the hcp and ccp structures, the atoms pack like stacked cannonballs or billiard balls, in layers with a six-coordinate arrangement. Each atom also has six more nearest neighbors from layers above and below. The stacking sequence is ABCABC... in the ccp lattice and ABAB... in hcp. In both cases, it can be shown that the spheres fill 74% of the volume of the lattice. This is the highest volume fraction that can be filled with a lattice of equal spheres.



Atoms in metallic crystals have a tendency to pack in dense arrangments that fill space efficiently. The simple square packing (above) upon which the simple cubic structure is based is inefficient and thus rare among metallic crystal structures. Body- or face-centered structures fill space more efficiently and more common.

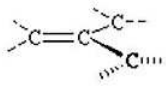
Periodic trends in structure and metallic behavior

Remember where we find the metallic elements in the periodic table - everywhere except the upper right corner. This means that as we go down a group in the p-block (let's say, group IVA, the carbon group, or group VA, the nitrogen group), the properties of the elements gradually change from nonmetals to metalloids to metals. The carbon group nicely illustrates the transition. Starting at the top, the element carbon has two stable allotropes - graphite and diamond. In each one, the valence of carbon atoms is exactly satisfied by making four electron pair bonds to neighboring atoms. In graphite, each carbon has three nearest neighbors, and so there are two single bonds and one double bond. In diamond, there are four nearest neighbors situated at the vertices of a tetrahedron, and so there is a single bond to each one.

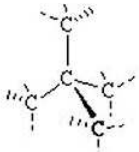
The two elements right under carbon (silicon and germanium) in the periodic table also have the diamond structure (recall that these elements cannot make double bonds to themselves easily, so there is no graphite allotrope for Si or Ge). While diamond is a good insulator, both silicon and germanium are semiconductors (i.e., metalloids). Mechanically, they are hard like diamond. Like carbon, each atom of Si and Ge satisfies its valence of four by making single bonds to four nearest neighbors.

The next element under germanium is tin (Sn). Tin has two allotropes, one with the diamond structure, and one with a slightly distorted bcc structure. The latter has metallic properties (metallic luster, malleability), and conductivity about 10^9 times higher than Si. Finally, lead (Pb), the element under Sn, has the ccp structure, and also is metallic. Note the trends in coordination number and conducting properties:

Element	Structure	Coord. no.	Conductivity
C	graphite, diamond	3, 4	semimetal, insulator
Si	diamond	4	semiconductor
Ge	diamond	4	semiconductor
Sn	diamond, distorted bcc	4, 8	semiconductor, metal
Pb	ccp	12	metal



trigonal bond network in graphite: 1 double bond + 2 single bonds to C



tetrahedral bond network in diamond: 4 single bonds to each C atom

The elements C, Si, and Ge obey the octet rule, and we can easily identify the electron pair bonds in their structures. Sn and Pb, on the other hand, adopt structures with high coordination numbers. They *do not have enough valence electrons* to make electron pair bonds to each neighbor (this is a common feature of metals). What happens in this case is that the valence electrons become "smeared out" or delocalized over all the atoms in the crystal. It is best to think of the bonding in metals as a crystalline arrangement of positively charged cores with a "sea" of shared valence electrons gluing the structure together. Because the electrons are not localized in any particular bond between atoms, they can move in an electric field, which is why metals conduct electricity well. Another way to describe the bonding in metals is nondirectional. That is, an atom's nearest neighbors surround it in every direction, rather than in a few particular directions (like at the corners of a tetrahedron, as we found for diamond). Nonmetals (insulators and semiconductors), on the other hand, have directional bonding. Because the bonding is non-directional and coordination numbers are high, it is relatively easy to deform the coordination sphere (i.e., break or stretch bonds) than it is in the case of a nonmetal. This is why elements like Pb are much more malleable than C, Si, or Ge.

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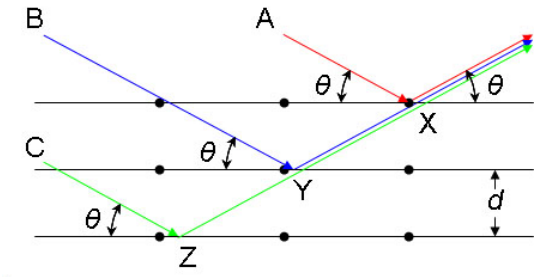
13.3: Bragg's Law

The structures of crystals and molecules are often being identified using x-ray diffraction studies, which are explained by Bragg's Law. The law explains the relationship between an x-ray light shooting into and its reflection off from crystal surface.

Introduction

Bragg's Law was introduced by Sir W.H. Bragg and his son Sir W.L. Bragg. The law states that when the x-ray is incident onto a **crystal** surface, its angle of incidence, θ, will reflect back with a same angle of scattering, θ. And, when the path difference, d is equal to a whole number, n, of wavelength, a constructive interference will occur.

Consider a single crystal with aligned planes of lattice points separated by a distance *d*. Monochromatic X-rays A, B, and C are incident upon the crystal at an angle θ. They reflect off atoms X, Y, or Z.



The path difference between the ray reflected at atom X and the ray reflected at atom Y can be seen to be 2YX. From the Law of Sines we can express this distance YX in terms of the lattice distance and the X-ray incident angle:

If the path difference is equal to an integer multiple of the wavelength, then X-rays A and B (and by extension C) will arrive at atom X in the same phase. In other words, given the following conditions:

then the scattered radiation will undergo constructive interference and thus the crystal will appear to have reflected the X-radiation. If, however, this condition is not satisfied, then destructive interference will occur.

Bragg's Law

$$n\lambda = 2d\sin\theta \tag{13.3.1}$$

where:

- λ is the wavelength of the x-ray,
- d is the spacing of the crystal layers (path difference),
- θ is the incident angle (the angle between incident ray and the scatter plane), and
- n is an integer

The principle of Bragg's law is applied in the construction of instruments such as Bragg spectrometer, which is often used to study the structure of crystals and molecules.

References

1. Bragg, W.L. *The Crystalline State: Volume I.* New York: The Macmillan Company, 1934.
2. McQuarrie, Donald A. *Physical Chemistry: A molecular Approach.* Sausalito: University Science Books, 1997.

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13.4: X-ray Diffraction

The construction of a simple powder diffractometer was first described by Hull in 1917[1] which was shortly after the discovery of X-rays by Wilhelm Conrad Röntgen in 1895[2]. Diffractometer measures the angles at which X-rays get reflected and thus get the structural information they contains. Nowadays resolution of this technique get significant improvement and it is widely used as a tool to analyze the phase information and solve crystal structures of solid-state materials.

Introduction

Since the wavelength of X-rays is similar to the distance between crystal layers, incident X-rays will be diffracted, interacting with certain crystalline layers and diffraction patterns containing important structural information about the crystal can be obtained. The diffraction pattern is considered the fingerprint of the crystal because each crystal structures produce unique diffraction patterns and every phase in a mixture produces its diffraction pattern independently. We can use grinded bulk sample into fine powders, which are typical under 10 μm,[2] as samples in powder X-ray Diffraction (XRD). Unlike single crystal X-ray diffraction (X-ray Crystallography) technique, the sample will distribute evenly at every possible orientation and powder XRD collects one-dimensional information, which is a diagram of diffracted beam intensity vs. Bragg angle θ, rather than three-dimensional information.

Theoretical consideration

In this section, let us take a look at the theoretical basis of powder X-ray diffraction technique. (e.g. lattice structures and how X-rays interacts with crystal structures)

Unit cells

“Crystals are built up of regular arrangements of atoms in three dimensions; these arrangements can be represented by a repeat unit or motif called the unit cell.”[2] In crystallography, all the crystal unit cells can be classied into 230 space groups. Some basic knowledge about crystallography is necessary for a well understanding of powder XRD technique. In crystallography, the basic possible classifications are: 6 crystal families, 7 crystal systems, 5 centering position, 14 Bravais lattices and 32 crystal classes.

Based on the angles and the length of the axes sides, unit cell can be divided into 6 crystal families, which are cubic, tetragonal, hexagonal, orthorhombic, monoclinic and triclinic. As the hexagonal family can have two different appearances, we can divide it into two systems which are trigonal lattice and hexagonal lattice. That is how the 7 crystal systems generate. If forget the shape of lattice and just consider the atoms' positions, we can divide the lattices into primitive lattices and non-primitive ones. A primitive lattice (also defined as simple) is the lattice with the smallest possible atomic coordination number[2], e.g.wheneight atoms lie in the eight corners. And all the other lattices are called non-primitive lattice. Based on the three-dimension position of the atoms in the unit cell, we can divided the non-primitive lattice into three types: face centered (F), side centered (C), body centered (I) and based centered(R).

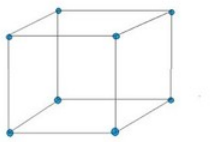


Figure2.1.1 Primitive cubic

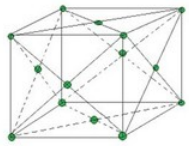


Figure 2.1.2 Face centered cubic

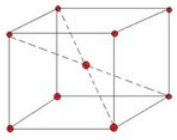


Figure2.1.3 Body centered cubic

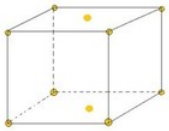


Figure 2.1.4 Side centered cubic

Bravais lattice is a “combination of lattice type and crystal systems”[1].And you can find a chart of examples of all the 14 Bravais lattice in outside link.

32 crystal classes refer to 32 crystallographic point group classfied by the possible symmetric operations, which are rotation, reflection and inversion. You may wonder why only 32 possible point group. The answer is crystallographic restriction, which means crystal system can only have 5 kinds of rotation axises: 1-fold, 2-fold, 3-fold, 4-fold and 6-fold. To be simplify, only the permissible rotation axises allow unit cells grow uniformly without any openings among them.

230 space groups are combinations of 14 Bravais lattice and 32 crystal classes. Those space groups are generated from translations of related Bravais lattice and glide plane and/or scew axis of relative crystal classes. They are represented by Hermann-Mauguin. For example, the NO.62 space group, Pnma is derived from D2h crystal class. P indicated it is primitive structure and n, m, a stand for a diagonal glide plane, a mirror plane and a axial glide planes. The space group belongs to orthorhombic crystal family.

Miller Indices and Reciprocal Lattice

Miller indices and reciprocal lattice are essential to understanding the geometry of lattice planes and X-ray diffraction technique, because they are widely used to index the planes and orientations in crystallography and allow data handling in a simple and mathematical method. To assign the Miller indices (h,k,l) to a certain set of parallel planes which are defined as a plane family , first we need to find the first plane next to the plane, passing through the origin. Then we can find the three intersection of this plane on the unit cell vectors, a, b, c. “The Miller indices would be the reciprocals of the fractional intersections.”[1] Why we want the reciprocal of fraction instead of the fraction directly? To get the answer, we need get to understand what reciprocal lattice is.

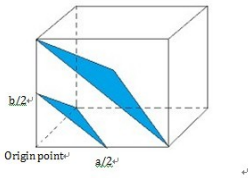


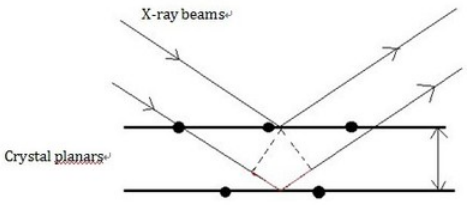
Figure 2.1.5 Miller indice (2,2,1)

“Geometrically, the planes can be specified by two quantities: (1) their orientation in the crystal and (2) their d-spacing.” [4] (d-spacing is the interplanar distance) This allows us to use a vector d^*, which is normal to the planes and whose length is inverse to d-spacing, i.e. $d^*=K/d$ [4] to stand for a certain family of planes. d^* is called reciprocal lattice vector and similarly in three dimension system, reciprocal lattice vector d^*_{hkl} stand for (h,k,l). And the end point of reciprocal lattice vector form a grid or lattice-reciprocal lattice unit cell[4]. Reciprocal lattice cell vector a^*, b^*, c^* is reciprocal form of direct unit cell vector a, b, c. Then it is easy to find out that $d^*_{hkl}=ha^*+kb^*+lc^*$. By take the reciprocal number of the intercepts of Miller indices, those two notation systems are very consistent and straightforward in indexing the crystal lattice.

Bragg’s Law

Bragg’ s law is the theoretical basis of X-ray diffractometer. Let us consider the crystalline as built up in planes. As shown in the diagram, X-ray beam shines into the planes and is reflected by different planes. The beam reflected by the lower plane will travel an extra distance （shown in Figure 2.2.1 in red） than that reflected by the upper one,which is 2dsinθ. If that distance equals nλ(n is an integer), we will get constructive interference, which corresponds to the bright contrast in diffraction pattern. So the Bragg equation as shown below defines the position of the existence of constructive diffraction at different orders.

$$2d\sin\theta=n\lambda.$$



2.2.1 Bragg’s Law

D-spacing, which is the inter plane distance d in Bragg's equation, is decided by the lattice parameter a, b, c, as shown below.

$$\frac{1}{d_{hkl}^2} = \frac{h^2}{a^2} + \frac{k^2}{b^2} + \frac{l^2}{c^2} \qquad 2.1$$

So after finding out d-spacing from detected Bragg's angle, we can figure out the lattice parameter which contains vital structural information. Also we can reconstruct the unknown structure by figuring out all the possible d-spacing. Powder XRD can define the phase contained in a mixture on the basis of separating and recognizing characteristic diffraction pattern.

Structure factor

The sample of powder X-ray diffraction will distribute evenly at every possible orientation, so after diffracted, the diffraction pattern appears as circles with same center point instead of dots in single crystal diffraction patterns. The circles in the diffraction patterns with smaller radius correspond to smaller h, k, l. In certain types of unit cells, not all the lattice planes will have their diffraction observed, which is usually called systematic absence, because the diffracted beam may happen to be out of phase by 180°and the overall intensity would be zero. Structure factor F_{hkl} can decide the systematic absences and intensity.Systematic absences arise when F=0, so no diffraction will be observed. For example:

For a fcc crystal, $F_{hkl}=f\{1+e^{\pi i(h+l)}+e^{\pi i(k+l)}+e^{\pi i(h+k)}\}$. When h, k, l are all odd or all even, F=4f. For the other situation, F=0 and thus diffraction intensity will also be zero. Structure factor is important in the structure determination step because it helps understand the Miller indices and intensities of diffraction peaks. The other common rules for reflection to be observed are listed as follows:

Table 2.3.1: Systematic absence due to lattice type.[2]

Lattice type	Rule for reflection to be observed
Primitive, P	None
Body centered, I	hkl: h+k+l=2n
Face centered, F	hkl: h, k, l either all odd or all even
Side centered, C	hkl: h+k=2n
Rhombohedral, R	hkl: -h+k+l=3n or (h-k+l=3n)

Instrumentation

Powder X-ray diffractometer consists of three components: X-ray source, sample holder and detector.



Figure 3.1 Powder X-ray diffractometer

Source

Possible X-ray sources are X-ray tube, Synchrotron radiation and cyclotron radiation. X-ray tube equipped with filter is commonly used in laboratory diffractometer. Synchrotron radiation is a brighter source and as a result can increase the resolution.

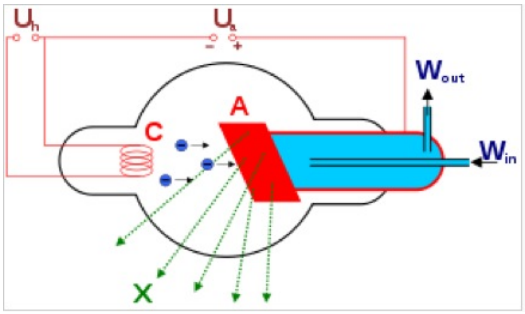


Figure 3.2 X-ray tube

The cathode part of X-ray tube generated electrons under electric current. Electrons travel from cathode to anode through a high acceleration voltage, typically 30~150kV. In this process, most of the energy is released as heat and X-ray only account for approximately 1% of total energy. The X-ray tube needs lasing cooling water to protect it from over heat while working. After X rays hit the anode(red part in the schematic), the anode generates characteristic X-rays, which comes from the process of excited electrons falling down to lower electron shell and correspond to the energy difference between electron shells. In Bruker D8 diffractometer, the anode is made of Cu, so the X-ray souce is Cu-Ka1 and Cu-Ka2. K means the electrons falls to K shell from higher shells. α means the excited electrons lies in L shell, one shell higher than K shell. If the excited electron comes from M shell which is two electron shell higher, then what we have is defined as K_β. The difference between Cu-K_{a1} and Cu-K_{a2} is that they come from different subshell, Cu-Ka1 corresponds to 2p2/3 to 1s shell while Cu-K_{a2} corresponds to 2p1/2 to 1s shell.

In a reflection geometry instrumentation, X-ray tube usually contains a side window made of Be to allow the generated X-rays to emit at the demanding angle. The reason that Be is used as a X-ray window, is that the fluorescence yield (ration between characteristic X ray and Auger emission) of Be is close to zero, so it can make sure the X-ray source is monochromatic and does not contain introduced chracteristic X-rays from other metals.

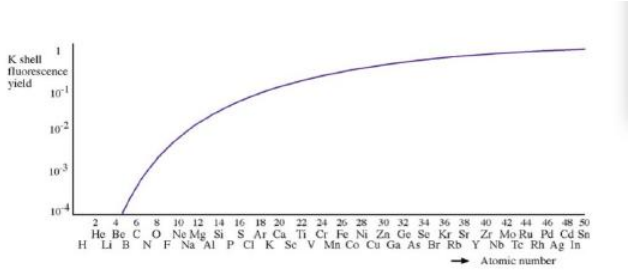


Figure 3.3 K shell fluorescence yield of different elements. 3

Sample Holder

There are many holder options to holder all kinds of samples and meet people's requirement. Usually, evenly grinded sample powder is dissolved in organic solvent such as acetone or pressed into a plain on a glass slide to make sure the sampel is flat. The sample holder has a press ring to fix the slide. At low angles, the signal to noise ratio can be relatively larger and we can use a zero background sample holder to avoid that. It is usually made of single crystal silicon.

Detector

Photographic film serves as detector in earlier methods, Debye-Scherrer camera and Guinier camera methods[2]. The film is placed around the sample as a circle and records the diffracted X-ray beams. The positions of diffraction lines correspond to Bragg angle. And Photographic film can record both the reflected and transmitted X-ray beams. Nowadays, people tend to only select the reflected beam and use radiation counter as detector. Compared to film, scintillationcounter can measure diffraction intensities and Bragg angles more accurately. And it is very convenient use computer to analyze data.To prevent the X-ray beam from going though the sample, we need more powder sample.

Application

Phase Analysis

X-ray diffractometer is most widely used in the phase analysis because compare to other characterization method, XRD gives a fast and reliable measurement(measurement time is determined by the step size, angle range and the number of second per step) and

easy sample preperation(well grinded powder). What people do after get their raw data is opening the data in a XRD data handling software (JADE, WinXPOW, ect.) and compare the raw data with the standard pattern in ICDD database. In many cases, the database may not contain the pattern of a specific compound you are working on, then you can easily generate a calculated pattern based on a crystal informtion file or the space group and lattice parameters. The diffraction pattern of a well-prepared sample should be very reliable (all the peaks should match the peaks in the reference pattern) and contains much information. When the sample has impurities, every kinds of substance will generate their own pattern independently and allows us to analysize seperately and help people control and optimize the reactions. Other factor that can influence the pattern may be the X-ray souce, sample crystallinity (smaller crystallinity can broaden the peaks), ect.

XRD technique is also capable for quantitative analysis of mixtures. The XRD data will not give the quantitative imformation because the intensity is not directly related to weight percantage. However, we can make a serie of controlled samples with different weight percentage of the impurity. Then XRD is performed on each of these sample and we can get a linear calibration curve which is the intensity ratio vs. weight percentage. The weight percentage in the sample can be determined based on the curve. If all the atomic and crystalline information are known, we can also conduct qualitative analysis with Rietveld method. A square least approximation method will be applied to modify all the parameters so that the difference between experimental point and the fitted pattern can be decreased to a least amount. During this process, the scale factor can also be determined. Rietveld method is widely used in samples containing more than one impurities.

Structure determination

Powder X-ray diffraction can not only be used to analyze phase information,but can also be used to determine the structure of unknown substances. However, since in powder XRD we can only get one-dimensional information rather than three-dimensional information, resolution in powder XRD is much lower than that from single crystal method and data refinement process is more sophisticated.“If representative single crystal method are available, then single crystal diffraction is the preferred method.”[1]

As shown in Figure 4.1, one Bragg Ring corresponds to a certain Miller plane. With the detected Bragg angle and equation 2.1, we can figure out the lattice parameters. The common method to manage data is direct method, Patterson method and Fourier method[2]. We can also use the square least approximation method, i.e. Rietveld method to refine the data, to refine the data and it has increased the resolution a lot.

Common single crystal methods are Laue method, four-circle diffractometer and rotating-crystal method.

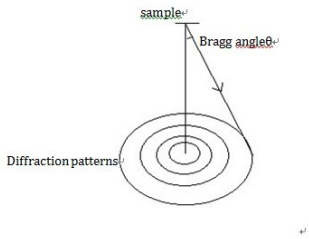


Figure 4.1 Structure determination from Powder XRD

Reference

1. W. I. F. David, K. Shankland, L. B. McCusker, Ch. Baerlocher; Structure Determination from Powder Diffraction Data; Oxford; New York : Oxford University Press, 2002
2. Anthony R. West; Basic Solid State Chemistry, Second Edition; New York : John Wiley & Sons, c1999
3. Transimission Electron Microscope, Volume 1, David B. Williams, C. Barry Carter Springer,2009
4. The Basics of Crystallography and Diffraction, Second Edition,Christopher Hammond;Oxford Science Publications, 2001

Problems

1. Draw the lattice planes (1,1,1) (0,1,2) and (1,0,1) in a cubic lattice.
2. If we use Cu αradiation as X-ray source, and the first order Bragg diffraction peak is found at the semi-angle 35° ， calculate the d-spacing of the crystal.
3. X-rays with wavelength 1.54 A are reflected from the (2,1,1) planes of a cubic crystal. The d-spacing is found to be 5.12A. Calculate the crystal parameter.

4. Prove that for a body centered cubic lattice, reflection can be observed only when h+l+k=2n
5. If you need to conduct powder XRD on an air sensitive crystal, choose a proper sample holder you need on line.

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CHAPTER OVERVIEW

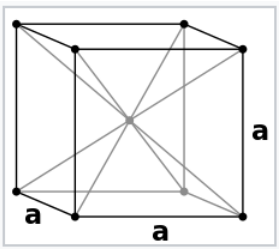
14: Metals and Alloys

14.1: Bonding in Metals
14.2: Defects in Metallic Crystals
14.3: Work Hardening, Alloying, and Annealing
14.4: Malleability of Metals and Alloys
14.5: Iron and Steel
14.6: Amorphous Alloys

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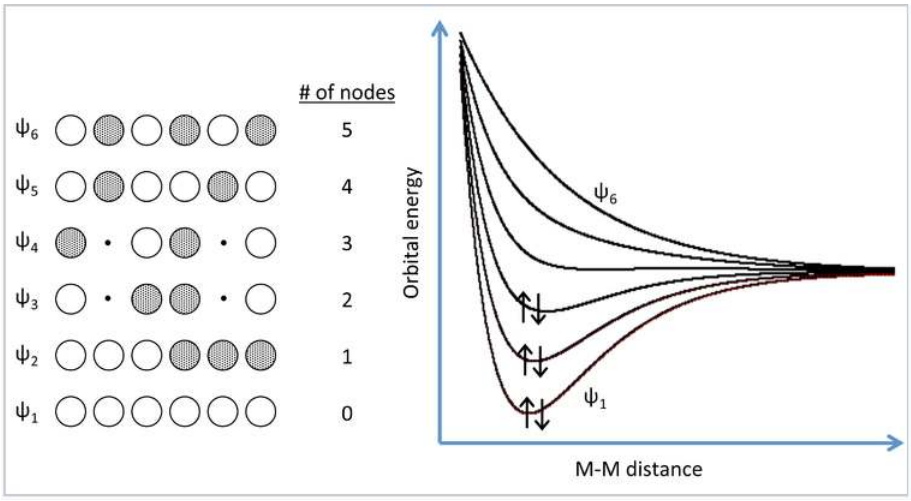
14.1: Bonding in Metals

The electron pair description of chemical bonds, which was the basis of the octet rule for p-block compounds, breaks down for metals. This is illustrated well by Na metal, the structure of which is shown at the left. Na has too few valence electrons to make electron pair bonds between each pair of atoms. We could think of the Na unit cell as having eight no-bond resonance structures in which only one Na-Na bond per cell contains a pair of electrons.



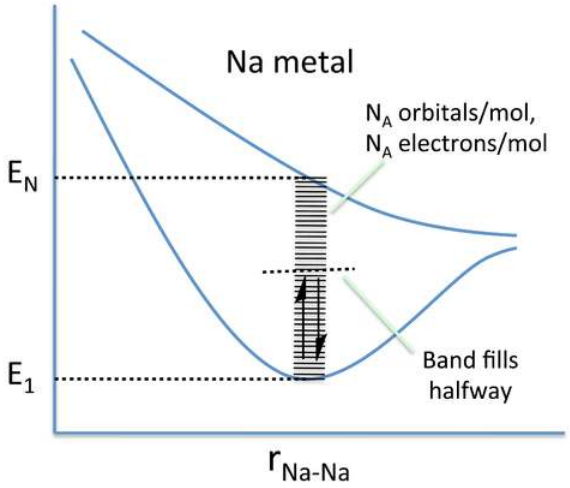
Sodium metal crystallizes in the body-centered cubic structure, in which each atom has eight nearest neighbors. Since the electronic configuration of Na is $[Ar]3s^1$, there are only two valence electrons per unit cell that are shared among eight Na-Na bonds. This means that the Na-Na bond order is 1/8 in Na metal.

A more realistic way to describe the bonding in metals is through **band theory**. The evolution of energy bands in solids from simple MO theory (Chapter 2) is illustrated at the right for a chain of six Na atoms, each of which has one 3s valence orbital and contributes one valence electron. In general, **n** atomic orbitals (in this case the six Na 3s orbitals) will generate **n** molecular orbitals with **n-1** possible nodes. In Chapter 2, we showed that the energy versus internuclear distance graph for a two hydrogen atom system has a low energy level and a high energy level corresponding to the bonding and antibonding molecular orbitals, respectively. These two energy levels were well separated from each other, and the two electrons in H_2 energetically prefer the lower energy level. If more atoms are introduced to the system, there will be a number of additional levels between the lowest and highest energy levels.



MO picture for a linear chain of six Na atoms. Three of the six MOs can accommodate all six valence electrons. Adding more atoms to the chain makes more molecular orbitals of intermediate energy, which eventually merge into a continuous band of orbitals. For Na, the 3s band is always half-filled because each MO can accommodate two electrons.

In band theory, the atom chain is extrapolated to a very large number - on the order of 10^{22} atoms in a crystal - so that the different combinations of bonding and anti-bonding orbitals create "bands" of possible energy states for the metal. In the language of physics, this approach of building the bands from discrete atomic orbitals is called the "tight-binding" approximation. The number of atoms is so large that the energies can be thought of as a continuum rather than a series of distinct levels. A metal will only partially fill this band, as there are fewer valence electrons than there are energy states to fill. In the case of Na metal, this results in a half-filled 3s band.



Nearly free electron model

In metals, the valence electrons are delocalized over many atoms. The total energy of each electron is given by the sum of its kinetic and potential energy:

$$E = KE + PE$$
$$E \approx p^2/2m + V$$

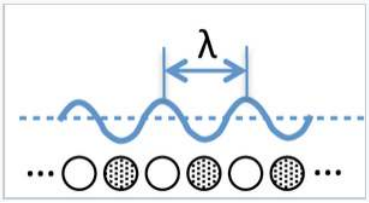
where **p** is the momentum of the electron (a vector quantity), m is its mass, and V is an average potential that the electron feels from the positive cores of the atoms. This potential holds the valence electrons in the crystal but, in the free electron model, is essentially uniform across the crystal.

Electron wavelength and wavenumber

What are the consequences of this model for band theory? For a hypothetical infinite chain (i.e., a 1D crystal) of Na atoms, the molecular orbitals at the bottom of the 3s band are fully bonding and the *wavelength* of electrons (2x the distance between nodes) in these orbitals is very long. At the top of the band, the highest orbital is fully antibonding and the wavelength is 2 times the distance between atoms (2a), since there is one node per atom. Remember that the **wavelength of an electron (λ)** is inversely proportional to its momentum p, according to the de Broglie relation **λ = h/p**.

For a (nearly) free electron, the kinetic energy can be expressed in terms of its wavelength, using $KE = p^2/2m$ and the de Broglie relation:

$$KE = \frac{p^2}{2m} = \frac{h^2}{2m\lambda^2} \tag{14.1.1}$$



We can think of the wavelength of an electron in a molecular orbital as twice the distance between nodes. If there are N atoms in a linear chain, the wavelength of the nth orbital is given by λ = 2Na/n, where a is the distance between atoms.

At this point, it is convenient to define the **wavenumber** of the electron as **k**, which has units of inverse length and is inversely proportional to λ. **k** is also directly proportional to the momentum **p**. Like **p**, **k** is a vector quantity. In a 1D crystal, **k** can be either positive or negative, corresponding to an electron moving to the left or right along the chain.

$$k = \frac{2\pi}{\lambda} = \frac{2\pi p}{h} \text{ where h is Planck's constant} \tag{14.1.2}$$

The most important property of **k** is that it is *directly proportional to the number of nodes* **n** in a molecular orbital within the band. For a 1D crystal of sodium atoms that contains **N** unit cells, each separated by a distance a, a molecular orbital with n nodes has a wavelength λ = 2Na/n and the wavenumber k = πn/Na. We can see from this definition that k = 0 at the bottom of the band (where λ is infinite) and k = π/a at the top of the band where the MO contains **N** nodes and λ = 2a.

Energies of orbitals in a metallic crystal

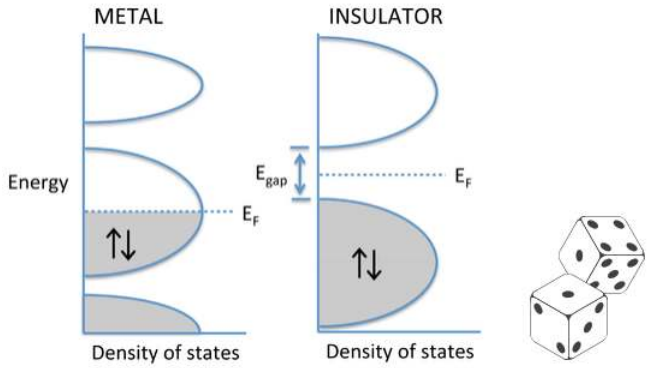
Electrons with long wavelengths do not "feel" the individual atoms in the lattice and so they behave as if they are *nearly free* (but confined to the crystal). Near the bottom of the band, the electron energy increases *parabolically* with the number of nodes (KE $\propto$ $\mathbf{n}^2$), since the momentum **p** is directly proportional to **n**. Because **p** is also directly proportional to **k**, we can write:

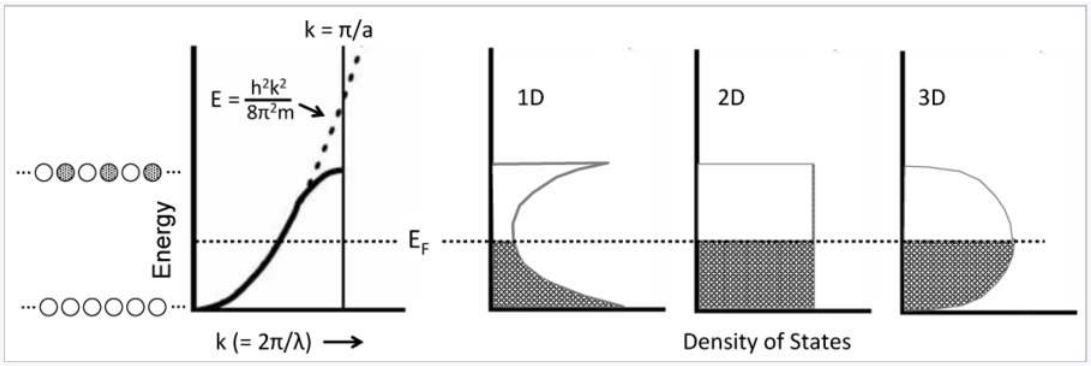
$$KE = \frac{p^2}{2m} = \frac{h^2k^2}{8\pi^2 m} \tag{14.1.3}$$

This parabolic relationship is followed as long as the electron wavelength is long compared to the distance between atoms. Near the top of the band, the wavelength becomes shorter and the electrons start to feel the positively charged atomic cores. In particular, the electrons prefer to have the maxima in their wavefunctions line up with the atomic cores, which is the most electrostatically favorable situation. The electron-atom attraction lowers the energy and causes the E vs. k curve to deviate from the parabolic behavior of a "free" electron as shown in the figure below.

Density of States (DOS)

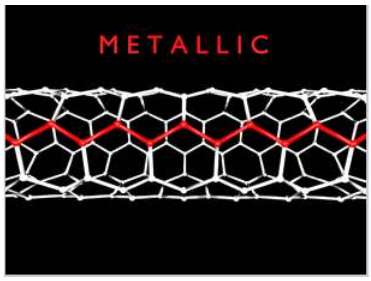
The density of states is defined as the number of orbitals per unit of energy within a band. Because of the parabolic relation between E and k, the density of states for a 1D metallic crystal is highest near the bottom and top of the energy band where the slope of the E vs. k curve is closest to zero. The shape of the DOS curve is different in crystals of higher dimensionality as shown in the figure in the left, because statistically there are more ways to make an orbital with N/2 nodes than there are with zero or N nodes. The situtation is analogous to the numbers you can make by rolling dice. With one die, the numbers 1-6 have equal probability. However, with two dice there is only one way to make a two (snake eyes) or a twelve (boxcars), but many ways to make a seven (a winner!).





Electrons in metals follow a parabolic dispersion curve, where the energy increases with the square of the wavenumber, k. Near the top of the band, the dispersion curve deviates from the parabolic dotted line. Because there is one MO for each value of k, the number of orbitals per unit energy (the density of states, DOS) is highest at the bottom and top of the band for a 1D chain of atoms. The density of states is constant with energy for a 2D crystal, and has a maximum in the middle of the band for a 3D crystal. At low temperature, all the MOs below the Fermi level E_F are occupied, and all the MOs above it are empty.

While most of the time we will talk about 3D crystals that have their maximum DOS near the middle of the energy band, there are examples of quasi-1D systems, such as carbon nanotubes. Metallic carbon nanotubes have strong optical absorption bands that correspond to transitions between the two regions of high DOS (the van Hove singularities) near the bottom and top of the bands.



Single-walled carbon nanotubes with "armchair" chirality are metallic and have characteristic sharp absorption bands in the infrared. Prof. Millie Dresselhaus (below) did foundational research on the electronic properties of carbon nanotubes and other low-dimensional conductors.

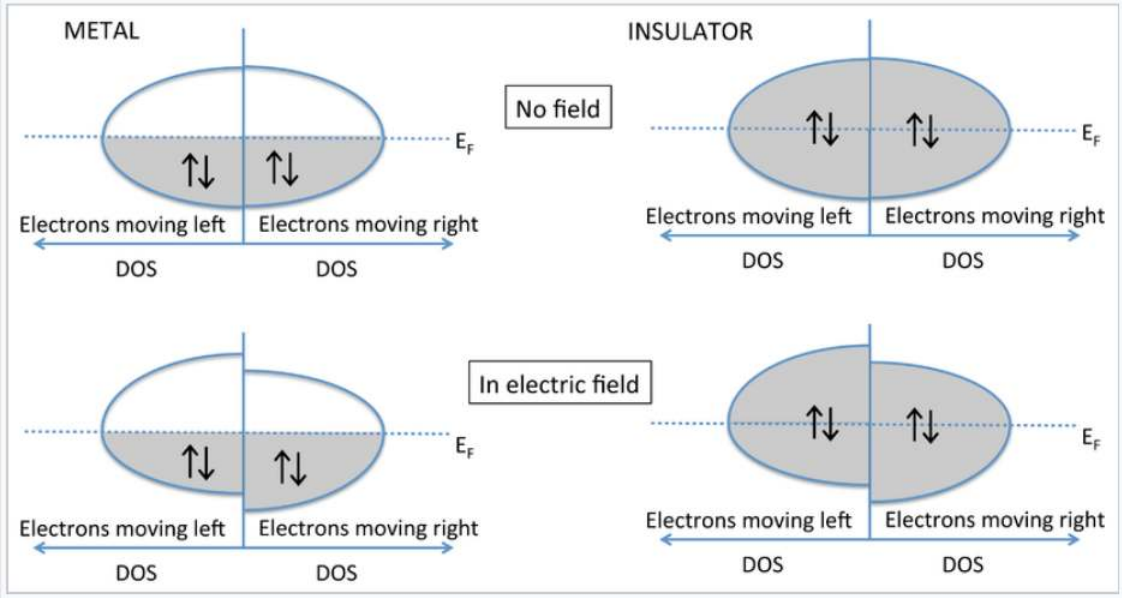


Metals, semiconductors, and insulators

The degree to which bands fill determines whether a crystalline solid is a metal, semiconductor, or insulator. If the highest occupied molecular orbitals lie within a band - i.e., if the Fermi level E_F cuts through a band of orbitals - then the electrons are free to change their speed and direction in an electric field and the solid is metallic. However, if the solid contains just enough electrons to completely fill a band, and the next highest set of molecular orbitals is empty, then it is a semiconductor or insulator. In this case, there is an energy gap between the filled and empty bands, which are called the valence and conduction bands, respectively. Although the distinction is somewhat arbitrary, materials with a large gap (> 3 eV) are called insulators, and those with smaller gaps are called semiconductors. We will learn more about the properties of semiconductors in Chapter 10.

Why don't insulators conduct electricity? The energy vs. DOS diagram below shows what happens when an electric field is applied to a metal or an insulator. In this case we have changed the diagram to show explicitly the energies of electrons moving left and right. These energies are the same in the absence of an electric field. Once we apply a field (e.g., by putting a voltage across a metal

wire), the electrons moving in the direction of the field have lower energy than those moving in the opposite direction. In the case of the metal, the populations of electrons moving with and against the electric field are different, and there is a net flow of current. Note that this can happen only when the Fermi level cuts through a partially filled band. With a semiconductor or insulator, the valence band is filled and the conduction band is empty. Applying an electric field changes the energies of electrons traveling with and against the field, but because the band is filled, the same number are going in both directions and there is no net current flow.



E vs. DOS diagrams comparing the behavior of metals and insulators in an applied electric field.

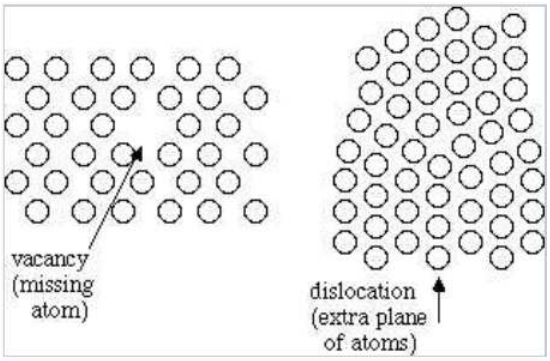
Note that in this picture, all the molecular orbitals extend over the entire crystal. The valence electrons are *delocalized*, even in the case of a semiconductor or insulator. However, there can be no net movement of electrons unless the band is partially filled.

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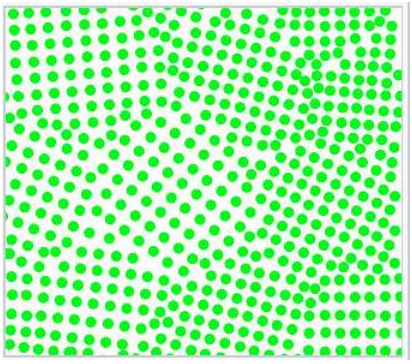
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14.2: Defects in Metallic Crystals

“Crystals are like people, it is the defects in them which tend to make them interesting!” - *Colin Humphreys.*



Metals, by virtue of their non-directional bonding, are more energetically tolerant of **defects** than are covalent network or ionic solids. Because there is no strong preference for one atomic position over another, the energy of a metallic crystal is not greatly impaired by the vacancy of a single atom or by the dislocation of a group of atoms. These kinds of "mistakes" in the packing of metal atoms within crystals are collectively called defects. The deformability of metals is the direct result of defects in the crystal structure. Defects in metals such as Al and Fe are responsible for the three orders of magnitude difference between the yield stress of annealed polycrystalline samples (i.e., normal articles of commerce) and perfect single crystals.



Grains and grain boundaries in a polycrystalline material

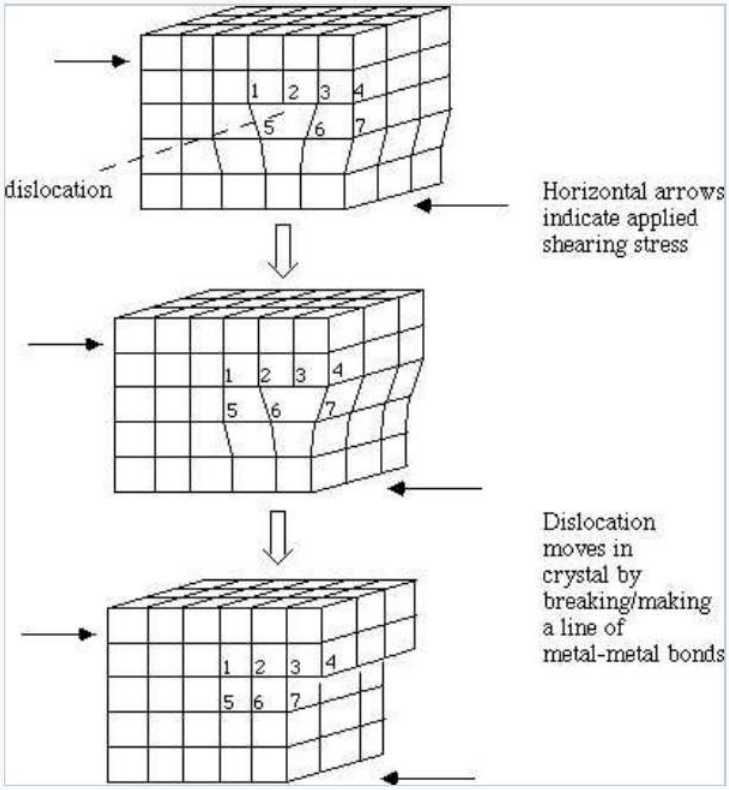
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14.3: Work Hardening, Alloying, and Annealing

One of the questions we would like to ask is, why are the yield stresses of normal (polycrystalline) metal samples so much lower (by a factor of 1000) than they are in perfect single crystals? The answer has to do with the motion of dislocations. Consider the picture below, which shows planes of metal atoms near a dislocation (the individual atoms are numbered to help you see which bonds are broken and which are formed). The arrows indicate force applied under shear stress. Notice how the dislocation moves by breaking/making metal-metal bonds.

The key point here is that we can induce plastic deformation (shear) by breaking only one line of metal-metal bonds at a time along the dislocation line. This involves far less force than breaking an entire plane of bonds, as we would need to do to shear a perfect crystal. In a given polycrystalline sample, there are many dislocation lines that run perpendicular to all possible shear directions, so their motion can be used to "tear" the metal apart. Turbine rotors on large jets are made of very expensive **single crystal** nickel-titanium alloys, so that these shearing deformations can be avoided.[1]



We can see that motion of dislocations is basically bad news if we want a metal to be strong and hard (e.g., if we want a structural material, or a knife that can hold a decent edge). There are several ways we can overcome (to some extent) this problem:

1. Use **single crystals** and anneal out all the dislocations (expensive - especially with large items like turbine blades, and impossible with very large items like airplane wings or bridges).

2. **Work hardening** of the metal - this moves all dislocations to grain boundaries (the dislocation essentially becomes part of the grain boundary). Since a grain boundary is a planar defect, it is much less responsive to stress than a line defect.

3. Introduce **impurity atoms** (that is alloying elements) or impurity phases that "pin" the motion of defects. An impurity atom stops the motion because it is a different size, or makes stronger bonds, than the other metal atoms; the line defect has a hard time moving away from rows of such atoms. An impurity phase (like Fe_3C in iron) makes extra grain boundaries that can stop the motion of defects. This effect is analogous to the graphite fibers in fiber-reinforced cross-linked polymers (used, e.g., in tennis rackets) that stop the propagation of cracks.

A simple illustration of work hardening can be done with a piece of copper wire. When struck many times with a hammer, the copper wire becomes stiffer, and it is possible to hang a weight from it. Dislocations move to the crystal grain boundaries during

work hardening, effectively halting their motion and at the same time making the individual crystal grains smaller. Because the crystal grains are now smaller, the amount of grain boundary area has increased, and with it the free energy of the material. Annealing reverses the process by lowering the free energy. When the wire is annealed in a flame (heated so that atoms can move and rearrange), the crystal grains grow, and the dislocations reappear. The copper again becomes ductile, and bends easily. Cold-working (work hardening) of metals is important for strengthening structural materials (e.g., iron beams) and for making brittle, hard edges (this is why blacksmiths hammer on knives and swords when they are making them. If you have ever watched them, they do the same thing to horseshoes, when they cool down, to make them stiff).



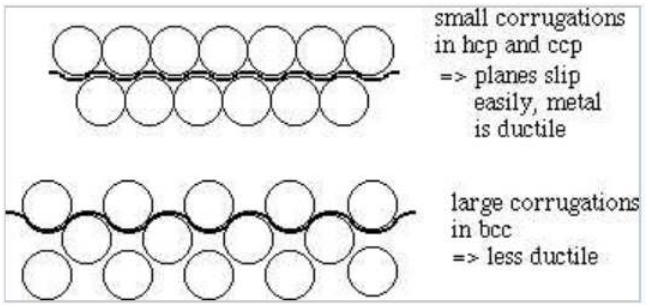
Blacksmith, 1606

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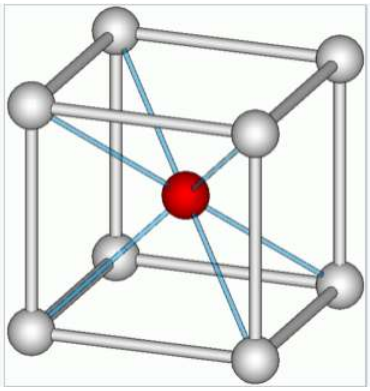
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14.4: Malleability of Metals and Alloys

Metals with close-packed structures (HCP and FCC) such as copper, gold, silver, zinc, magnesium, etc. are in general more malleable than those with the BCC structure (tungsten, vanadium, chromium, etc.). Why? In the close-packed structure, there is relatively little corrugation between sheets of metal atoms. This means that these planes can slip past each other relatively easily. In the BCC structure, there are no close-packed planes, and much greater corrugation between atoms at different levels. This makes it much harder for one row to slide past another.



This effect explains the hardness of alloys like brass (CuZn, which has the BCC structure), which are made by combining two soft metals (Cu and Zn, which are respectively FCC and HCP as pure metals, are both soft and ductile). Bronzes - originally made as alloys of copper and arsenic, but later as alloys of copper and tin - are harder than either of the constituent metals for the same reason.



The history of bronzes and brass dates to pre-historic times, with the earliest brasses made by smelting copper-zinc ores. In the Bronze Age, possession of these hard alloys provided a tactical advantage in warfare (see image at right), that was later supplanted when the technology for smelting iron was developed.



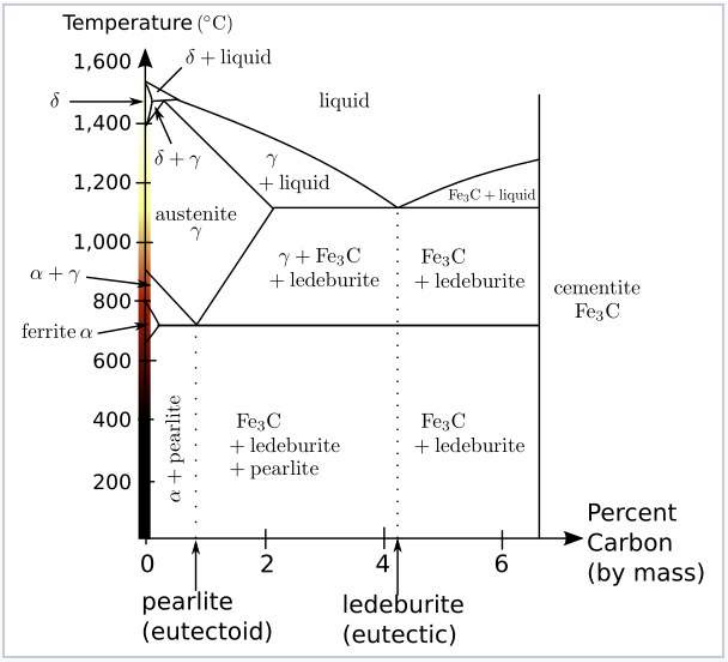
Bronze age weapons from Romania.

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14.5: Iron and Steel

One other very important place where the difference between the hardness of a BCC and a close-packed metal is important is in steelmaking. Between room temperature and 912°C, iron has the BCC structure, and is a tough, hard metal ("tough as nails"). Above 912°C, pure iron switches over to the FCC (austenite) structure, which is much more ductile. So hot iron can be bent and worked into a variety of shapes when it is very hot but still solid (it melts at 1535°C). Rapid quenching of hot iron - e.g., when the blacksmith plunges a red hot piece directly into cold water - cools it to room temperature, but doesn't allow time for the FCC --> BCC phase transition to occur; therefore, such pieces are still relatively malleable and can be shaped.



The iron–iron carbide (Fe–Fe_3C) phase diagram. Below 912 °C, pure iron exists as the alpha phase, ferrite, which has the BCC structure. Between 912 and 1,394 °C, pure iron exists as the gamma phase, austenite, which has the FCC structure. Carbon is more soluble in the FCC phase, which occupies area "γ" on the phase diagram, than it is in the BCC phase. The percent carbon determines the type of iron alloy that is formed upon cooling from the FCC phase, or from liquid iron: alpha iron, carbon steel (pearlite), or cast iron.

Carbon is added (about 1% by weight) to iron to make "carbon steel", which is a very hard material. Carbon is rather soluble in the FCC phase of iron, but not in the BCC phase. Therefore, when the ductile FCC phase cools and turns into BCC ("tempering" the steel, which means cooling it slowly enough so the FCC to BCC transformation can occur), the iron can no longer dissolve the excess carbon. The carbon forms layers or grains of an extra phase, Fe_3C ("cementite" - a very hard material) which are layered or dotted throughout the matrix of BCC iron grains. The effect of all these little grains of Fe_3C is to stop the motion of dislocations, making for a harder but (with higher carbon content) increasingly brittle material. This is why knives and swords are quenched from the FCC phase, cold worked into the appropriate shapes, and then heated up again and tempered (before they are sharpened) when they are made. Cast iron objects (frying pans, radiators, etc) have a higher carbon content and are therefore very strong, but tend to fracture rather than bend because of the larger fraction of the brittle Fe_3C phase in the alloy.

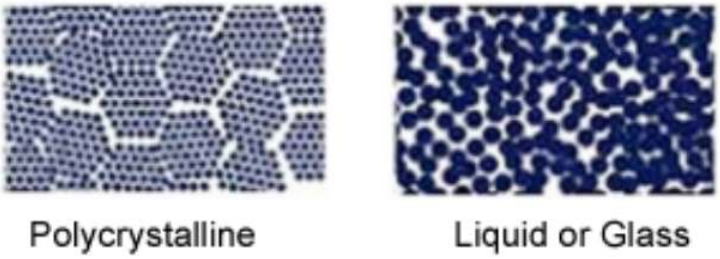


Upon cooling, high carbon steels phase segregate into a mixture of bcc iron (light gray) and Fe3C (dark gray) microscopic grains.

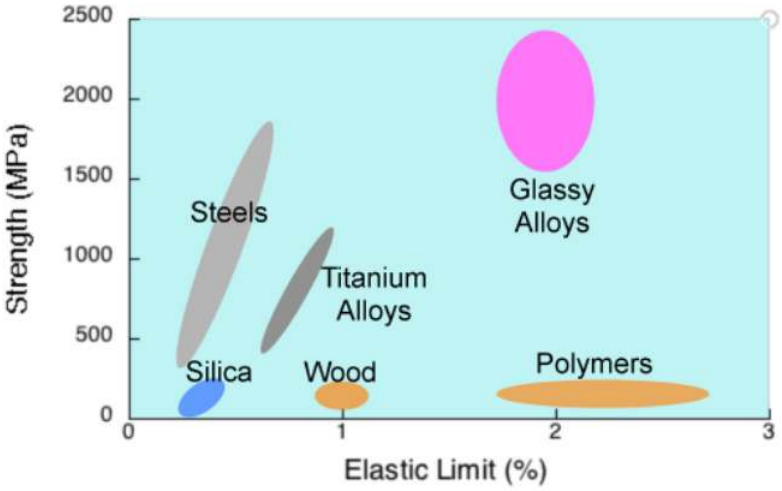
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14.6: Amorphous Alloys



Alloys of metals with more complex stoichiometries can be made in amorphous form by slower cooling from the melt. These alloys have been prepared and studied since the 1960s, and since the 1990s amorphous alloys have been discovered that can be prepared in bulk form at cooling rates on the order of 1 deg/s, similar to the cooling rates of other kinds of glasses.



Currently amorphous metals (marketed under the tradenames Vitreloy and Liquidmetal) are used commercially in golf clubs, watches, USB flash drives, and other applications where very high elasticity, yield strength, and/or wear resistance are needed.

Year	Alloy	Cooling Rate (K/s)
1960	$Au_{75}Si_{24}$	10^6 - thin films & ribbons[3]
1969	Pd-Cu-Si	100-1000
1980s	La-Al-Cu & others	1-100
1990s	Zr-Ti-Cu-Ni-Be	~1 (similar to oxide glasses)

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CHAPTER OVERVIEW

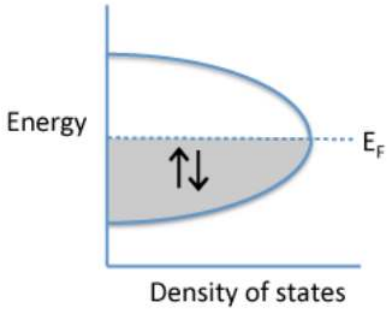
15: Conductivity and Magnetism

15.1: Conduction in Metals
15.2: Semiconductors- Band Gaps, Colors, Conductivity and Doping
15.3: Semiconductor p-n Junctions
15.4: Diodes, LEDs and Solar Cells
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15.1: Conduction in Metals

In metals, the valence electrons are in molecular orbitals that extend over the entire crystal lattice. As we will learn in Chapter 7, metals are almost always crystalline and the individual crystal grains are typically micron size. This means that the spatial extent of the orbitals is *very large* compared to the size of the atoms or the unit cell. The diagram at the left shows a generic plot of electron energy vs. density of states for a metal such as Na, Cu, or Ag. In these cases, there are N orbitals for N electrons, and each orbital can accommodate two electrons. Therefore the Fermi level, which corresponds to the energy of the highest occupied MO at zero temperature, is somewhere in the middle of the band of orbitals. The energy level spacing between orbitals is very small compared to the thermal energy kT, so we can think of the orbitals as forming a continuous band.



Classically, if the electrons in this band were free to be thermally excited, we would expect them to have a specific heat of 3R per mole of electrons. However, experimentally we observe that C_p is only about 0.02 R per mole. This suggests that *only about 1%* of the electrons in the metal can be thermally excited at room temperature. However, essentially *all* of the valence electrons are free to move in the crystal and contribute to electrical conduction. To understand this apparent paradox, we need to recall that the electrons exist in *quantized energy levels.*

Because of quantization, electrons in metals have a Fermi-Dirac distribution of energies. In this distribution, most of the electrons are spin-paired, although the individual electrons in these pairs can be quite far apart since the orbitals extend over the entire crystal. A relatively small number of electrons at the top of the Fermi sea are unpaired by thermal excitation. This is the origin of the Pauli paramagnetism of metals.

How fast are electrons traveling in a typical metal? Because of the bell shape of the E vs. DOS curve, most of the electrons have $E \approx E_F$. At the midpoint energy (E_F) of the band, the MO's have one node for every two atoms. We can calculate the de Broglie wavelength as twice the distance between nodes and thus:

> $\lambda = \mathbf{4a}$ at the midpoint of the band.

where **a** is the interatomic spacing. Since a typical value of **a** is about 2 Å, we obtain the **de Broglie wavelength λ ≈ 8 Å**.

Using the de Broglie relation p = h/λ, we can write:

$$\mathbf{p} = \frac{\mathbf{h}}{\lambda} = \mathbf{m_e v_F} \tag{15.1.1}$$

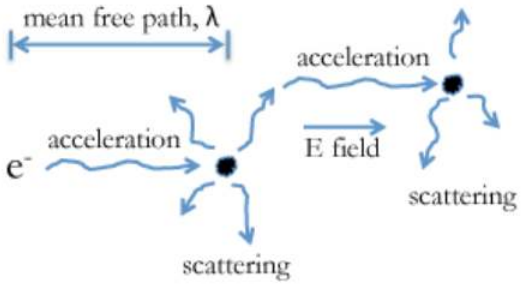
where $\mathbf{m_e}$ is the mass of the electron and $\mathbf{v_F}$ is the velocity of electrons with energy E_F.

Solving for $V_F = \frac{h}{m_e \lambda}$ we obtain $\mathbf{v_F} = \frac{(6.62\times10^{-34}\,Js)}{(9.1\times10^{-31}\,kg)(8\times10^{-10}\,m)} = \mathbf{1.0 \times 10^6 m/s}$

Experimental values of v_F are 1.07 x 10^6 and 1.39 x 10^6 m/s for Na and Ag, respectively, so our approximations are pretty good.

How fast are electrons moving in metals? Really, really fast!! **1,000,000 meters per second!** This is about 1/300 the speed of light, and about 3000 times the speed of sound in air (3 x 10^2 m/s).

However, the **drift velocity** of electrons in metals - the speed at which electrons move in applied electric field - is quite slow, on the order of 0.0001 m/s, or .01 cm/s. You can easily outrun an electron drifting in a metal, even if you have been drinking all night and have been personally reduced to a very slow crawl.



In order to understand the great disparity between the Fermi velocity and the drift velocity of electrons in metals, we need to consider a picture for the scattering of electrons, and their acceleration in an electric field, as shown at the left. If we apply a voltage across a metal (e.g., a metal wire), the electrons are subjected to an electric field **E**, which is the voltage divided by the length of the wire. This electric field exerts a force on the electron, causing it to accelerate. However, the electron is frequently scattered, mostly by phonons (lattice vibrations). Each time the electron is scattered its acceleration starts all over again. The time between scattering events is **τ** and the distance the electrons travel between scattering events is the **mean free path**, **λ**. (Note that this is NOT the same λ as the de Broglie wavelength, they just unfortunately have the same symbol!)

We can write the force on the electron as:

$$\mathbf{F = eE = m_e a = \frac{m_e v_{drift}}{\tau}} \tag{15.1.2}$$

In this equation, **a** is the acceleration in the electric field, $\mathbf{m_e}$ is the mass, and v_{drift} is the **drift velocity** of the electron.

Experimentally, the mean free path is typically obtained by measuring the scattering time. For an electron in Cu metal at 300 K, the scattering time τ is about 2 x 10^{-14} s. From this we can calculate the mean free path as:

$$\lambda = \mathbf{v_{avg}}\tau \approx \mathbf{v_F}\tau = (1 \times 10^6 m/s)(2 \times 10^{-14}) = \mathbf{40nm} \tag{15.1.3}$$

The mean free path (40 nm = 400 Å) is quite long compared to the interatomic spacing (2 Å). To put it in perspective, if the interatomic spacing were scaled to the length of a football (0.3 m), the mean free path would be over half the length of the football field (60 m). Thus an electron travels a fairly long way between scattering events and scarcely notices the atomic structure of the metal in which it is traveling.

To summarize, electrons are traveling in metals at the Fermi velocity v_F, which is very, very fast (10^6 m/s), but the flux of electrons is the same in all directions. That is, they are *going nowhere fast*. In an electric field, a very small but directional *drift velocity* is superimposed on this fast random motion of valence electrons.

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For ordinary metals, the mean free path of a valence electron (λ) is quite long relative to the interatomic spacing, represented in this analogy as the length of a football.

We can calculate the drift velocity of electrons as the acceleration in the electric field times the scattering time:

From F = ma, we obtain the acceleration (a) as:

$$\mathbf{a} = \frac{\mathbf{F}}{\mathbf{m_e}} = \frac{\mathbf{eE}}{\mathbf{m_e}} \tag{15.1.4}$$

And thus,

$$\mathbf{v_{drift}} = \mathbf{a}\tau = \frac{\mathbf{eE}\tau}{\mathbf{m_e}} \tag{15.1.5}$$

If we divide both sides of this equation by the magnitude of the electric field (**E**), we obtain the **mobility (μ)**:

$$\mu = \frac{\mathbf{v_{drift}}}{\mathbf{E}} = \frac{\mathbf{e}\tau}{\mathbf{m_e}} \tag{15.1.6}$$

μ has units of velocity/field = cm/s / V/cm = cm^2/Vs

An important consequence of the calculation of v_{drift} is **Ohm's Law**, V = iR. From the equations above, we can see that the drift velocity increases linearly with the applied electric field. The drift velocity (cm/s) is proportional to the current (i, coul/s), and the electric field (E, V/cm) is proportional to the voltage (V):

$$\mathbf{Current\ (i)} = \mathbf{nev_{drift}} \times \mathbf{area} \tag{15.1.7}$$

$$\mathbf{Voltage\ (V)} = \mathbf{E} \times \mathbf{length} \tag{15.1.8}$$

Here **n** is the density of valence electrons (#/cm^3) and **e** is the charge of the electron (coul). Combining these equations with our equation for v_{drift} we obtain:

$$V = i(\frac{m_e}{ne^2\tau})\frac{(}{length}area) = iR \tag{15.1.9}$$

Thus, V = iR, where R is the combination of the two terms in parentheses. The first of these is the **resistivity**, ρ, and the second is a geometrical factor.

The **conductivity (σ)** of a metal, which is the inverse of ρ, is proportional to μ, which in turn is proportional to τ (and λ):

$$\sigma = \mathbf{ne}\mu = \frac{\mathbf{ne^2}\tau}{\mathbf{m_e}} \tag{15.1.10}$$

We can use this equation to work out the conductivity of a specific metal (Cu), for which n = 8.5 x 10^{22} cm^{-3} and τ = 2 x 10^{-14} s. Putting in the numbers for m_e and e, we obtain σ = 7 x 10^5 Ω^{-1} cm^{-1} for Cu, in good agreement with the measured value (6 x 10^5 $\Omega^{-1}cm^{-1}$).

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15.2: Semiconductors- Band Gaps, Colors, Conductivity and Doping

Semiconductors, as we noted above, are somewhat arbitrarily defined as insulators with **band gap energy ≤ 3.0 eV** (~290 kJ/mol). This cutoff is chosen because, as we will see, the conductivity of undoped semiconductors drops off exponentially with the band gap energy and at 3.0 eV it is very low. Also, materials with wider band gaps (e.g. $SrTiO_3$, E_{gap} = 3.2 eV) do not absorb light in the visible part of the spectrum

There are a number of places where we find semiconductors in the periodic table:

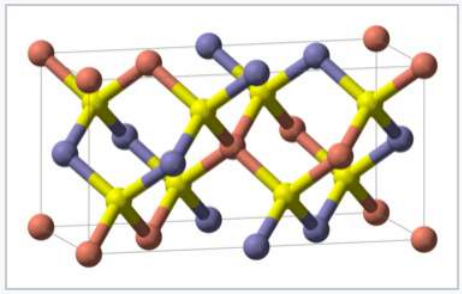
- Early transition metal oxides and nitrides, especially those with d^0 electron counts such as TiO_2, TaON, and WO_3
- Oxides of later 3d elements such as Fe_2O_3, NiO, and Cu_2O
- Layered transition metal chalcogenides with d^0, d^2 and d^6 electron counts including TiS_2, ZrS_2, MoS_2, WSe_2, and PtS_2
- d^{10} copper and sliver halides, e.g., CuI, AgBr, and AgI
- Zincblende- and wurtzite-structure compounds of the p-block elements, especially those that are isoelectronic with Si or Ge, such as GaAs and CdTe. While these are most common, there are other p-block semiconductors that are not isoelectronic and have different structures, including GaS, PbS, and Se.



A 2" wafer cut from a GaAs single crystal. GaAs, like many p-block semiconductors, has the zincblende structure.

The **p-block octet semiconductors** are by far the most studied and important for technological applications, and are the ones that we will discuss in detail.

Zincblende- and wurtzite-structure semiconductors have 8 valence electrons per 2 atoms. These combinations include 4-4 (Si, Ge, SiC,…), 3-5 (GaAs, AlSb, InP,…), 2-6 (CdSe, HgTe, ZnO,…), and 1-7 (AgCl, CuBr,…) semiconductors. Other variations that add up to an octet configuration are also possible, such as $Cu^{I}In^{III}Se_2$, which has the **chalcopyrite** structure, shown at the right.



The **chalcopyrite structure** is adopted by ABX_2 octet semiconductors such as $Cu^{I}In^{III}Se_2$ and $Cd^{II}Sn^{IV}P_2$. The unit cell is doubled relative to the parent **zincblende structure** because of the ordered arrangement of cations. Each anion (yellow) is coordinated by two cations of each type (blue and red).

How does the **band gap energy** vary with **composition**? There are two important trends

(1) Going **down a group** in the periodic table, the gap **decreases**:

C (diamond) > Si > Ge > α-Sn

E_{gap} (eV): 5.4 1.1 0.7 0.0

This trend can be understood by recalling that E_{gap} is related to the **energy splitting between bonding and antibonding orbitals**. This difference decreases (and bonds become weaker) as the principal quantum number increases.

(2) For isoelectronic compounds, **increasing ionicity** results in a **larger band gap**.

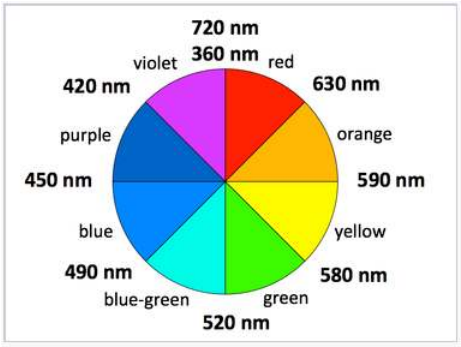
Ge < GaAs < ZnSe
0.7 1.4 2.8 eV

Sn < InSb < CdTe < AgI
0.0 0.2 1.6 2.8 eV

This trend can also be understood from a simple MO picture, as we discussed in Ch. 2. As the electronegativity difference $\Delta\chi$ increases, so does the energy difference between bonding and antibonding orbitals.

The band gap is a very important property of a semiconductor because it determines its color and conductivity. Many of the applications of semiconductors are related to band gaps:

- Narrow gap materials ($Hg_xCd_{1-x}Te$, VO_2, InSb, Bi_2Te_3) are used as infrared photodetectors and thermoelectrics (which convert heat to electricity).
- Wider gap materials (Si, GaAs, GaP, GaN, CdTe, $CuIn_xGa_{1-x}Se_2$) are used in electronics, light-emitting diodes, and solar cells.



Color wheel showing the colors and wavelengths of emitted light.

Semiconductor solid solutions such as $GaAs_{1-x}P_x$ have band gaps that are intermediate between the end member compounds, in this case GaAs and GaP (both zincblende structure). Often, there is a linear relation between composition and band gap, which is referred to as **Vegard's Law**. This "law" is often violated in real materials, but nevertheless offers useful guidance for designing materials with specific band gaps. For example, red and orange light-emitting diodes (LED's) are made from solid solutions with compositions of $GaP_{0.40}As_{0.60}$ and $GaP_{0.65}As_{0.35}$, respectively. Increasing the mole fraction of the lighter element (P) results in a larger band gap, and thus a higher energy of emitted photons.

Colors of semiconductors

The color of absorbed and emitted light both depend on the band gap of the semiconductor. Visible light covers the range of approximately 390-700 nm, or 1.8-3.1 eV. The **color of emitted light** from an LED or semiconductor laser corresponds to the band gap energy and can be read off the color wheel shown at the right.



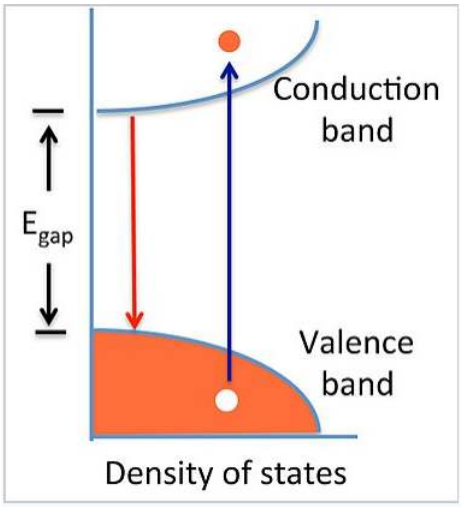
Fe_2O_3 powder is reddish orange because of its 2.2 eV band gap

The color of **absorbed light** includes the band gap energy, but also all colors of higher energy (shorter wavelength), because electrons can be excited from the valence band to a range of energies in the conduction band. Thus semiconductors with band gaps in the infrared (e.g., Si, 1.1 eV and GaAs, 1.4 eV) appear black because they absorb all colors of visible light. Wide band gap semiconductors such as TiO_2 (3.0 eV) are white because they absorb only in the UV. Fe_2O_3 has a band gap of 2.2 eV and thus absorbs light with $\lambda < 560$ nm. It thus appears reddish-orange (the colors of light reflected from Fe_2O_3) because it absorbs green, blue, and violet light. Similarly, CdS (E_{gap} = 2.6 eV) is yellow because it absorbs blue and violet light.

Electrons and holes in semiconductors

Pure (undoped) semiconductors can conduct electricity when electrons are promoted, either by heat or light, from the valence band to the conduction band. The promotion of an **electron** (e^-) leaves behind a **hole** (h^+) in the valence band. The hole, which is the absence of an electron in a bonding orbital, is also a mobile charge carrier, but with a positive charge. The motion of holes in the lattice can be pictured as analogous to the movement of an empty seat in a crowded theater. An empty seat in the middle of a row can move to the end of the row (to accommodate a person arriving late to the movie) if everyone moves over by one seat. Because the movement of the hole is in the opposite direction of electron movement, it acts as a positive charge carrier in an electric field.

The opposite process of excitation, which creates an electron-hole pair, is their recombination. When a conduction band electron drops down to recombine with a valence band hole, both are annihilated and energy is released. This release of energy is responsible for the emission of light in LEDs.



An electron-hole pair is created by adding heat or light energy $E \geq E_{gap}$ to a semiconductor (blue arrow). The electron-hole pair recombines to release energy equal to E_{gap} (red arrow).

At equilibrium, the creation and annihilation of electron-hole pairs proceed at equal rates. This dynamic equilibrium is analogous to the dissociation-association equilibrium of H^+ and OH^- ions in water. We can write a mass action expression:

$$n \times p = K_{eq} = n_i^2$$

where n and p represent the number density of electrons and holes, respectively, in units of cm^{-3}. The intrinsic carrier concentration, n_i, is equal to the number density of electrons or holes in an undoped semiconductor, where $n = p = n_i$.

Note the similarity to the equation for water autodissociation:

$[H^+][OH^-] = K_w$

By analogy, we will see that when we increase n (e.g., by doping), p will decrease, and vice-versa, but their product will remain constant at a given temperature.

Temperature dependence of the carrier concentration. Using the equations $K_{eq} = e^{(\frac{-\Delta G^o}{RT})}$ and $\Delta G^o = \Delta H^o - T\Delta S^o$, we can write:

$$n \times p = n_i^2 = e^{(\frac{\Delta S^o}{R})} e^{(\frac{-\Delta H^o}{RT})} \tag{15.2.1}$$

The entropy change for creating electron hole pairs is given by:

$$\Delta S^o = Rln(N_V) + Rln(N_V) = Rln(N_C N_V) \tag{15.2.2}$$

where N_V and N_C are the effective density of states in the valence and conduction bands, respectively.

and thus we obtain

$$n_i^2 = N_C N_V e^{(-\Delta H^o RT)} \tag{15.2.3}$$

Since the volume change is negligible, $\Delta H^o \approx \Delta E^o$, and therefore $\frac{\Delta H^o}{R} \approx \frac{E_{gap}}{k}$, from which we obtain

$$n_i^2 = N_C N_V e^{(\frac{-E_{gap}}{kT})} \tag{15.2.4}$$

and finally

$$\mathbf{n = p = n_i = (N_C N_V)^{\frac{1}{2}} e^{(\frac{-E_{gap}}{2kT})}} \tag{15.2.5}$$

For pure Si (E_{gap} = 1.1 eV) with N ≈ $10^{22}/cm^3$, we can calculate from this equation a carrier density n_i of approximately $10^{10}/cm^3$ at 300 K. This is about 12 orders of magnitude lower than the valence electron density of Al, the element just to the left of Si in the periodic table. Thus we expect the conductivity of pure semiconductors to be many orders of magnitude lower than those of metals.

Conductivity of intrinsic semiconductors

The conductivity (σ) is the product of the number density of carriers (n or p), their charge (e), and their mobility (μ). Recall from Chapter 6 that μ is the ratio of the carrier drift velocity to the electric field and has units of cm^2/Volt-second. Typically electrons and holes have somewhat different mobilities (μ_e and μ_h, respectively) so the conductivity is given by:

$$\sigma = ne\mu_e + pe\mu_h \tag{15.2.6}$$

For either type of charge carrier, we recall from Ch. 6 that the mobility μ is given by:

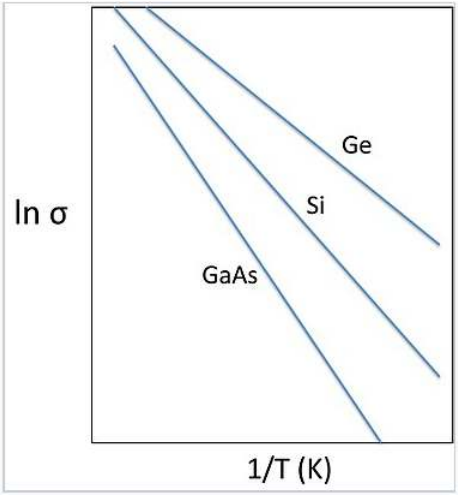
$$\mu = \frac{v_{drift}}{E} = \frac{e\tau}{m} \tag{15.2.7}$$

where e is the fundamental unit of charge, τ is the scattering time, and m is the effective mass of the charge carrier.

Taking an average of the electron and hole mobilities, and using n = p, we obtain

$$\sigma = \sigma_o \mathbf{e}^{(\frac{-E_{gap}}{2kT})},\ where\ \sigma_o = 2(N_C N_V)^{\frac{1}{2}} e\mu \tag{15.2.8}$$

By measuring the conductivity as a function of temperature, it is possible to obtain the activation energy for conduction, which is $E_{gap}/2$. This kind of plot, which resembles an Arrhenius plot, is shown at the right for three different undoped semiconductors. The slope of the line in each case is $-E_{gap}/2k$.

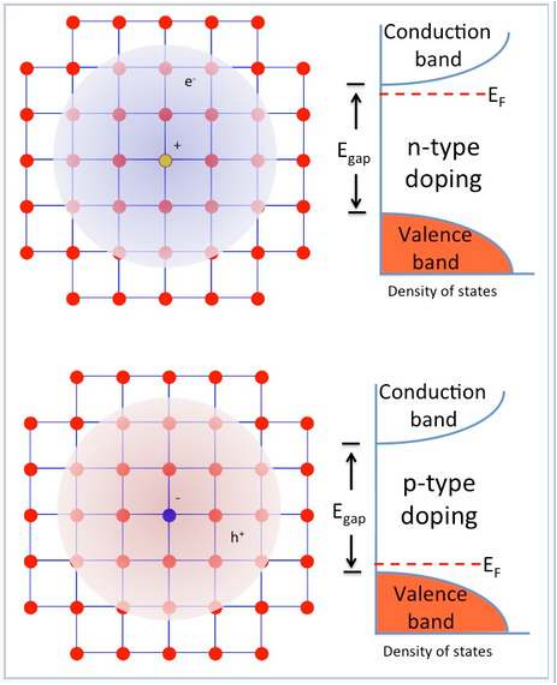


Plots of ln(σ) vs. inverse temperature for intrinsic semiconductors Ge (E_{gap} = 0.7 eV), Si (1.1 eV) and GaAs (1.4 eV). The slope of the line is $-E_{gap}/2k$.

Doping of semiconductors. Almost all applications of semiconductors involve controlled **doping**, which is the substitution of impurity atoms, into the lattice. Very small amounts of dopants (in the parts-per-million range) dramatically affect the conductivity of semiconductors. For this reason, very pure semiconductor materials that are carefully doped - both in terms of the concentration and spatial distribution of impurity atoms - are needed.

n- and p-type doping. In crystalline Si, each atom has four valence electrons and makes four bonds to its neighbors. This is exactly the right number of electrons to completely fill the valence band of the semiconductor. Introducing a phosphorus atom into the lattice (the positively charged atom in the figure at the right) adds an extra electron, because P has five valence electrons and only needs four to make bonds to its neighbors. The extra electron, at low temperature, is bound to the phosphorus atom in a hydrogen-like molecular orbital that is much larger than the 3s orbital of an isolated P atom because of the high dielectric constant of the semiconductor. In silicon, this "expanded" Bohr radius is about 42 Å, i.e., 80 times larger than in the hydrogen atom. The energy needed to ionize this electron – to allow it to move freely in the lattice - is only about 40–50 meV, which is not much larger the thermal energy (26 meV) at room temperature. Therefore the Fermi level lies just below the conduction band edge, and a large fraction of these extra electrons are promoted to the conduction band at room temperature, leaving behind fixed positive charges on the P atom sites. The crystal is **n-doped**, meaning that the majority carrier (electron) is negatively charged.

Alternatively, boron can be substituted for silicon in the lattice, resulting in **p-type** doping, in which the majority carrier (hole) is positively charged. Boron has only three valence electrons, and "borrows" one from the Si lattice, creating a positively charged hole that exists in a large hydrogen-like orbital around the B atom. This hole can become delocalized by promoting an electron from the valence band to fill the localized hole state. Again, this process requires only 40–50 meV, and so at room temperature a large fraction of the holes introduced by boron doping exist in delocalized valence band states. The Fermi level (the electron energy level that has a 50% probability of occupancy at zero temperature) lies just above the valence band edge in a p-type semiconductor.



n- and p-type doping of semiconductors involves substitution of electron donor atoms (light orange) or acceptor atoms (blue) into the lattice. These substitutions introduce extra electrons or holes, respectively, which are easily ionized by thermal energy to become free carriers. The Fermi level of a doped semiconductor is a few tens of mV below the conduction band (n-type) or above the valence band (p-type).

As noted above, the doping of semiconductors dramatically changes their conductivity. For example, the intrinsic carrier concentration in Si at 300 K is about 10^{10} cm^{-3}. The mass action equilibrium for electrons and holes also applies to doped semiconductors, so we can write:

$$n \times p = n_i^2 = 10^{20} cm^{-6} \; at \; 300K \tag{15.2.9}$$

If we substitute P for Si at the level of one part-per-million, the concentration of electrons is about 10^{16} cm^{-3}, since there are approximately 10^{22} Si atoms/cm^3 in the crystal. According to the mass action equation, if n = 10^{16}, then p = 10^4 cm^{-3}. There are three consequences of this calculation:

- The density of carriers in the doped semiconductor (10^{16} cm^{-3}) is much higher than in the undoped material (~10^{10} cm^{-3}), so the conductivity is also many orders of magnitude higher.
- The activation energy for conduction is only 40–50 meV, so the conductivity does not change much with temperature (unlike in the intrinsic semiconductor)
- The minority carriers (in this case holes) do not contribute to the conductivity, because their concentration is so much lower than that of the majority carrier (electrons).

Similarly, for p-type materials, the conductivity is dominated by holes, and is also much higher than that of the intrinsic semiconductor.

Chemistry of semiconductor doping. Sometimes it is not immediately obvious what kind of doping (n- or p-type) is induced by "messing up" a semiconductor crystal lattice. In addition to substitution of impurity atoms on normal lattice sites (the examples given above for Si), it is also possible to dope with vacancies - missing atoms - and with interstitials - extra atoms on sites that are not ordinarily occupied. Some simple rules are as follows:

- For substitutions, adding an **atom to the right** in the periodic table results in **n-type** doping, and an atom to the **left** in **p-type** doping.

  For example, when TiO_2 is doped with Nb on some of the Ti sites, or with F on O sites, the result is n-type doping. In both cases, the impurity atom has one more valence electron than the atom for which it was substituted. Similarly, substituting a small amount of Zn for Ga in GaAs, or a small amount of Li for Ni in NiO, results in p-type doping.

- **Anion vacancies** result in **n-type** doping, and **cation vacancies** in **p-type** doping.

  Examples are anion vacancies in CdS_{1-x} and WO_{3-x}, both of which give n-type semiconductors, and copper vacancies in $Cu_{1-x}O$, which gives a p-type semiconductor.

- **Interstitial cations** (e.g. Li) donate electrons to the lattice resulting in **n-type** doping. Interstitial anions are rather rare but would result in p-type doping.

Sometimes, there can be both p- and n-type dopants in the same crystal, for example B and P impurities in a Si lattice, or cation and anion vacancies in a metal oxide lattice. In this case, the two kinds of doping **compensate** each other, and the doping type is determined by the one that is in higher concentration. A dopant can also be present on more than one site. For example, Si can occupy both the Ga and As sites in GaAs, and the two substitutions compensate each other. Si has a slight preference for the Ga site, however, resulting in n-type doping.

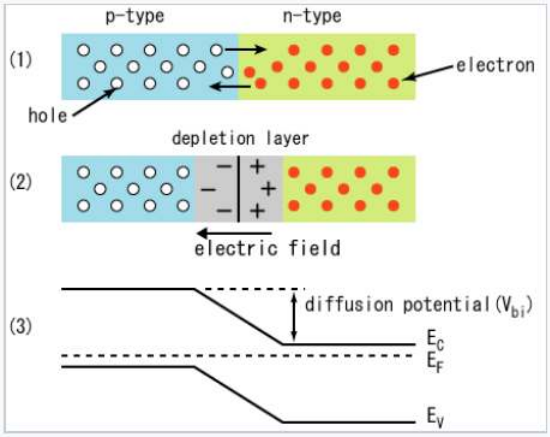
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15.3: Semiconductor p-n Junctions

Semiconductor p-n junctions are important in many kinds of electronic devices, including diodes, transistors, light-emitting diodes, and photovoltaic cells. To understand the operation of these devices, we first need to look at what happens to electrons and holes when we bring p-type and n-type semiconductors together. At the junction between the two materials, mobile electrons and holes annihilate each other, leaving behind the fixed + and - charges of the electron donor and electron acceptor dopants, respectively. For example, on the n-side of a silicon p-n junction, the positively charged dopants are P^+ ions and on the p-side the negatively charged dopants are B^-. The presence of these uncompensated electrical charges creates an electric field, the **built-in field** of the p-n junction. The region that contains these charges (and a very low density of mobile electrons or holes) is called the **depletion region**.

The electric field, which is created in the depletion region by electron-hole recombination, repels both the electrons (on the n-side) and holes (on the p-side) away from the junction. The concentration gradient of electrons and holes, however, tends to move them in the opposite direction by diffusion. At equilibrium, the flux of mobile carriers is zero because the field-driven migration flux is equal and opposite to the concentration-driven diffusion flux.



When p-type and n-type semiconductors are joined, electrons and holes are annihilated at the interface, leaving a depletion region that contains positively and negatively charged donor and acceptor atoms, respectively. At equilibrium, the Fermi level (E_F) is uniform throughout the junction. E_F lies just above the valence band on the p-type side of the junction and just below the conduction band on the n-type side.

The width of the depletion layer depends on the screening length in the semiconductor, which in turn depends on the dopant density. At high doping levels, the depletion layer is narrow (tens of nanometers across), whereas at low doping density it can be as thick as 1 µm. The depletion region is the only place where the electric field is nonzero, and the only place where the bands bend. Elsewhere in the semiconductor the field is zero and the bands are flat.

In the middle of p-n junction, the Fermi level energy, E_F, is halfway between the valence band, VB, and the conduction band, CB, and the semiconductor is intrinsic ($n = p = n_i$)

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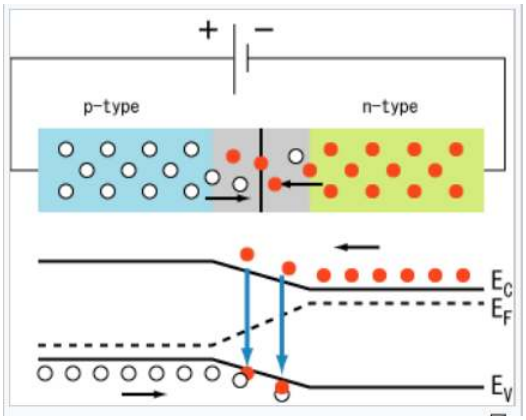
15.4: Diodes, LEDs and Solar Cells

Diodes are semiconductor devices that allow current to flow in only one direction. Diodes act as rectifiers in electronic circuits, and also as efficient light emitters (in LEDs) and solar cells (in photovoltaics). The basic structure of a diode is a junction between a p-type and an n-type semiconductor, called a p-n junction. Typically, diodes are made from a single semiconductor crystal into which p- and n- dopants are introduced.



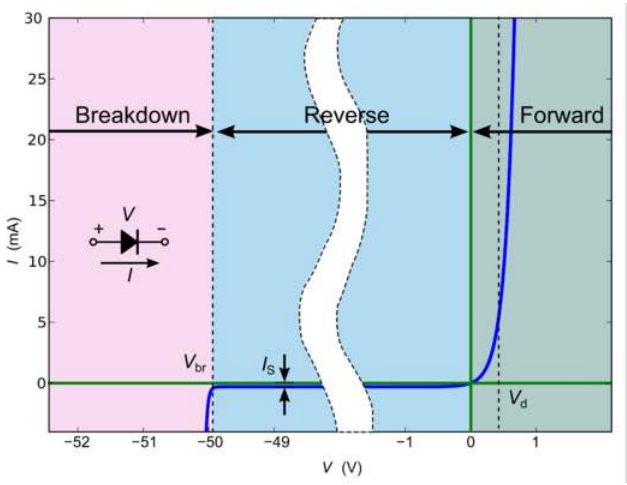
Closeup of a diode, showing the square-shaped semiconductor crystal *(black object on left)* (John Maushammer, Wikipedia, CC-BY-SA)

If the n-side of a diode is biased at positive potential and the p-side is biased negative, electrons are drawn to the n-side and holes to the p-side. This reinforces the built in potential of the p-n junction, the width of the depletion layer increases, and very little current flows. This polarization direction is referred to as "back bias." If the diode is biased the other way, carriers are driven into the junction where they recombine. The electric field is diminished, the bands are flattened, and current flows easily since the applied bias lowers the built-in potential. This is called "forward bias."



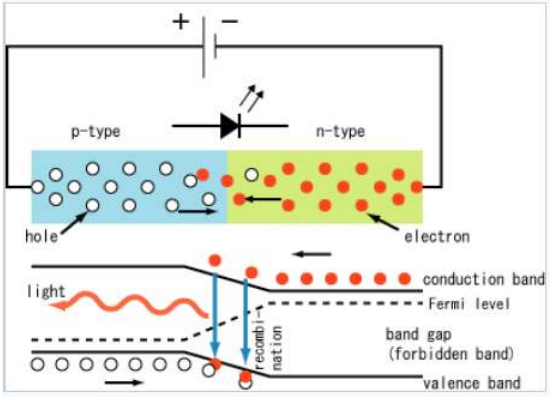
Electrons (red) and holes (white) in a forward-biased diode. (S-kei. Wikipedia, CC-BY-SA)

The figure on the left illustrates a forward-biased diode, through which current flows easily. As electrons and holes are driven into the junction (black arrows in lower left figure), they recombine (downward blue arrows), producing light and/or heat. The Fermi level in the diode is indicated as the dotted line. There is a drop in the Fermi level (equal to the applied bias) across the depletion layer. The corresponding diode i-V curve is shown on the right. The current rises exponentially with applied voltage in the forward bias direction, and there is very little leakage current under reverse bias. At very high reverse bias (typically tens of volts) diodes undergo avalanche breakdown and a large reverse current flows.



Diode i-V curve

A **light-emitting diode** or **LED** is a kind of diode that converts some of the energy of electron-hole recombination into light. This radiative recombination process always occurs in competition with non-radiative recombination, in which the energy is simply converted to heat. When light is emitted from an LED, the photon energy is equal to the bandgap energy. Because of this, LED lights have pure colors and narrow emission spectra relative to other light sources, such as incandescent and fluorescent lights. LED lights are energy-efficient and thus are typically cool to the touch.



Light-emitting diode (LED). (S-kei. Wikipedia, CC-BY-SA)

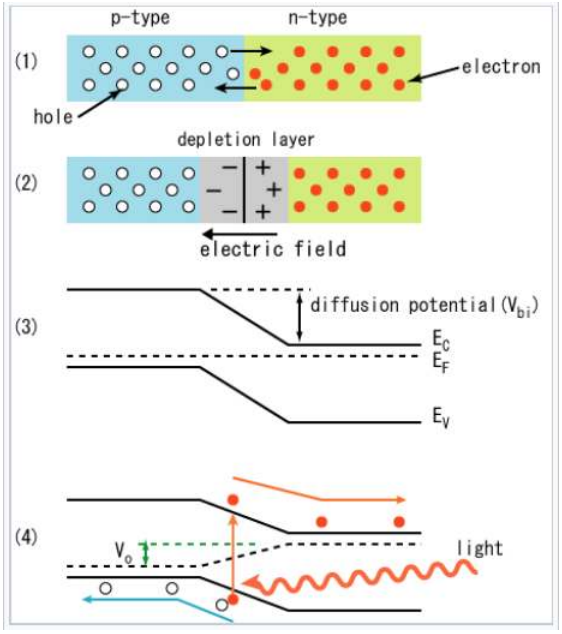
Direct-gap semiconductors such as GaAs and GaP have efficient luminescence and are also good light absorbers. In direct gap semiconductors, there is no momentum change involved in electron-hole creation or recombination. That is, the electrons and holes originate at the same value of the momentum wavevector **k**, which we encountered in Ch. 6. **k** is related to the momentum (also a vector quantity) by **p** = h**k**/2π. In a direct-gap semiconductor, the top of the valence band and the bottom of the conduction band most typically both occur at **k** = 0. Since the momentum of the photon is close to zero, photon absorption and emission are strongly allowed (and thus kinetically fast). Polar semiconductors such as GaAs, GaN, and CdSe are typically direct-gap materials. **Indirect-gap** semiconductors such as Si and Ge absorb and emit light very weakly because the valence band maximum and conduction band minimum do not occur at the same point in k-space. This means that a lattice vibration (a phonon) must also be created or annihilated in order to conserve momentum. Since this "three body" (electron, hole, phonon) process has low probability, the radiative recombination of electrons and holes is slow relative to non-radiative decay - the thermalization of electron-hole energy as lattice vibrations - in indirect-gap semiconductors. The momentum selection rule thus prevents light absorption/emission and there are no pure Si LEDs or Si-based lasers.



Prof. Shuji Nakamura holding a blue LED.

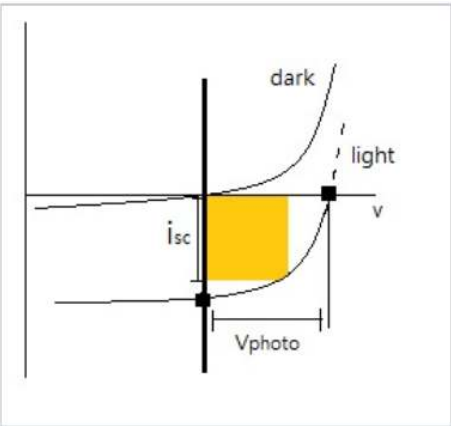
While red, orange, yellow, and green LEDs can be fabricated relatively easily from AlP-GaAs solid solutions, it was initially very difficult to fabricate blue LEDs because the best direct gap semiconductor with a bandgap in the right energy range is a nitride, GaN, which is difficult to make and to dope p-type. Working at Nichia Corporation in Japan, Shuji Nakamura succeeded in developing a manufacturable process for p-GaN, which is the basis of the blue LED. Because of the importance of this work in the development of information storage (Blu-Ray technology) and full-spectrum, energy-efficient LED lighting, Nakamura shared the 2014 Nobel Prize in Physics with Isamu Asaki and Hiroshi Amano, both of whom had made earlier contributions to the development of GaN diodes.

A **Solar cell**, or photovoltaic cell, converts light absorbed in a p-n junction directly to electricity by the photovoltaic effect. Photovoltaics is the field of technology and research related to the development of solar cells for conversion of solar energy to electricity. Sometimes the term solar cell is reserved for devices intended specifically to capture energy from sunlight, whereas the term photovoltaic cell is used when the light source is unspecified.



Photovoltaic effect in a semiconductor p-n junction. (S-kei. Wikipedia, CC-BY-SA)

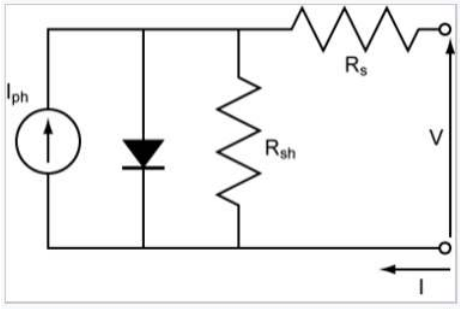
Photocurrent in p-n junction solar cells flows in the diode reverse bias direction. In the dark, the solar cell simply acts as a diode. In the light, the photocurrent can be thought of as a constant current source, which is added to the i-V characteristic of the diode. The relationship between the dark and light current in a photovoltaic cell is shown in the diagram at the left.



Current-voltage characteristic of a solar cell in the dark and under illumination with band gap light. The short-circuit photocurrent is indicated as i_{sc}, and the open-circuit photovoltage is V_{photo}. The maximum power generated by the solar cell is determined by the area of the orange box.

The built-in electric field of the p-n junction separates e^- h^+ pairs that are formed by absorption of bandgap light in the depletion region. The electrons flow downhill, towards the n-type side of the junction, the holes flow uphill towards the p-side. If $h\nu \geq E_{gap}$, light can be absorbed by promoting an electron from the valence band to the conduction band. Any excess energy is rapidly thermalized. Light with $h\nu > E_g$ thus can store only E_g worth of energy in an e^- h^+ pair. If light is absorbed outside of depletion region, i.e., on the n- or p-side of the junction where there is no electric field, minority carriers must diffuse into the junction in order to be collected. This process occurs in competition with electron-hole recombination. Because impurity atoms and lattice defects make efficient recombination centers, semiconductors used in solar cells (especially indirect-gap materials such as Si, which must be relatively thick in order to absorb most of the solar spectrum) must be very pure. Most of the cost of silicon solar cells is associated with the process of purifying elemental silicon and growing large single crystals from the melt.

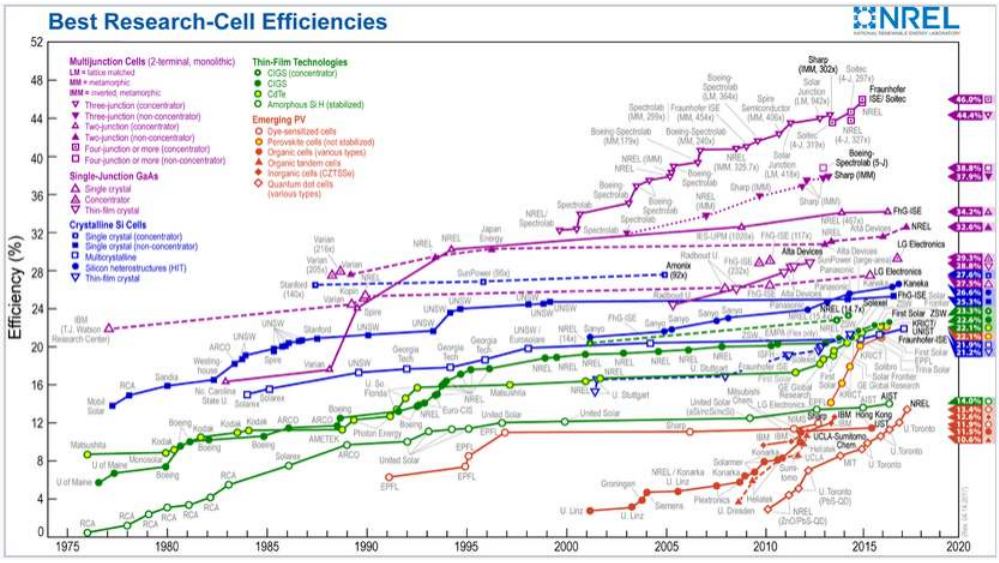
In the photodiode i-V curve above, V_{photo} is typically only about 70% of the bandgap energy E_{gap}. The photocurrent is limited by the photon flux, the recombination rate, and the re-emission of absorbed light.[6] The area of the orange rectangle indicates the power generated by the solar cell, which can be calculated as P = i x V. In good single crystal or polycrystalline solar cells made of Si, GaAs, CdTe, $CuIn_xGa_{1-x}Se_2$, or $(CH_3NH_3)PbI_3$ the quantum yield (the ratio of short circuit photocurrent to photon flux) is close to unity.



The equivalent circuit of a p-n junction solar cell, which results in the "light" i-V curve shown in the figure above. The solar cell is effectively a diode with a reverse-bias current source provided by light-generated electrons and holes. The shunt resistance (R_{sh}) in the equivalent circuit represents parasitic electron-hole recombination. A high shunt resistance (low recombination rate) and low series resistance (R_s) are needed for high solar cell efficiency.

Solar cells have many current applications. Individual cells are used for powering small devices such as electronic calculators. Photovoltaic arrays generate a form of renewable electricity, particularly useful in situations where electrical power from the grid is unavailable such as in remote area power systems, Earth-orbiting satellites and space probes, remote radio-telephones and water pumping applications. Photovoltaic electricity is also increasingly deployed in grid-tied electrical systems.

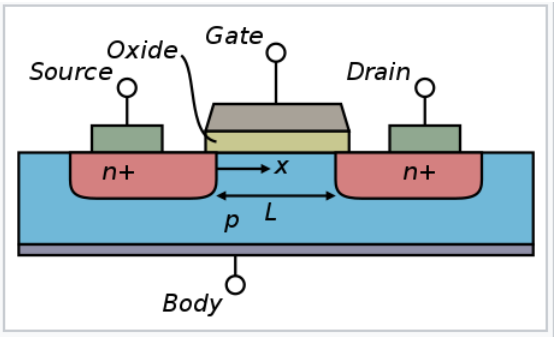
The cost of installed photovoltaics (calculated on a per-watt basis) has dropped over the past decade at a rate of about 13% per year, and has already reached grid parity in Germany and a number of other countries.[7] Photovoltaic grid parity is anticipated in U.S. power markets in the 2020 timeframe.[8] A major driver in the progressively lower cost of photovoltaic power is the steadily increasing efficiency of solar cells, which is shown in the graphic at the right. Higher efficiency solar cells require less area to deliver the same amount of power, and this lowers the "balance of system" costs such as wiring, roof mounting, etc., which scale as the area of the solar panels. Progress towards higher efficiency reflects improved processes for making photovoltaic materials such as silicon and gallium arsenide, as well as the discovery of new materials. Silicon solar cells are a mature technology, so they are now in the flat part of the learning curve and are approaching their maximum theoretical efficiencies. Newer technologies such as organic photovoltaics, quantum dot solar cells, and lead halide perovskite cells are still in the rising part of the learning curve.



Reported timeline of solar cell energy conversion efficiencies since 1976 (National Renewable Energy Laboratory)

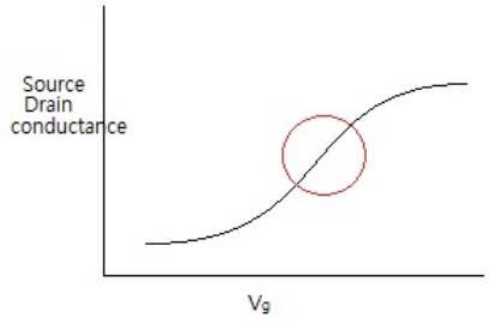
A **field effect transistor (FET)** is a transistor that uses an electric field to control the width of a conducting channel and thus the current in a semiconductor material. It is classified as unipolar transistor, in contrast to bipolar transistors.

Field effect transistors function as current amplifiers. The typical structure of Si-based FETs is one in which two n-type regions (the source and the drain) are separated by a p-type region. An oxide insulator over the p-type region separates a metal gate lead from the semiconductor. This structure is called a metal-oxide-semiconductor FET (or MOSFET). When voltage is applied between source and drain, current cannot flow because either the n-p or the p-n junction is back-biased. When a positive potential is applied to the gate, however, electrons are driven towards the gate, and locally the semiconductor is "inverted" to n-type. Then the current flows easily between the n-type source and drain through the n-channel. The current flow between the source and drain is many times larger than the current through the gate, and thus the FET can act as an amplifier. Current flow can also represent a logical "1," so FETs are also used in digital logic.



Cross section of an n-type MOSFET

In electronic devices such as microprocessors, field-effect transistors are kept in the off-state most of the time in order to minimize background current and power consumption. The FET shown above, which has n-type source and drain regions, is called an NMOS transistor. In a PMOS transistor, the source and drain regions are p-type and the gate is n-type. In **CMOS** (complementary metal-oxide semiconductor) integrated circuits, both NMOS and PMOS transistors are used. CMOS circuits are constructed in such a way that all PMOS transistors must have either an input from the voltage source or from another PMOS transistor. Similarly, all NMOS transistors must have either an input from ground or from another NMOS transistor. This arrangement results in low static power consumption.



Transistors are most useful in the range of gate voltage (indicated by the red circle in the figure at the left) where the source-drain current changes rapidly. In this region it is possible to effect a large change in current between source and drain when a small signal is applied to the gate. An important figure of merit for FETs is the **subthreshold slope**, which is the slope a plot of log(current) vs. V_{gate}. An ideal subthreshold slope is one decade of current per 60 mV of gate bias. Typically, a decade change in source-drain current can be achieved with a change in gate voltage of ~70 mV. The performance of FETs as switches and amplifiers is limited by the subthreshold slope, which in turn is limited by the capacitance of the gate. It is desirable to have a very high gate capacitance, which requires a thin insulating oxide, but also to have a small leakage current, which requires a thick oxide. A current challenge in the semiconductor industry is to continue to scale FETs to even smaller nanoscale dimensions while maintaining acceptable values of these parameters. This is being done by developing new gate insulator materials that have higher dielectric constants than silicon oxide and do not undergo redox reactions with silicon or with metal gate leads. Only a few known materials (such as hafnium oxynitride and hafnium silicates) currently meet these stringent requirements.

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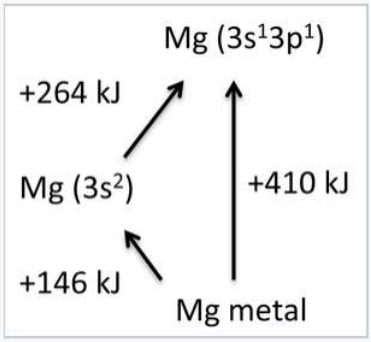
15.5: Atomic Orbitals and Magnetism

The MO picture we developed in Section 6.4 helps us rationalize the electrical conductivity of Na ($3s^1$), but what about Mg, which (as an atom in the gas phase) has a $3s^2$ electronic configuration? The two valence electrons are spin-paired in atomic Mg, as they are in the helium atom ($1s^2$). When the 3s orbitals of Mg combine to form a band, we would expect the band to be completely filled, since Mg has two electrons per orbital. By this reasoning, solid Mg should be an insulator. But Mg has all the properties of a metal: high electrical and thermal conductivity, metallic luster, malleability, etc. In this case the 3s and 3p bands are sufficiently broad (because of strong orbital overlap between Mg atoms) that they form a continuous band. This band, which contains a total of four orbitals (one 3s and three 3p) per atom, is only partially filled by the two valence electrons.



Mg crystals

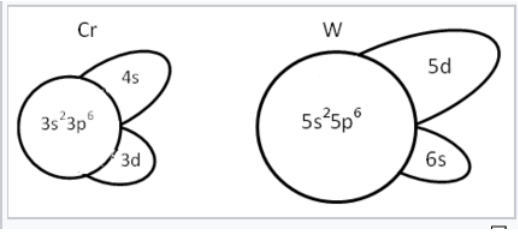
Another way to think about this is to consider the **hybridization** of the 3s and 3p electrons in Mg. Hybridization requires promotion from the $3s^23p^0$ ground state of an Mg atom to a $3s^13p^1$ excited state. The **promotion energy** (+264 kJ/mol) is more than offset by the **bonding energy** (-410 kJ/mol), the energy released when gaseous atoms in the excited state condense to form the metallic solid. The heat of vaporization, or the cohesive energy of a metal, is the difference between the bonding energy and the promotion energy. Experimentally, we can measure the vaporization energy (+146 kJ/mol) and the promotion energy and use them to calculate the bonding energy. From this we learn that each s or p electron is worth about 200 kJ/mol in bonding energy. The concepts of promotion energy and bonding energy are very useful in rationalizing periodic trends in the bond strengths and magnetic properties of metals, which are described below.



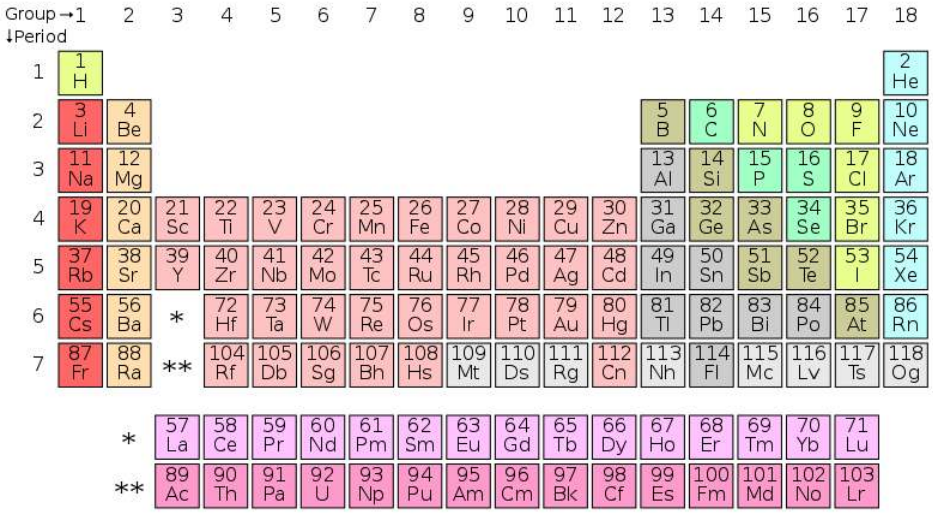
The cohesive energy of Mg metal is the difference between the bonding and promotion energies. The ground state of a gas phase Mg atom is $[Ar]3s^2$, but it can be promoted to the $[Ar]3s^13p^1$ state, which is 264 kJ/mol above the ground state. Mg uses two electrons per atom to make bonds, and the sublimation energy of the metal is 146 kJ/mol.

Periodic trends in d-electron bonding

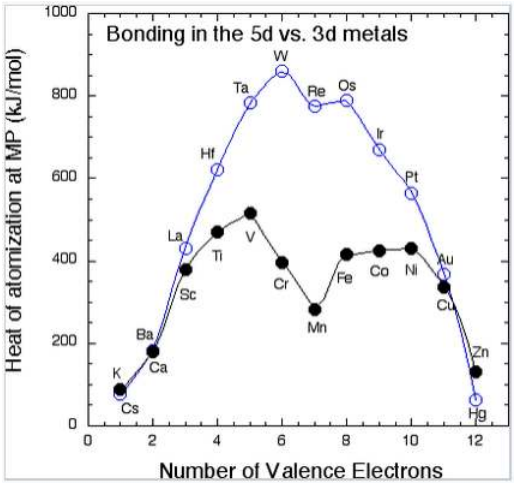
While electrons in s and p orbitals tend to form strong bonds, d-electron bonds can be strong or weak. There are two important periodic trends that are related to orbital size and orbital overlap. As we move *across the periodic table* (Sc - Ti - V - Cr - Fe), the *d orbitals contract* because of increasing nuclear charge. Moving *down the periodic table* (V - Nb - Ta), the *d orbitals expand* because of the increase in principal quantum number. These trends explain the distinct behavior of the 3d elements relative to those in the 4d and 5d series. In the 3d series, the contraction of orbitals affects the ability of the d electrons to contribute to bonding. Past V in the first row of the transition metals, the 3d electrons become much less effective in bonding because they overlap weakly with their neighbors. Weak overlap of 3d orbitals gives narrow d-bands and results in the emergence of magnetic properties as discussed below.



Schematic representation of the sizes of different orbitals of Cr and W. In the first transition series, shielding of the 3d orbitals is poor. Therefore the 4s and 4p orbitals are more effective in bonding than the 3d. In the third transition series, the situation is reversed. The increased nuclear charge is felt most strongly by the 6s, which takes on the character of an inert electron pair. The 5d orbitals are well shielded by the complete n=4 shell so they have good orbital overlap with neighboring atoms.

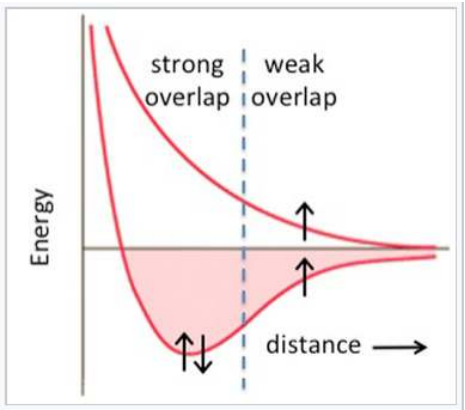


In the **4d and 5d series**, a plot of cohesive energy vs. number of valence electrons (below left) has a "volcano" shape that is peaked at the elements Mo and W ($5s^1 4d^5$ and $6s^1 5d^5$, respectively). The number of bonding electrons, and therefore the bonding energy, increases steadily going from Rb to Mo in the 4d series, and from Cs to W in the 5d series. Mo and W have the most bonding energy because they can use all six of their valence electrons in bonding without promotion. Elements past Mo and W have more d electrons, but some of them are spin paired and so some promotion energy is needed to prepare these electrons for bonding. For example, Pt metal must be promoted from the $6s^1 5d^9$ atomic ground state to $6s^1 5d^7 6p^2$ in order to make six bonds per atom, and the energy cost of promoting electrons from the 5d to the 6p orbitals is reflected in the net bonding energy. Because of their strong bonding energy, elements in the middle of the 4d and 5d series have very high melting points. We do not see magnetism in the 4d or 5d metals or their alloys because orbital overlap is strong and the bonding energy exceeds the electron pairing energy.



The heat of vaporization (the cohesive energy) of metals in the 3d and 5d series, measured at the melting point of the metal.

The **3d elements** (Sc through Zn) are distinctly different from the 4d and 5d elements in their bonding (and consequently in their magnetic properties). In the 3d series, we see the expected increase in cohesive energy going from Ca ($4s^2$) to Sc ($4s^23d^1$) to Ti ($4s^23d^2$) to V ($4s^23d^3$), but then something very odd happens. The 3d series has a "crater" in the cohesive energy plot where there was a peak in the 5d series. The cohesive energy actually *decreases* going from V to Mn, even though the number of valence electrons is increasing. We can explain this effect by remembering that the 3d orbitals are progressively contracting as more protons are added to the nucleus. For elements beyond V, the orbital overlap is so poor that the 3d electrons are no longer effective in bonding, and the valence electrons begin to unpair. At this point the elements become **magnetic**. Depending on the way the spins order, metals and alloys in this part of the periodic table can be ferromagnetic (spins on neighboring atoms aligned parallel, as in the case of Fe or Ni) or antiferromagnetic (spins on neighboring atoms antiparallel, as in the case of Mn). We have seen the trade-off between orbital overlap and magnetism before (in Chapter 5) in the context of paramagnetic transition metal complexes. It is worth recalling that this behavior is predicted in the energy vs. distance diagram of the hydrogen atom (from Chapter 2). At short interatomic distances (or with strong overlap between atomic orbitals), the spins of the electrons pair and a bond is formed. Unpairing the electrons becomes favorable at larger interatomic distances where the overlap between orbitals is poor.



With strong overlap between orbitals of neighboring atoms, the bonding energy exceeds the pairing energy and electrons spin-pair. With weaker overlap, bonding is weak and spins unpair, resulting in magnetic behavior.

Interestingly, many alloys of the **4f elements** (the lanthanides) are also magnetic because the 4f orbitals, like the 3d orbitals, are poorly shielded from the nuclear charge and are ineffective in bonding. Strong permanent magnets often contain alloys of Nd, Sm, or Y, usually with magnetic 3d elements such as Fe and Co.

Because the 4f orbitals are contracted and not very effective in bonding, other physical properties of the lanthanides can also be affected. For example, it has been proposed that oxides of the 4f elements have weak surface interactions with polar molecules such

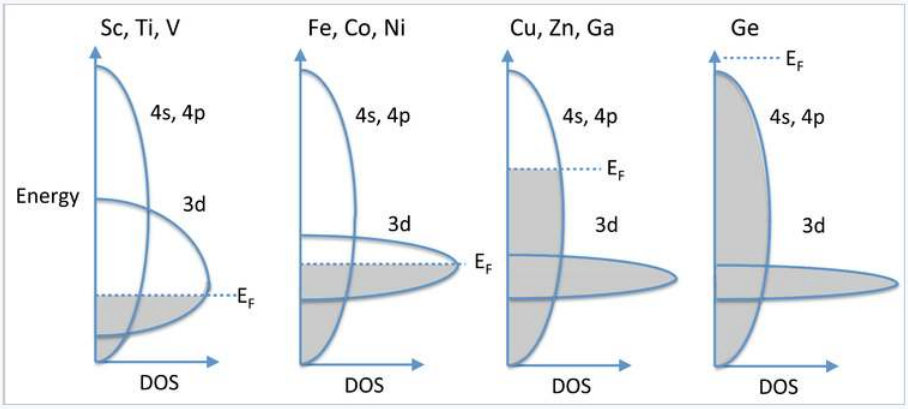
as water because of f-orbital contraction. Experimentally, CeO_2, Er_2O_3, and Ho_2O_3 are observed to be hydrophobic, whereas main group and early transition metal oxides (e.g., Al_2O_3, SiO_2, TiO_2) are quite hydrophilic.[1]

Late transition metal alloys

Although the bonding in the 5d series follows a "normal" volcano plot, the situation is a bit more complex for alloys of Re, Os, Ir, Pt, and Au. There is strong overlap between the 5d orbitals, but because these elements contain more than five d-electrons per atom, they cannot make as many bonds as 4d or 5d elements with half-filled d-shells such as Mo or W. This progressive filling of the d-band explains the steady decrease in bonding energy going from Os to Au. Pt and Au are both soft metals with relatively low heats of vaporization. However, these metals (especially Ir, Pt, and Au) can combine with early transition metals to form stable alloys with very negative heats of formation and high melting points. For example, ZrC and Pt react to form a number of stable alloys (ZrPt, Zr_9Pt_{11}, Zr_3Pt_4, $ZrPt_3$)[2] plus carbon. This reactivity is unusual because we normally think of Pt as a "noble" (i.e., unreactive) metal, and because ZrC is a very stable, refractory metal carbide. The favorable combination of early and late transition metals has been interpreted as arising from a d-electron "acid-base" interaction.[3] For example, in $HfPt_3$, Hf is the "acid" with an electron configuration of $6s^25d^2$, while Pt is the "base" with the electron configuration of $6s^15d^9$. They combine to create a stable "salt" product with a filled 5d electron configuration without promoting any electrons to higher orbitals. The implication is that Pt donates d-electrons to the "d-acid," Zr or Hf. However, electronic structure calculations on model compounds show that much of the bonding energy in ZrPt and $ZrPt_3$ arises from electron transfer from Zr to Pt (not the other way around) and the polarity of the resulting metal-metal bonds.[4] Regardless of the source of their stability, some early-late transition metal alloys are of particular interest for use in catalysis. For example, the alloy $ScPt_3$ is a good catalyst for oxygen reduction in fuel cells. Even though Sc is an active metal that is easily oxidized, it is stabilized in the aqueous acid environment of the fuel cell by its strong interaction with Pt.[5]

Filling of the 3d and 4s,4p bands

In the 3d series, we see magnetic behavior for elements and alloys between Cr and Ni. Past Ni, the elements (Cu, Zn, Ga,...) are no longer magnetic and they are very good electrical conductors, implying that their valence electrons are highly delocalized. We can understand this behavior by considering the overlap of 4s, 4p, and 3d orbitals, all of which are close in energy. The 4s and 4p have strong overlap and form a broad, continuous band. On the other hand, the 3d electrons are contracted and form a relatively narrow band. Progressing from the early 3d elements (Sc, Ti, V), we begin to fill the 3d orbitals, which are not yet so contracted that they cannot contribute to bonding. Thus, the valence electrons in Sc, Ti, and V are all spin-paired, except for a small number near the Fermi level that give rise to a weak Pauli paramagnetism. Moving across the 3d series to the magnetic elements (Fe, Co, Ni), the d-orbitals are now so contracted that their electrons unpair and we see cooperative ordering of spins (ferromagnetism and antiferromagnetism). Referring to the band diagram at the right, the 3d band is only partially filled and the Fermi level cuts through it. For Cu, Zn, and Ga, the 3d orbitals are even more contracted and the 3d band is thus more narrow, but now it is completely filled and the Fermi level is in the 4s,4p band. The strong orbital overlap in these bands results in spin pairing and a high degree of electron delocalization. Consequently, metals in this part of the periodic table (Cu, Ag) are diamagnetic and are among the best electrical conductors at room temperature. Finally, at Ge, the 4s,4p band is completely filled and the solid is a semiconductor.



Progressive filling of the 3d and 4s,4p bands going across the periodic table from Sc to Ge.

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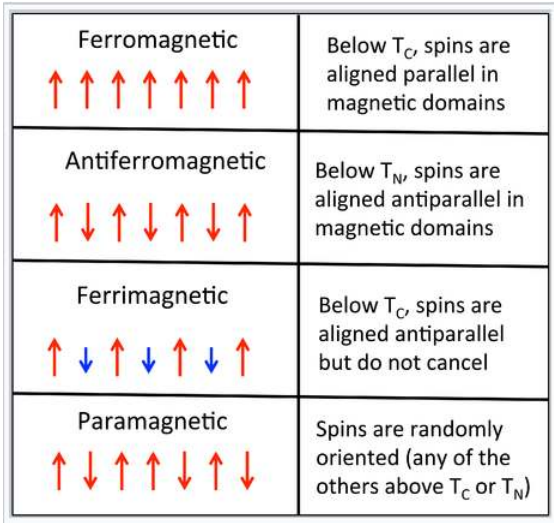
Materials are classified as diamagnetic if they contain no unpaired electrons. Diamagnetic substances are very weakly repelled from an inhomogeneous magnetic field. As we learned in Chapter 5, molecules or ions that have unpaired spins are paramagnetic and are attracted to a magnet, i.e., they move towards the high field region of an inhomogeneous field. This attractive force results from the alignment of spins with the field, but in the case of paramagnetism each molecule acts independently. In metals, alloys, oxides, and other solid state compounds, the unpaired spins interact strongly with each other and can order spontaneously, resulting in the cooperative magnetic phenomena described below.

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15.6: Ferro-, Ferri- and Antiferromagnetism

The magnetism of metals and other materials are determined by the orbital and spin motions of the unpaired electrons and the way in which unpaired electrons align with each other. All magnetic substances are **paramagnetic** at sufficiently high temperature, where the thermal energy (kT) exceeds the interaction energy between spins on neighboring atoms. Below a certain critical temperature, spins can adopt different kinds of ordered arrangements.



A pictorial description of the ordering of spins in ferromagnetism, antiferromagnetism, ferrimagnetism, and paramagnetism

Let's begin by considering an individual atom in the bcc structure of iron metal. Fe is in group VIIIb of the periodic table, so it has eight valence electrons. The atom is promoted to the $4s^1 3d^7$ state in order to make bonds. A localized picture of the d-electrons for an individual iron atom might look like this:



Since each unpaired electron has a spin moment of 1/2, the total spin angular momentum, **S**, for this atom is:

$S = 3\frac{1}{2} = \frac{3}{2}$ (in units of h/2π)

We can think of each Fe atom in the solid as a little bar magnet with a spin-only moment **S** of 3/2. The spin moments of neigboring atoms can align in parallel (↑ ↑), antiparallel (↑ ↓), or random fashion. In bcc Fe, the tendency is to align parallel because of the positive sign of the exchange interaction. This results in **ferromagnetic** ordering, in which all the spins within a magnetic domain (typically hundreds of unit cells in width) have the same orientation, as shown in the figure at the right. Conversely, a negative exchange interaction between neighboring atoms in bcc Cr results in **antiferromagnetic** ordering. A third arrangement, **ferrimagnetic** ordering, results from an antiparallel alignment of spins on neighboring atoms when the magnetic moments of the neighbors are unequal. In this case, the spin moments do not cancel and there is a net magnetization. The ordering mechanism is like that of an antiferromagnetic solid, but the magnetic properties resemble those of a ferromagnet. Ferrimagnetic ordering is most common in metal oxides, as we will learn in Chapter 7.

Magnetization and susceptibility

The **magnetic susceptibility**, **χ**, of a solid depends on the ordering of spins. Paramagnetic, ferromagnetic, antiferromagnetic, and ferrimagnetic solids all have $\chi > 0$, but the magnitude of their susceptibility varies with the kind of ordering and with temperature. We will see these kinds of magnetic ordering primarily among the **3d** and **4f** elements and their alloys and compounds. For example, Fe, Co, Ni, $Nd_2Fe_{14}B$, $SmCo_5$, and YCo_5 are all ferromagnets, Cr and MnO are antiferromagnets, and Fe_3O_4 and $CoFe_2O_4$ are ferrimagnets. Diamagnetic compounds have a weak *negative* susceptibility ($\chi < 0$).

Definitions

- H = applied magnetic field (units: Henry (H))
- B = induced magnetic field in a material (units: Tesla (T))
- M = magnetization, which represents the magnetic moments within a material in the presence of an external field H.

Magnetic susceptibility $\chi = M/H$

Usually, χ is given in *molar* units in the *cgs system*:

χ_M = molar susceptibility (units: cm^3/mol)

Typical values of χ_M:

Compound	Type of Magnetism	χ at 300K (cm^3/mol)
SiO_2	Diamagnetic	-3×10^{-4}
Pt metal	Pauli paramagnetic	$+2 \times 10^{-4}$
$Gd_2(SO_4)_3 \cdot 8H_2O$	Paramagnetic	$+5 \times 10^{-2}$
Ni-Fe alloy	Ferromagnetic	$+10^4 - 10^6$

To correlate χ with the number of unpaired electrons in a compound, we first correct for the small diamagnetic contribution of the core electrons:

$$\chi^{corr} = \chi^{obs} - \chi^{diamagnetic\ cores} \tag{15.6.1}$$

Susceptibility of paramagnets

For a paramagnetic substance,

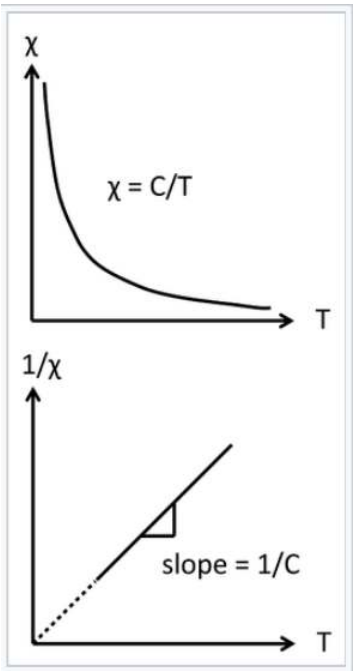
$$\chi_M^{corr} = \frac{C}{T} \tag{15.6.2}$$

The inverse relationship between the magnetic susceptibility and T, the absolute temperature, is called **Curie's Law**, and the proportionality constant C is the **Curie constant**:

$$C = \frac{N_A}{3k_B}\mu_{eff}^2 \tag{15.6.3}$$

Note that C is not a "constant" in the usual sense, because it depends on μ_{eff}, the **effective magnetic moment** of the molecule or ion, which in turn depends on its number of unpaired electrons:

$$\mu_{eff} = \sqrt{n(n+2)}\,\mu_B \tag{15.6.4}$$



Curie law behavior of a paramagnet. A plot of 1/χ vs. absolute temperature is a straight line, with a slope of 1/C and an intercept of zero.

Here μ_B is the Bohr magneton, a physical constant defined as $\mu_B = eh/4\pi m_e = 9.274 \times 10^{-21}$ erg/gauss (in cgs units).

In cgs units, we can combine physical constants,

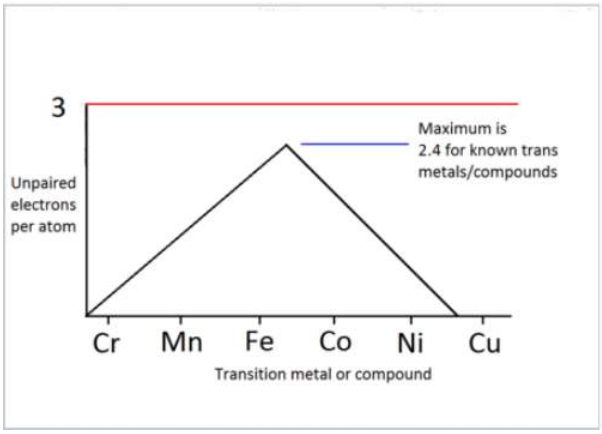
$$\frac{N_A}{3k_B}\mu_B^2 = .125 \tag{15.6.5}$$

Combining these equations, we obtain

$$\chi_M^{corr} = \frac{.125}{T}\left(\frac{\mu_{eff}}{\mu_B}\right)^2 \tag{15.6.6}$$

These equations relate the molar susceptibility, a bulk quantity that can be measured with a magnetometer, to μ_{eff}, a quantity that can be calculated from the number of unpaired electrons, n. Two important points to note about this formula are:

- The magnetic susceptibility is inversely proportional to the absolute temperature, with a proportionality constant C (Curie's Law)
- So far we are talking only about paramagnetic substances, where there is no interaction between neighboring atoms.



Number of unpaired electrons per atom, determined from Curie constants of transition metals and their 1:1 alloys.

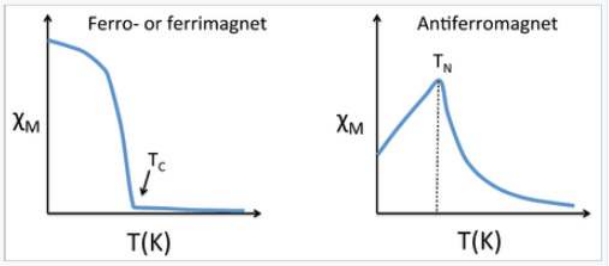
Returning to the isolated Fe atom with its three unpaired electrons, we can measure the Curie constant for iron metal (above the temperature of its transition to a paramagnetic solid) and compare it to the calculation of μ_{eff}. Since n = 3, we calculate:

$$\mu_{eff} = \sqrt{(3)(5)}\mu_B = 3.87\mu_B \tag{15.6.7}$$

The plot at the right shows the number of unpaired electrons per atom, calculated from measured Curie constants, for the magnetic elements and 1:1 alloys in the 3d series. The plot peaks at a value of 2.4 spins per atom, slightly lower than we calculated for an isolated iron atom. This reflects that fact that there is some pairing of d-electrons, i.e., that they do contribute somewhat to bonding in this part of the periodic table.

Susceptibility of ferro-, ferri-, and antiferromagnets

Below a certain critical temperature, the spins of a solid paramagnetic substance order and the susceptibility deviates from simple Curie-law behavior. Because the ordering depends on the short-range exchange interaction, this critical temperature varies widely. Metals and alloys in the 3d series tend to have high critical temperatures because the atoms are directly bonded to each other and the interaction is strong. For example, Fe and Co have critical temperatures (also called the Curie temperature, T_c, for ferromagnetic substances) of 1043 and 1400 K, respectively. The Curie temperature is determined by the strength of the magnetic exchange interaction and by the number of unpaired electrons per atom. The number of unpaired electrons peaks between Fe and Co as the d-band is filled, and the exchange interaction is stronger for Co than for Fe. In contrast to ferromagnetic metals and alloys, paramagnetic salts of transition metal ions typically have critical temperatures below 1K because the magnetic ions are not directly bonded to each other and thus their spins are very weakly coupled in the solid state. For example, in gadolinium sulfate, the paramagnetic Gd^{3+} ions are isolated from each other by SO_4^{2-} ions.

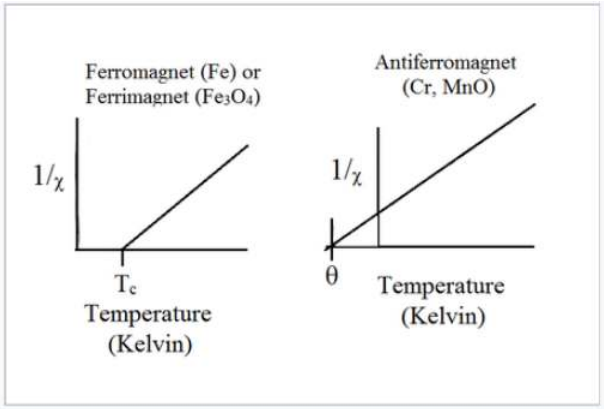


Magnetic susceptibility vs temperature (Kelvin) for ferrimagnetic, ferromagnetic, and antiferromagnetic materials

Above the critical temperature T_C, **ferromagnetic** compounds become paramagnetic and obey the **Curie-Weiss law:**

$$\chi = \frac{C}{T - T_c} \tag{15.6.8}$$

This is similar to the Curie law, except that the plot of $1/\chi$ vs. T is shifted to a positive intercept T_C on the temperature axis. This reflects the fact that ferromagnetic materials (in their paramagnetic state) have a greater tendency for their spins to align in a magnetic field than an ordinary paramagnet in which the spins do not interact with each other. Ferrimagnets follow the same kind of ordering behavior. Typical plots of χ vs. T and $1/\chi$ vs. T for ferro-/ferrimagnets are shown above and below.



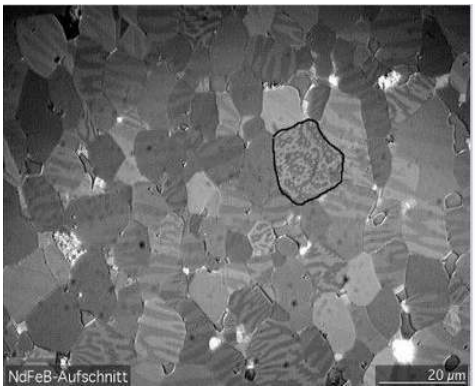
Plots of $1/\chi$ vs. T for ferromagnets, ferrimagnets, and antiferromagnets.

Antiferromagnetic solids are also paramagnetic above a critical temperature, which is called the Néel temperature, T_N. For antiferromagnets, χ reaches a maximum at T_N and is smaller at higher temperature (where the paramagnetic spins are further disordered by thermal energy) and at lower temperature (where the spins pair up). Typically, antiferromagnets retain some positive susceptibility even at very low temperature because of canting of their paired spins. However the maximum value of χ is much lower for an antiferromagnet than it is for a ferro- or ferrimagnet. The Curie-Weiss law is also modified for an antiferromagnet, reflecting the tendency of spins (in the paramagnetic state above T_N) to resist parallel ordering. A plot of $1/\chi$ vs. T intercepts the temperature axis at a negative temperature, $-\theta$, and the Curie-Weiss law becomes:

$$\chi = \frac{C}{T+\theta} \tag{15.6.9}$$

Ordering of spins below T_C

Below T_C, the spins align spontaneously in ferro- and ferrimagnets. Complex magnetization behavior is observed that depends on the history of the sample. For example, if a ferromagnetic material is cooled in the absence of an applied magnetic field, it forms a mosaic structure of magnetic domains that each have internally aligned spins. However, neighboring domains tend to align the opposite way in order to minimize the total energy of the system. This is illustrated in the figure at the left for a Nd-Fe-B magnet. The sample consists of 5-10 µm wide crystal grains that can be easily distinguished by the sharp boundaries in the image. Within each grain are a series of lighter and darker stripes (imaged by using the optical Kerr effect) that are ferromagnetic domains with opposite orientations. Averaged over the whole sample, these domains have random orientation so the net magnetization is zero.

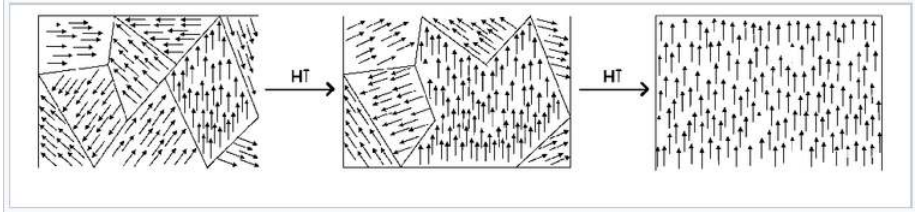


Microcrystalline grains within a piece of $Nd_2Fe_{14}B$ (the alloy used in neodymium magnets) with magnetic domains made visible with a Kerr microscope. The domains are the light and dark stripes visible within each grain.

When a sample like this one is magnetized (i.e., exposed to a strong magnetic field), the domain walls move and the favorably aligned domains grow at the expense of those with the opposite orientation. This transformation can be seen in real time in the Kerr microscope. The domain walls are typically hundreds of atoms wide, so movement of a domain wall involves a cooperative tilting of spin orientation (analogous to "the wave" in a sports stadium) and is a relatively low energy process.

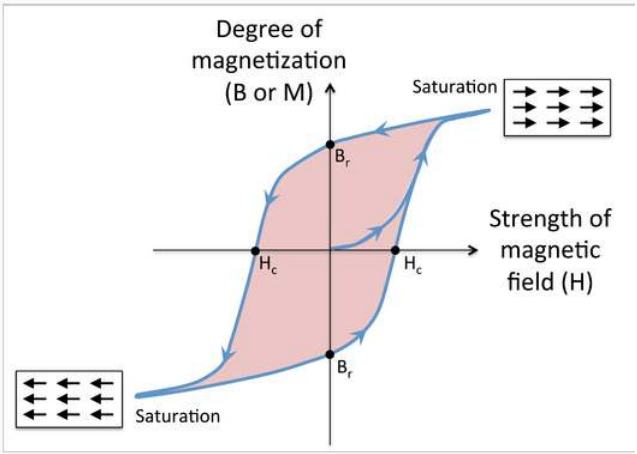
The movement of domain walls in a grain of silicon steel is driven in this movie by increasing the external magnetic field in the "downward" direction, and is imaged using a Kerr microscope. White areas are domains with their magnetization directed up, dark areas - which eventually comprise the entire grain - are domains with their magnetization directed down.

The process of magnetization moves the solid away from its lowest energy state (random domain orientation), so magnetization involves input of energy. When the external magnetic field is removed, the domain walls relax somewhat, but the solid (especially in the case of a "hard" magnet) can retain much of its magnetization. If you have ever magnetized a nail or a paper clip by using a permanent magnet, what you were doing was moving the walls of the magnetic domains inside the ferromagnet. The object thereafter retains the "memory" of its magnetization. However, annealing a permanent magnet destroys the magnetization by returning the system to its lowest energy state in which all the magnetic domains cancel each other.



Rotation of orientation and increase in size of magnetic domains in response to an externally applied magnetic field.

Magnetic hysteresis. Cycling a ferro- or ferrimagnetic material in a magnetic field results in hysteresis in the magnetization of the material, as shown in the figure at the left. At the beginning, the magnetization is zero, but it begins to rise rapidly as the magnetic field is applied. At high field, the magnetic domains are aligned and the magnetization is said to be saturated. When the field is removed, a certain **remanent magnetization** (indicated as the point $\mathbf{B_r}$ on the graph) is retained, i.e., the material is magnetized. Applying a field in the opposite direction begins to orient the magnetic domains in the other direction, and at a field $\mathbf{H_c}$ (the **coercive field**), the magnetization of the sample is reduced to zero. Eventually the material reaches saturation in the opposite direction, and when the field is removed again, it has remanent magnetization Br, but in the opposite direction. As the field continues to reverse, the magnet follows the hysteresis loop as indicated by the arrows. The area of colored region inside the loop is proportional to the magnetic work done in each cycle. When the field cycles rapidly (for example, in the core of a transformer, or in read-write cycles of a magnetic disk) this work is turned into heat.



Magnetization of a ferro- or ferrimagnet vs. applied magnetic field H. Starting at the origin, the upward curve is the initial magnetization curve. The downward curve after saturation, along with the lower return curve, form the main loop. The intercepts Hc and Br are the coercivity and remanent magnetization.

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CHAPTER OVERVIEW

16: Basic Science of Nanomaterials

Learning Objectives

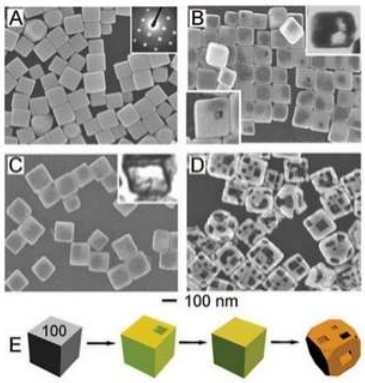
- Understand the physical basis of mesoscopic behavior in nanoscale semiconducting and magnetic particles.
- Describe how the particle-in-a-box equation applies to electrons in quantum wells.
- Use the Brus formula to calculate the band gap energy of nanoscale semiconductor particles.
- Use the surface energy concept to calculate changes in the melting point and vapor pressure of nanoparticles.
- Describe the methods used to make semiconducting and metal nanocrystals of uniform size.
- Explain the origin of the localized surface plasmon resonance effect in metal nanoparticles.
- Describe the emerging analytical and biomedical applications of metal nanoparticles.

Nanomaterials describe materials of which a single unit is sized (in at least one dimension) between 1 and 1000 nanometers, but is usually 1—100 nm. Nanomaterials research takes a materials science-based approach to nanotechnology, leveraging advances in materials metrology and synthesis which have been developed in support of microfabrication research. Materials with structure at the nanoscale often have unique optical, electronic, or mechanical properties. In this chapter we will learn about the basic science of nanomaterials, i.e., what it is about their size that makes them different.

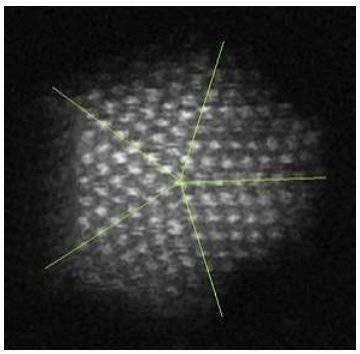
16.1: Nanoscale Metal Particles
16.2: Semiconductor Quantum Dots
16.3: Synthesis of Semiconductor Nanocrystals
16.4: Surface Energy
16.5: Carbon Nanomaterials
16.6: Transmission Electron Microscopy
16.7: Scanning Probe Microscopy - STM and AFM
16.8: Scanning Tunneling Microscopy
16.9: Atomic Force Microscopy

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16.1: Nanoscale Metal Particles



Nanoscale metal particles have been the subject of intense research over the past 20 years, especially because of their unusual **optical**, **magnetic**, and **catalytic** properties. The synthesis of metal nanocrystals in various shapes has become increasingly sophisticated and rational, like the synthesis of semiconductor nanocrystals described above. By controlling the separate phases of nucleation and growth, and by using ligands that cap specific crystal faces during growth, it is possible to make metal nanocrystals of uniform size in a variety of interesting and useful shapes including cubes, truncated cubes, octahedra, triangular prisms, and high aspect ratio rods. By exploiting displacement reactions that replace one metal with another, complex hollow shapes such as nanocages (as shown at the left) can be made starting with other shapes. In this case, solid silver nanocubes are transformed to gold nanocages.



Five-fold twinning in a gold nanoparticle

The interesting optical properties of nanocrystalline Au, Ag, Cu, and a number of other metals, derive from the collective oscillation of their valence electrons, a phenomenon known as **plasmon resonance**. Remember that in these metals, the electron mean free path is long (about 100 times larger than the size of the atoms), so the valence electrons feel only the average positive charge of the atomic cores as they zoom around the crystal. Light impinging on the metal acts as an oscillating electric field, pushing and pulling on the valence electrons at the characteristic frequency of the light wave. The situation is very much like a pendulum or a weight on a spring. The electrons, pushed away from their equilibrium positions, feel a restoring force that is proportional to their displacement. Their motion can be described by **Hooke's Law**:

$$F = kx \tag{16.1.1}$$

where the spring constant k determines the "stiffness" of the spring. In the case of the plasmon resonance, k is proportional to the number density of valence electrons n, and the square of the electronic charge e:

$$k = \frac{ne^2}{\varepsilon_0} \tag{16.1.2}$$

The **resonant frequency** of the plasma oscillation is given by:

$$\omega_p = (\frac{k}{m})^{\frac{1}{2}} = (\frac{ne^2}{m_e \varepsilon_0}^{\frac{1}{2}} \tag{16.1.3}$$

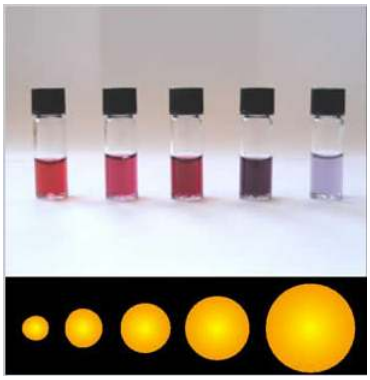
where m_e is the electron mass. For most metals, the plasmon resonance is in the ultraviolet part of the spectrum, but for a few metals like Au, Ag, and Cu it is in the visible.



The Lycurgus cup (4th century Roman glass) derives its unique coloration from noble metal nanoparticles. The cup is red in transmitted light and green in scattered (reflected) light.

For metal particles that are much smaller than the wavelength of light, this effect is called the **localized surface plasmon resonance**, or LSPR. There are three important consequences of the LSPR effect:

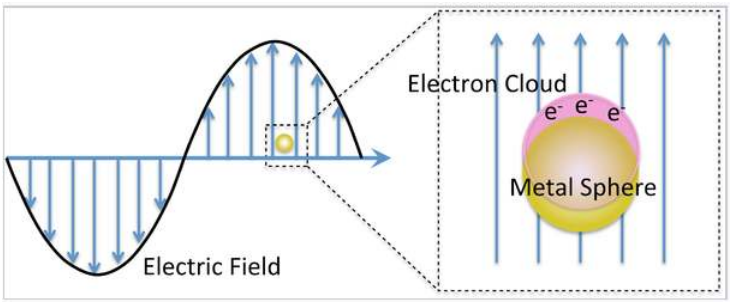
- The **local electric field** of the incoming light wave is greatly **enhanced** at the particle surface. This gives rise to huge enhancement factors in optical processes such as **Raman scattering** and **fluorescence**. Thus, certain analytical spectroscopic techniques are greatly enhanced by LSPR.
- Near the plasmon resonance frequency, metal nanocrystals **absorb** and **scatter light** very strongly. This makes them brightly reflective, and the strong light absorption can be exploited for light-induced local heating. These properties are being applied in medical diagnostics and therapy, e.g., for detection and photothermal destruction of cancer cells. By adjusting the size and shape of the gold nanoparticles, which are more stable than Ag and Cu in biological media, the plasmon frequency can be tuned to the tissue-transparent near-IR region of the spectrum between 700 and 900 nm. Small quantities of plasmonic Ag and Au particles also make brightly colored and strongly scattering pigments, e.g. in stained glass as shown above at the right.
- The plasmon frequency is sensitive to the refractive index of the particle's surroundings, i.e., its chemical environment. This makes metal nanoparticles of special interest for **sensing and biosensing** applications.



The colors of plasmonic gold nanoparticles depend on their size and shape.

Theory of light scattering and absorption by metal nanoparticles

The valence electrons in metal nanoparticles oscillate in the electric field of a light wave. While the nature of these oscillations is somewhat complex in metal particles that are non-spherical, the theory for spherical particles is relatively simple and in fact was worked out over 100 years ago by German physicist Gustav Mie.



Mie considered the interaction of a spherical particle with a **uniform electric field, E,** oscillating at angular frequency ω (= 2π f). This is a good approximation when the particle diameter is much smaller than the wavelength of light, as shown on the left. The particle is embedded in a uniform, insulating material (e.g. a solvent) that has a dielectric constant ε_{diel}. For insulators, ε_{diel} is a positive real number.

The dielectric constant ε of a metal is actually a complex number:

$$\varepsilon = \varepsilon^{'} + i\varepsilon'' \tag{16.1.4}$$

Here the real part, ε', is related to the refraction of light, and the imaginary part, ε", is related to light absorption. Both ε' and ε" are dependent on the frequency of the light. For metals near the plasmon resonance frequency, ε' is typically a *negative number.*

The **cross-section for absorption** of the light wave by the particle is:

$$\sigma_{absorption} = \frac{9\omega}{c}\epsilon_{diel}^{\frac{3}{2}} V \frac{\epsilon''_{metal}}{(\epsilon^{'}_{metal} + 2\epsilon_{diel})^2 + (\epsilon''_{metal})^2} \tag{16.1.5}$$

and the **cross-section for scattering** is:

$$\sigma_{scattering} = \frac{3}{2\pi}(\frac{\omega^4}{c})\epsilon_{diel}^2 V^2 \frac{(\epsilon^{'}_{metal} - \epsilon_{diel})^2 + (\epsilon''_{metal})^2}{(\epsilon^{'}_{metal} + 2\epsilon_{diel})^2 + (\epsilon''_{metal})^2} \tag{16.1.6}$$

The sum of these two is the **cross-section for extinction**:

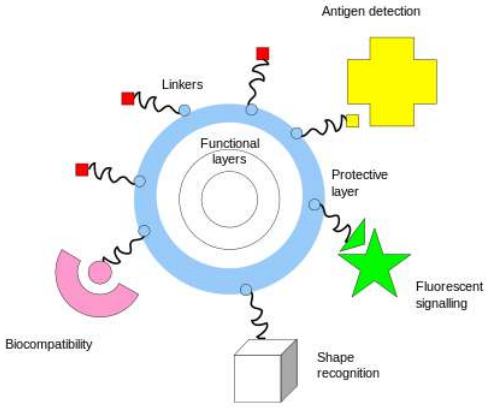
$$\sigma_{extinction} = \sigma_{absorption} + \sigma_{scattering} \tag{16.1.7}$$

These cross-sections become large when the (ε'_{metal} + $2\varepsilon_{diel}$) term in the denominator becomes small. This occurs when

$$\epsilon^{'}_{metal} \simeq -2\epsilon_{diel} \tag{16.1.8}$$

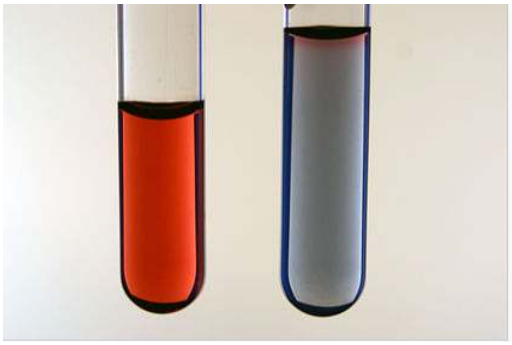
For 15 nm diameter gold nanoparticles in water, this happens at about 580 nm, resulting in the characteristic wine-red color of colloidal gold solutions. Changing the solution environment (e.g., by adsorbing a molecule onto the gold surface) changes ε_{diel} and thus alters the color slightly.

It is important to note that the cross-section for **scattering** is proportional to the **square of the volume** of the particle, V^2, whereas the absorption is proportional to V. This means that very small gold particles (< 5 nm) are strongly absorbing but not strongly scattering. Larger particles (>30 nm) scatter light very strongly. Depending on the application, therefore, we choose larger or smaller particles.



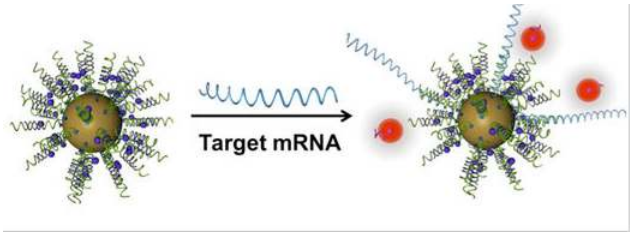
One of the key complementary properties of noble metal nanoparticles that is important to their use in biomedicine is the ease with which they can be **covalently conjugated** with polymers or small molecules, typically via thiol or amine bonds at their surface. This imparts biological recognition properties to the particles that enables them to bind to specific biomolecular targets. The figure at the left illustrates some of the functionality that can be imparted to nanoparticles through surface functionalization.

Functionalization of gold nanoparticles with thiol-terminated single-stranded DNA was the basis of one of the first nanoparticle sensors, developed by the Mirkin group at Northwestern University. **DNA-coated nanoparticles** have the characterstic wine-red plasmonic color of spherical nano-gold. However, when these particles are linked together by a complementary DNA strand, the resonance frequency shifs, resulting in a blue color. This color change, illustrated in the figure at the right, provides a "litmus test" for the presence of the target DNA sequence.[10] "Melting" of the DNA - heating it to the temperature at which double stranded DNA dissociates to make single strands - reverses the color change. The DNA hybridization/melting transition is highly **cooperative** because of the aggregation of many gold particles, so the transition temperature is very sharp. With proper temperature control, the color change can be sensitive to a **single base mismatch** in the target DNA that is detected by this method.



Aggregation of Au nanoparticles (in this case by adding salt to a colloidal solution) causes a color change from wine red (left) to blue (right). Photo credit: George Lisensky, Beloit College

Subsequent research has developed sophisticated diagnostic and therapeutic ("theranostic") applications for these **spherical nucleic acid**[11] particles. These particles easily penetrate cell membranes and can report on the chemistry happening inside living cells.



General schematic of nanoflare-based detection.

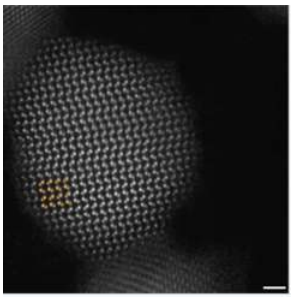
An important property of gold nanoparticles in these applications is their ability to **quench** the **fluorescence** of reporter molecules that are near their surface. Nucleic acid strands that contain a hairpin loop can position fluorescent molecules near the gold surface, where their fluorescence is turned off by nanoparticle quenching. Hybridization of these sequences to target RNA or DNA causes the fluorescence to turn on by moving the fluorescent molecule away from the nanoparticle surface. These so called "nanoflares" can thus signal the up- or down-regulation of specific genes inside cells. Nanoflares are the basis of the Verigene System, developed and commercialized by Nanosphere, Inc. to detect markers for infectious diseases and cancers.

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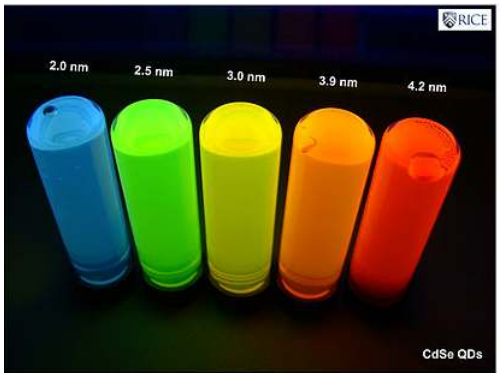
16.2: Semiconductor Quantum Dots

One of the most fascinating and well-studied mesoscopic effects occurs with semiconductor particles of various shapes when one or more of their dimensions is in the range of a few nanometers. These so-called "quantum dots" (0D), "quantum rods" (1D) and "nanosheets" (2D) acquire striking new electronic and optical properties.



Atomic resolution image of a CdSe nanoparticle.

The synthesis of semiconductor quantum dots, which is discussed in more detail below, is sufficiently well controlled to give essentially perfect crystals of a few thousand atoms, something that is statistically impossible in a macroscopic crystal. An image of such a crystal is shown at the right. In the synthesis, these crystals can be capped with an epitaxial layer of ligands or by a shell of a wider bandgap semiconductor (such as ZnS in the case of CdSe), so that the inner core is effectively a quantum well. Electron-hole pairs formed by excitation of the core semiconductor are confined there and cannot reach the external surface of the particle, where they might otherwise be trapped and recombine thermally. Consequently, the quantum yield for bandgap emission of semiconductor quantum dots is typically high, giving rise to the bright emission colors shown at the right for CdSe particles of different sizes. Because of their strong and narrow emission bands, quantum dots are of interest as luminescent tags for biological imaging applications, and also as light absorbers and emitters in solar cells and LEDs.



Emission colors of CdSe nanoparticles of different sizes. Smaller particles emit blue light because the exciton energy increases as the size decreases.

The size-dependence of the emission color comes primarily from a particle-in-a-box effect. The electron and hole that are created when the quantum dot absorbs light are bound together as an **exciton** by the confines of the "box". Louis Brus used first-order perturbation theory to determine that the bandgap of a semiconductor quantum dot is given approximately by:[4]

$$E_{gap} = E_{gap,bulk} + \frac{h^2}{8\mu R^2} - \frac{1.8e^2}{4R\pi\varepsilon\varepsilon_0} + \ldots \tag{16.2.1}$$

where R is the particle radius, μ is the electron-hole reduced mass ($1/\mu = 1/m_e^* + 1/m_h^*$), m_e^* and m_h^* are the electron and hole effective masses, and ε is the dielectric constant of the semiconductor. In this equation, the first term after the bulk bandgap is the kinetic energy due to confinement of the exciton, and the second term represents the electrostatic attractive energy between the confined electron and hole. Because the energy is a function of R^2, it can be widely tuned across the visible spectrum by changing the size of the quantum dot.

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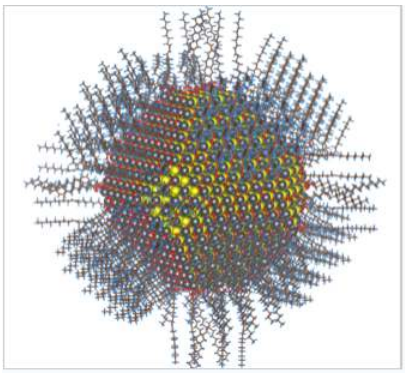
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16.3: Synthesis of Semiconductor Nanocrystals

Early work on the quantum size effect in semiconductor nanoparticles used simple metathesis reactions in the synthesis. For example, CdSe and PbS can be precipitated at ambient temperature by the reactions:

$$CdCl_{2(aq)} + H_2Se_{(g)} = CdSe_{(s)} + 2\,HCl_{(aq)}$$

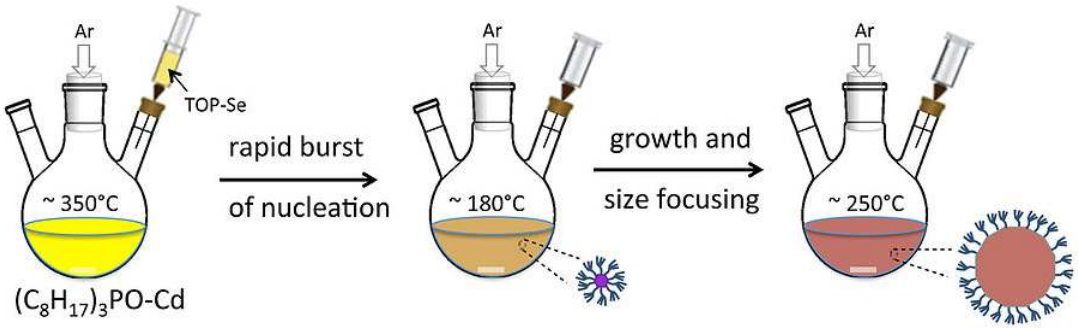
$$Pb(NO_3)_2 + H_2S_{(g)} = PbS_{(s)} + 2\,HNO_{3(aq)}$$



Complete atomistic model of a 5 nm diameter colloidal lead sulfide nanoparticle with surface passivation by oleic acid, oleyl and hydroxyl groups.

The growth of the particles was restricted by carrying out these reactions in different matrices, such as in polymer films or the silicate cages of zeolites, and capping ligands were also sometimes used to limit particle growth. While these reactions did produce nanoparticles, in general a broad distribution of particle sizes was obtained. The particles were also unstable to **Ostwald ripening** - in which large particles grow at the expense of smaller ones in order to minimize the total surface energy - because of the reversibility of the acid-forming synthetic reactions in aqueous media. The lack of good samples prevented detailed studies and the development of applications for semiconductor quantum dots.

A very important development in nanoparticle synthesis came in the early 1990's, when Murray, Norris, and Bawendi introduced the first non-aqueous, controlled growth process for II-VI semiconductor quantum dots.[5] The keys to this synthesis were (1) to use non-aqueous solvents and capping ligands to stabilize the products against ripening, (2) to carry out the reaction at high temperature to ensure good crystallinity, and (3) to separate the steps of particle **nucleation** and **growth**, and thereby obtain particles of uniform size. This procedure is illustrated below:

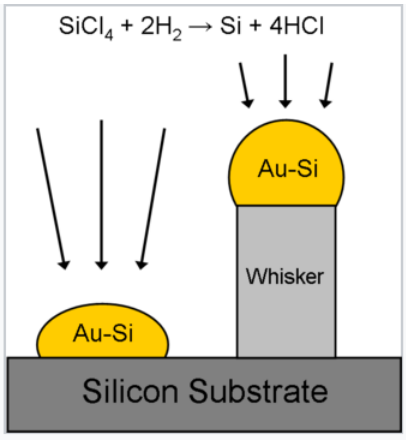


The synthesis is carried out in a coordinating, high boiling solvent that is a mixture of trioctylphosphine (**TOP**) and trioctylphosphine oxide (**TOPO**). In early experiments, organometallic cadmium compounds such as diethylcadmium were used as the metal source, but it was later found that these highly toxic and pyrophoric compounds could be replaced by CdO. At the start of the reaction, a selenium source, typically bis(trimethylsilyl)selenium, $[(CH_3)_3Si]_2Se$, dissolved in TOP is rapidly injected into the hot (350 °C) reaction mixture. The reaction causes a rapid burst of nanoparticle nucleation, but the temperature also drops as the cold solvent is injected and so the nucleation event ends quickly. The cooled solution now contains nanocrystal seeds. It is supersaturated in TOPO-Cd and TOP-Se, but particle growth proceeds slowly until the solution is heated again to the growth temperature, ca. 250°C. Particle growth and **size-focusing** occurs because small particles require less added material to grow by an

amount ΔR than larger particles. This is because the volume of an added shell around a spherical seed is $4\pi R^2\Delta R$, so for larger R, ΔR is smaller. Very narrow particle size distributions can be obtained under conditions of high supersaturation, where the rate of nanoparticle growth is fast relative to particle dissolution and Ostwald ripening.[6] The size distribution can then be narrowed further by adding a non-solvent such as hexane to the cooled reaction mixture. The largest particles precipitate first, followed by smaller particles. Because the nanoparticles are capped with a ligand shell of TOP, they can be re-suspended in organic solvents once they are size-separated.

The high temperature synthesis of semiconductor quantum dots has been applied to a broad variety of materials including II-VI, III-V, and IV-VI semiconductors. Monodisperse nanoparticles of **controlled shapes** can be made by variants of this method. For example, it is possible to adjust the conditions so that CdSe nucleates in the zincblende polymorph as tetrahedrally shaped seeds, and then grow polar wurtzite "arms" onto each triangular face, resulting in nanocrystal tetrapods. Numerous other nanocrystal shapes such as rods, arrowheads, rice (tapered rods), and polar structures such as Janus rods can be made by variants of this technique. These shape-control strategies often involve the use of ligands that adsorb specifically to certain crystal faces and inhibit their growth. For example, hexylphosphonic acid ligands adsorb selectively to Cd-rich crystal faces and thus lead to the growth of prismatic wurtzite-phase CdSe nanocrytals.

A second widely used method of semiconductor nanocrystal synthesis involves growth from molecular precursors and molten metal droplets, as shown in the figure at the right. The **vapor-liquid-solid (VLS)** and related **solution-liquid-solid (SLS)** growth processes rely on the fact that semiconductors such as Si, Ge, GaAs, InP, and others are soluble at high temperatures in liquid metals such as Au and Cu. The catalytic reduction of a molecule such as silicon tetrachloride ($SiCl_4$) at the surface of a gold nanocrystal liberates HCl gas and creates a solid solution of Si in Au. The presence of Si lowers the melting point of Au, and as more $SiCl_4$ reacts, a liquid **eutectic** droplet of the Si-Au alloy is formed. When this droplet becomes supersaturated in Si, a silicon nanocrystal nucleates and grows. This reaction can be performed on the surface of a macroscopic Si crystal, in which case nanocrystal "whiskers" grow from the surface, typically as single crystals and with an epitaxial orientation that is determined by the Si crystal face of the substrate. The diameter of the whiskers is controlled by the radius of the Au drops, which can be as small as a few nanometers and as large as several microns. Using this technique, "forests" of nanowires or microwires can be grown. Because the composition of the nanowire depends on the precursor being fed to the Au droplets, it is possible to make "totem pole" structures with varied compositions along the nanowire axis. Semiconductor shells can also be grown around the wires by **chemical vapor deposition (CVD)**. The VLS process can also be adapted to complex compositions for which no molecular precursor is available by using a laser to ablate the semiconductor from a solid target.



Epitaxial growth of silicon nanowires catalyzed by gold nanoparticles in the vapor-liquid-solid (VLS) process.

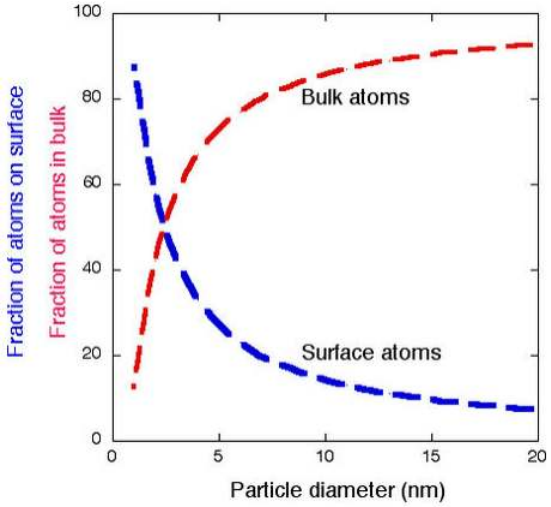
Semiconductor nanowires made by this method are the basis of extremely sensitive **biosensors**, in which a molecular binding event anywhere along the wire strongly affects its electrical conductivity.[7] Nanowire and microwire arrays are also being studied as **solar cell** and **lithium battery** materials, as well as nanoscale electronic and optoelectronic devices.

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16.4: Surface Energy

Nanoparticles have a substantial fraction of their atoms on the surface, as shown in the plot at the right.[8] This high surface area to volume ratio is an important factor in many of the physical properties of nanoparticles, such as their **melting point** and **vapor pressure**, and also in their **reactivity**. Heterogeneous catalysts, for example, are often based on nanoparticles because the catalytically reactive atoms are those that are on the surface of the particle.



The surface energy is always positive. A key quantity that is connected with the chemistry of all surfaces is the **surface energy**. This is the (thermodynamically unfavorable) energy of making "dangling bonds" at the surface. Atoms at the surface are under-coordinated, and because breaking bonds costs energy, surface atoms always have higher energy than atoms in the bulk. This happens regardless of whether the bonding is covalent (as in a metal), ionic (in a salt), or non-covalent (in a liquid such as water). We see this effect, for example, in water droplets that bead up on a waxy surface. The droplet contracts into a sphere (against the force of gravity that works to flatten it) in order to minimize the number of dangling hydrogen bonds at the surface.

In the case of metal or semiconductor particles, strong covalent bonds are broken at the surface. For example, a gold atom in bulk face-centered cubic Au has 12 nearest neighbors, but a gold atom on the (111) surface of the crystal (the most dense crystal plane of gold) has six nearest neighbors in-plane and three underneath, for a total of 9. We might expect the surface energy of this crystal face to be a little less (because the remaining bonds will become slightly stronger) than 3/12 = **1/4 of the bonding energy** of bulk Au, and this is in fact a fairly good rule of thumb for many materials. When translated into energy per unit area, the surface energy of metals and inorganic salts is usually in the range of 1-2 J/m^2.

Example: The sublimation energy of bulk gold is 334 kJ/mol, and the surface energy is 1.5 J/m^2. What percentage of the bulk bonding energy is lost by atoms at the (111) surface of a gold crystal?

To solve this problem, we need to know the surface area per Au atom. Gold has the face-centered cubic structure, and the unit cell edge length is 4.08 Å. From this we can determine that the Au-Au distance is 4.08/1.414 = 2.88 Å. In a hexagonal array of gold atoms with this interatomic spacing, the surface area per atom is (2.88 Å)^2 x 0.866 = 7.2 Å^2. Multiplying by Avogadro's number, we find that the area per mole of Au surface atoms on the (111) crystal face is **4.3 x 10^4 m^2.**

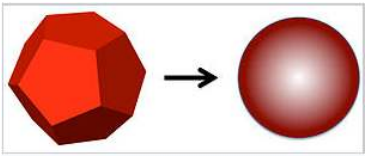
Now we multiply this area by the surface energy:

$(4.3 \times 10^4 \frac{m^2}{mol}) \times (1.5 \frac{J}{mol}) \times (\frac{1kJ}{1000J}) = \mathbf{+65kJ}$ per mole of Au surface atoms.

$\frac{65kJ}{334kJ} \times 100\% = \mathbf{19\%}$ of the bulk bonding energy is lost by atoms at the surface.

It is clear from this example that the surface energy of nanoparticles can have a major effect on their physical properties, since a large fraction of the atoms in a nanoparticle are on the surface. A good example of this is the dramatic depression of the **melting point**.

Solid nanocrystals are in general faceted, whereas liquid droplets made by melting nanocrystals adopt a spherical shape to minimize the surface area.



A faceted solid nanocrystal melts into a spherical droplet in order to minimize its surface energy.

Let's consider melting a silver nanocrystal that is 2 nm in diameter, meaning that about 1/2 of the atoms are on the surface. The spherical liquid droplet has lower surface area than the faceted crystal. For example, a cube has 1.24 times the surface area of a sphere of the same volume. If the decrease in surface area is about 20% upon melting, and the surface energy is about 1/4 of the bulk bonding energy of the atoms, then for a 2 nm diameter nanocrystal we would estimate that:

$$\Delta H^o_{fusion} \approx \Delta H^o_{fusion,\ bulk} - (\frac{1}{2})(0.25)(\frac{1}{4})\Delta H^o_{vap} = \Delta H^o_{fusion,\ bulk} - 0.025\Delta H^o_{vap,\ bulk} \tag{16.4.1}$$

where $\Delta H°_{vap,\ bulk}$, the heat of vaporization, is the total bonding energy of atoms in a bulk crystal. For silver, $\Delta H°_{fusion,\ bulk}$ = 11.3 kJ/mol and $\Delta H°_{vap,\ bulk}$ = 250 kJ/mol. From this we can calculate the heat of fusion of a 2 nm Ag nanocrystal:

$$\Delta H^o_{fusion} \approx 11.3 - (0.025)(25) = 5.1 \frac{kJ}{mol} \tag{16.4.2}$$

The melting point of bulk silver is 962 °C = 1235 K. Assuming that the entropy of fusion is the same in the bulk and in the nanocrystal, the melting point of the nanocrystal should be $1234K \times (\frac{5.1}{11.3}) = 557K = 284^{\circ}C$, a drop of almost 700 degrees from the bulk value. Experimentally, the melting point of a 2 nm diameter silver nanocrystal drops about **800 degrees below that of the bulk,** to 127 °C.[9] This is a whopping big change in the melting point, which is in reasonable agreement with our rough estimate.

The same effect - energetic destabilization of the surface atoms relative to bulk atoms - results in the **lower boiling point**, **higher vapor pressure**, **higher solubility**, and **higher reactivity** of nanocrystals relative to microcrystals (or larger crystals) of the same material.

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16.5: Carbon Nanomaterials

Fullerenes and Nanotubes

Introduction

Although nanomaterials had been known for many years prior to the report of C_{60} the field of nanoscale science was undoubtedly founded upon this seminal discovery. Part of the reason for this explosion in nanochemistry is that while carbon materials range from well-defined nano sized molecules (i.e., C_{60}) to tubes with lengths of hundreds of microns, they do not exhibit the instabilities of other nanomaterials as a result of the very high activation barriers to their structural rearrangement. As a consequence they are highly stable even in their unfunctionalized forms. Despite this range of carbon nanomaterials possible they exhibit common reaction chemistry: that of organic chemistry.

The previously unknown allotrope of carbon: C_{60}, was discovered in 1985, and in 1996, Curl, Kroto, and Smalley were awarded the Nobel Prize in Chemistry for the discovery. The other allotropes of carbon are graphite (sp^2) and diamond (sp^3). C_{60}, commonly known as the "buckyball" or "Buckminsterfullerene", has a spherical shape comprising of highly pyramidalized sp^2 carbon atoms. The C_{60} variant is often compared to the typical soccer football, hence buckyball. However, confusingly, this term is commonly used for higher derivatives. Fullerenes are similar in sheet structure to graphite but they contain pentagonal (or sometimes heptagonal) rings that prevent the sheet from being planar. The unusual structure of C_{60} led to the introduction of a new class of molecules known as fullerenes, which now constitute the third allotrope of carbon. Fullerenes are commonly defined as "any of a class of closed hollow aromatic carbon compounds that are made up of twelve pentagonal and differing numbers of hexagonal faces."

The number of carbon atoms in a fullerene range from C_{60} to C_{70}, C_{76}, and higher. Higher order fullerenes include carbon nanotubes that can be described as fullerenes that have been stretched along a rotational axis to form a tube. As a consequence of differences in the chemistry of fullerenes such as C_{60} and C_{70} as compared to nanotubes, these will be dealt with separately herein. In addition there have also been reports of nanohorns and nanofibers, however, these may be considered as variations on the general theme. It should be noted that fullerenes and nanotubes have been shown to be in flames produced by hydrocarbon combustion. Unfortunately, these naturally occurring varieties can be highly irregular in size and quality, as well as being formed in mixtures, making them unsuitable for both research and industrial applications.

Fullerenes

Carbon-60 (C_{60}) is probably the most studied individual type of nanomaterial. The spherical shape of C_{60} is constructed from twelve pentagons and twenty hexagons and resembles a soccer ball (Figure 16.5.1a). The next stable higher fullerene is C_{70} (Figure 16.5.1b) that is shaped like a rugby or American football. The progression of higher fullerenes continues in the sequence C_{74}, C_{76}, C_{78}, etc. The structural relationship between each involves the addition of six membered rings. Mathematically (and chemically) two principles define the existence of a stable fullerene, i.e., Euler's theorem and isolated pentagon rule (IPR). Euler's theorem states that for the closure of each spherical network, n ($n \geq 2$) hexagons and 12 pentagons are required while the IPR says no two pentagons may be connected directly with each other as destabilization is caused by two adjacent pentagons.

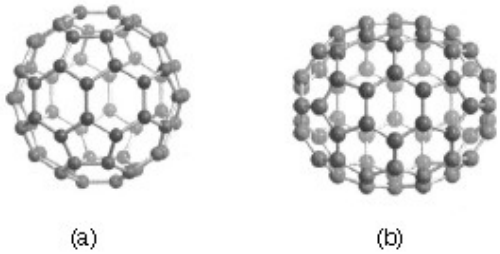


Figure 16.5.1: Molecular structures of (a) C_{60} and (b) C_{70}.

Although fullerenes are composed of sp^2 carbons in a similar manner to graphite, fullerenes are soluble in various common organic solvents. Due to their hydrophobic nature, fullerenes are most soluble in CS_2 (C_{60} = 7.9 mg/mL) and toluene (C_{60} = 2.8 mg/mL). Although fullerenes have a conjugated system, their aromaticity is distinctive from benzene that has all C-C bonds of equal lengths, in fullerenes two distinct classes of bonds exist. The shorter bonds are at the junctions of two hexagons ([6, 6] bonds) and the longer bonds at the junctions of a hexagon and a pentagon ([5,6] bonds). This difference in bonding is responsible for some of the observed reactivity of fullerenes.

Synthesis of fullerenes

The first observation of fullerenes was in molecular beam experiments at Rice University. Subsequent studies demonstrated that C_{60} it was relatively easy to produce grams of fullerenes. Although the synthesis is relatively straightforward fullerene purification remains a challenge and determines fullerene's commercial price. The first method of production of measurable quantities of fullerenes used laser vaporization of carbon in an inert atmosphere, but this produced microscopic amounts of fullerenes. Laboratory scales of fullerene are prepared by the vaporization of carbon rods in a helium atmosphere. Commercial production ordinarily employs a simple ac or dc arc. The fullerenes in the black soot collected are extracted in toluene and purified by liquid chromatography. The magenta C_{60} comes off the column first, followed by the red C_{70}, and other higher fullerenes. Even though the mechanism of a carbon arc differs from that of a resistively heated carbon rod (because it involves a plasma) the He pressure for optimum C_{60} formation is very similar.

A ratio between the mass of fullerenes and the total mass of carbon soot defines fullerene yield. The yields determined by UV-Vis absorption are approximately 40%, 10-15%, and 15% in laser, electric arc, and solar processes. Interestingly, the laser ablation technique has both the highest yield and the lowest productivity and, therefore, a scale-up to a higher power is costly. Thus, fullerene commercial production is a challenging task. The world's first computer controlled fullerene production plant is now operational at the MER Corporation, who pioneered the first commercial production of fullerene and fullerene products.

Endohedral fullerenes

Endohedral fullerenes are fullerenes that have incorporated in their inner sphere atoms, ions or clusters. Endohedral fullerenes are generally divided into two groups: endohedral metallofullerenes and non-metal doped fullerenes. The first endohedral metallofullerenes was called $La@C_{60}$. The @ sign in the name reflects the notion of a small molecule trapped inside a shell.

Doping fullerenes with metals takes place *in-situ* during the fullerene synthesis in an arc reactor or via laser evaporation. A wide range of metals have been encased inside a fullerene, i.e., Sc, Y, La, Ce, Ba, Sr, K, U, Zr, and Hf. Unfortunately, the synthesis of endohedral metallofullerenes is unspecific because in addition a high yield of unfilled fullerenes, compounds with different cage sizes are prepared (e.g., $La@C_{60}$ or $La@C_{82}$). A characteristic of endohedral metallofullerenes is that electrons will transfer from the metal atom to the fullerene cage and that the metal atom takes a position off-center in the cage. The size of the charge transfer is not always simple to determine, but it is usually between 2 and 3 units (e.g., $La_2@C_{80}$) but can be as high as 6 electrons (e.g., $Sc_3N@C_{80}$). These anionic fullerene cages are very stable molecules and do not have the reactivity associated with ordinary empty fullerenes (see below). This lack of reactivity is utilized in a method to purify endohedral metallofullerenes from empty fullerenes.

The endohedral $He@C_{60}$ and $Ne@C_{60}$ form when C_{60} is exposed to a pressure of around 3 bar of the appropriate noble gases. Under these conditions it was possible to dope 1 in every 650,000 C_{60} cages with a helium atom. Endohedral complexes with He, Ne, Ar, Kr and Xe as well as numerous adducts of the $He@C_{60}$ compound have also been proven with operating pressures of 3000 bars and incorporation of up to 0.1 % of the noble gases. The isolation of $N@C_{60}$, $N@C_{70}$ and $P@C_{60}$ is very unusual and unlike the metal derivatives no charge transfer of the pnictide atom in the center to the carbon atoms of the cage takes place.

Chemically functionalized fullerenes

Although fullerenes have a conjugated aromatic system all the carbons are quaternary (i.e., containing no hydrogen), which results in making many of the characteristic substitution reactions of planar aromatics impossible. Thus, only two types of chemical transformations exist: redox reactions and addition reactions. Of these, addition reactions have the largest synthetic value. Another remarkable feature of fullerene addition chemistry is the thermodymics of the process. Since the sp^2 carbon atoms in a fullerene are paramidalized there is significant strain energy. For example, the strain energy in C_{60} is *ca* 8 kcal/mol, which is 80% of its heat of formation. So the relief of this strain energy leading to sp^3 hybridized C atoms is the major driving force for addition reactions (Figure 16.5.2). As a consequence, most additions to fullerenes are exothermic reactions.

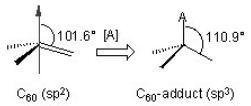


Figure 16.5.2: Strain release after addition of reagent A to a pyramidalize carbon of C_{60}.

Cyclic voltammetry (CV) studies show that C_{60} can be reduced and oxidized reversibly up to 6 electrons with one-electron transfer processes. Fulleride anions can be generated by electrochemical method and then be used to synthesize covalent organofullerene derivatives. Alkali metals can chemically reduce fullerene in solution and solid state to form M_xC_{60} (x = 3 - 6). C_{60} can also be

reduced by less electropositive metals like mercury to form C_{60}^- and C_{60}^{2-}. In addition, salts can also be synthesized with organic molecules, for example $[TDAE^+][C_{60}^-]$ possesses interesting electronic and magnetic behavior.

Geometric and electronic analysis predicted that fullerene behaves live an electro-poor conjugated polyolefin. Indeed C_{60} and C_{70} undergo a range of nucleophilic reactions with carbon, nitrogen, phosphorous and oxygen nucleophiles. C60 reacts readily with organolithium and Grignard compounds to form alkyl, phenyl or alkanyl fullerenes. Possibly the most widely used additions to fullerene is the Bingel reaction (Figure 16.5.3), where a carbon nucleophile, generated by deprotonation of α-halo malonate esters or ketones, is added to form a cyclopropanation product. The α-halo esters and ketones can also be generated in situ with I_2 or CBr_4 and a weak base as 1,8-diazabicyclo[5.4.0]unde-7ene (DBU). The Bingel reaction is considered one of the most versatile and efficient methods to functionalize C_{60}.

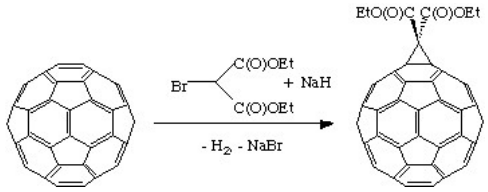


Figure 16.5.3: Bingel reaction of C_{60} with 2-bromoethylmalonate.

Cycloaddition is another powerful tool to functionalize fullerenes, in particular because of its selectivity with the 6,6 bonds, limiting the possible isomers (Figure 16.5.4). The dienophilic feature of the [6,6] double bonds of C_{60} enables the molecule to undergo various cycloaddition reactions in which the monoadducts can be generated in high yields. The best studies cycloadditon reactions of fullerene are [3+2] additions with diazoderivatives and azomethine ylides (Prato reactions). In this reaction, azomethine ylides can be generated *in situ* from condensation of α-amino acids with aldehydes or ketones, which produce 1,3 dipoles to further react with C_{60} in good yields (Figure 16.5.5). Hundreds of useful building blocks have been generated by those two methods. The Prato reactions have also been successfully applied to carbon nanotubes.

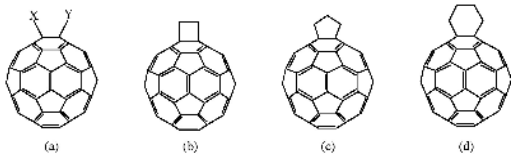


Figure 16.5.4: Geometrical shapes built onto a [6,6] ring junction: a) open, b) four-membered ring, c) five-membered ring, and d) six-membered ring.

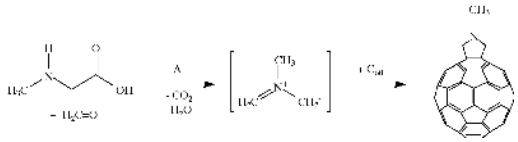


Figure 16.5.5: Prato reaction of C_{60} with N-methyglycine and paraformaldehyde.

The oxidation of fullerenes, such as C_{60}, has been of increasing interest with regard to applications in photoelectric devices, biological systems, and possible remediation of fullerenes. The oxidation of C_{60} to $C_{60}O_n$ (n = 1, 2) may be accomplished by photooxidation, ozonolysis, and epoxidation. With each of these methods, there is a limit to the isolable oxygenated product, $C_{60}O_n$ with $n < 3$. Highly oxygenated fullerenes, $C_{60}O_n$ with $3 \leq n \leq 9$, have been prepared by the catalytic oxidation of C_{60} with $ReMeO_3/H_2O_2$.

Carbon nanotubes

A key breakthrough in carbon nanochemistry came in 1993 with the report of needle-like tubes made exclusively of carbon. This material became known as carbon nanotubes (CNTs). There are several types of nanotubes. The first discovery was of multi walled tubes (MWNTs) resembling many pipes nested within each other. Shortly after MWNTs were discovered single walled nanotubes (SWNTs) were observed. Single walled tubes resemble a single pipe that is potentially capped at each end. The properties of single walled and multi walled tubes are generally the same, although single walled tubes are believed to have superior mechanical strength and thermal and electrical conductivity; it is also more difficult to manufacture them.

Single walled carbon nanotubes (SWNTs) are by definition fullerene materials. Their structure consists of a graphene sheet rolled into a tube and capped by half a fullerene (Figure 16.5.6). The carbon atoms in a SWNT, like those in a fullerene, are sp2 hybridized. The structure of a nanotube is analogous to taking this graphene sheet and rolling it into a seamless cylinder. The

different types of SWNTs are defined by their diameter and chirality. Most of the presently used single-wall carbon nanotubes have been synthesized by the pulsed laser vaporization method, however, increasingly SWNTs are prepared by vapor liquid solid catalyzed growth.

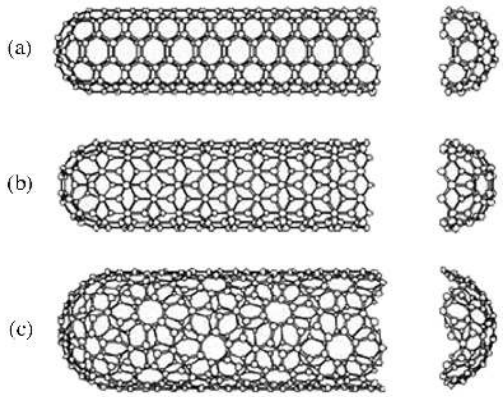


Figure 16.5.6: Structure of single walled carbon nanotubes (SWNTs) with (a) armchair, (b) zig-zag, and (c) chiral chirality.

The physical properties of SWNTs have made them an extremely attractive material for the manufacturing of nano devices. SWNTs have been shown to be stronger than steel as estimates for the Young's modulus approaches 1 Tpa. Their electrical conductance is comparable to copper with anticipate current densities of up to 10^{13} A/cm^2 and a resistivity as low as 0.34 x 10^{-4} Ω.cm at room temperatures. Finally, they have a high thermal conductivity (3000 - 6000 W.m/K).

The electronic properties of a particular SWNT structure are based on its chirality or twist in the structure of the tube which is defined by its *n*,*m* value. The values of *n* and *m* determine the chirality, or "twist" of the nanotube. The chirality in turn affects the conductance of the nanotube, its density, its lattice structure, and other properties. A SWNT is considered metallic if the value *n*-*m* is divisible by three. Otherwise, the nanotube is semi-conducting. The external environment also has an effect on the conductance of a tube, thus molecules such as O_2 and NH_3 can change the overall conductance of a tube, while the presence of metals have been shown to significantly effect the opto-electronic properties of SWNTs.

Multi walled carbon nanotubes (MWNTs) range from double walled NTs, through many-walled NTs (Figure 16.5.7) to carbon nanofibers. Carbon nanofibers are the extreme of multi walled tubes (Figure 16.5.8) and they are thicker and longer than either SWNTs or MWNTs, having a cross-sectional of ca. 500 Å^2 and are between 10 to 100 μm in length. They have been used extensively in the construction of high strength composites.

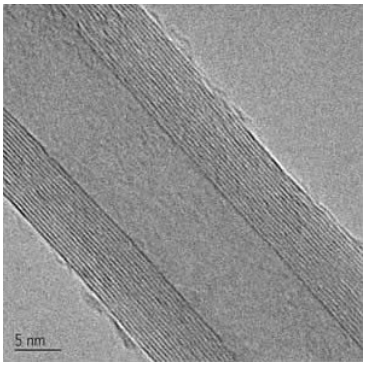


Figure 16.5.7: TEM image of an individual multi walled carbon nanotube (MWNTs). Copyright of Nanotech Innovations.

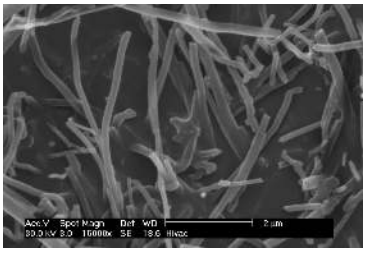


Figure 16.5.8: SEM image of vapor grown carbon nanofibers.

Synthesis of carbon nanotubes

A range of methodologies have been developed to produce nanotubes in sizeable quantities, including arc discharge, laser ablation, high pressure carbon monoxide (HiPco), and vapor liquid solid (VLS) growth. All these processes take place in vacuum or at low pressure with a process gases, although VLS growth can take place at atmospheric pressure. Large quantities of nanotubes can be synthesized by these methods; advances in catalysis and continuous growth processes are making SWNTs more commercially viable.

The first observation of nanotubes was in the carbon soot formed during the arc discharge production of fullerenes. The high temperatures caused by the discharge caused the carbon contained in the negative electrode to sublime and the CNTs are deposited on the opposing electrode. Tubes produced by this method were initially multi walled tubes (MWNTs). However, with the addition of cobalt to the vaporized carbon, it is possible to grow single walled nanotubes. This method it produces a mixture of components, and requires further purification to separate the CNTs from the soot and the residual catalytic metals. Producing CNTs in high yield depends on the uniformity of the plasma arc, and the temperature of the deposit forming on the carbon electrode.

Higher yield and purity of SWNTs may be prepared by the use of a dual-pulsed laser. SWNTs can be grown in a 50% yield through direct vaporization of a Co/Ni doped graphite rod with a high-powered laser in a tube furnace operating at 1200 °C. The material produced by this method appears as a mat of “ropes”, 10 - 20 nm in diameter and up to 100 μm or more in length. Each rope consists of a bundle of SWNTs, aligned along a common axis. By varying the process parameters such as catalyst composition and the growth temperature, the average nanotube diameter and size distribution can be varied. Although arc-discharge and laser vaporization are currently the principal methods for obtaining small quantities of high quality SWNTs, both methods suffer from drawbacks. The first is that they involve evaporating the carbon source, making scale-up on an industrial level difficult and energetically expensive. The second issue relates to the fact that vaporization methods grow SWNTs in highly tangled forms, mixed with unwanted forms of carbon and/or metal species. The SWNTs thus produced are difficult to purify, manipulate, and assemble for building nanotube-device architectures for practical applications.

In order to overcome some of the difficulties of these high-energy processes, the chemical catalysis method was developed in which a hydrocarbon feedstock is used in combination with a metal catalyst. The catalyst is typically, but not limited to iron, colbalt, or iron/molybdenum, it is heated under reducing conditions in the presence of a suitable carbon feedstock, e.g., ethylene. This method can be used for both SWNTs and MWNTs; the formation of each is controlled by the identity of the catalyst and the reaction conditions. A convenient laboratory scale apparatus is available from Nanotech Innovations, Inc., for the synthesis of highly uniform, consistent, research sample that uses pre-weighed catalyst/carbon source ampoules. This system, allows for 200 mg samples of MWNTs to be prepared for research and testing. The use of CO as a feedstock, in place of a hydrocarbon, led to the development of the high-pressure carbon monoxide (HiPco) procedure for SWNT synthesis. By this method, it is possible to produce gram quantities of SWNTs, unfortunately, efforts to scale beyond that have not met with complete success.

Initially developed for small-scale investigations of catalyst activity, vapor liquid solid (VLS) growth of nanotubes has been highly studied, and now shows promise for large-scale production of nanotubes. Recent approaches have involved the use of well-defined nanoparticle or molecular precursors and many different transition metals have been employed, but iron, nickel, and cobalt remain to be the focus of most research. The nanotubes grow at the sites of the metal catalyst; the carbon-containing gas is broken apart at the surface of the catalyst particle, and the carbon is transported to the edges of the particle, where it forms the nanotube. The length of the tube grown in surface supported catalyst VLS systems appears to be dependent on the orientation of the growing tube with the surface. By properly adjusting the surface concentration and aggregation of the catalyst particles it is possible to synthesize vertically aligned carbon nanotubes, i.e., as a carpet perpendicular to the substrate.

Of the various means for nanotube synthesis, the chemical processes show the greatest promise for industrial scale deposition in terms of its price/unit ratio. There are additional advantages to the VLS growth, which unlike the other methods is capable of growing nanotubes directly on a desired substrate. The growth sites are controllable by careful deposition of the catalyst. Additionally, no other growth methods have been developed to produce vertically aligned SWNTs.

Chemical functionalization of carbon nanotubes

The limitation of using carbon nanotubes in any practical applications has been its solubility; for example SWNTs have little to no solubility in most solvent due to the aggregation of the tubes. Aggregation/roping of nanotubes occurs as a result of the high van der Waals binding energy of *ca*. 500 eV per mm of tube contact. The van der Waals force between the tubes is so great, that it take tremendous energy to pry them apart, making it very to make combination of nanotubes with other materials such as in composite applications. The functionalization of nanotubes, i.e., the attachment of “chemical functional groups” provides the path to

overcome these barriers. Functionalization can improve solubility as well as processibility, and has been used to align the properties of nanotubes to those of other materials. The clearest example of this is the ability to solubilize nanotubes in a variety of solvents, including water. It is important when discussing functionalization that a distinction is made between covalent and non-covalent functionalization.

Current methods for solubilizing nanotubes without covalent functionalization include highly aromatic solvents, super acids, polymers, or surfactants. Non-covalent "functionalization" is generally on the concept of supramolecular interactions between the SWNT and some macromolecule as a result of various adsorption forces, such as van der Waals' and π-stacking interactions. The chemical speciation of the nanotube itself is not altered as a result of the interaction. In contrast, covalent functionalization relies on the chemical reaction at either the sidewall or end of the SWNT. As may be expected the high aspect ratio of nanotubes means that sidewall functionalization is much more important than the functionalization of the cap. Direct covalent sidewall functionalization is associated with a change of hybridization from sp^2 to sp^2 and a simultaneous loss of conjugation. An alternative approach to covalent functionalization involves the reaction of defects present (or generated) in the structure of the nanotube. Defect sites can be the open ends and holes in the sidewalls, and pentagon and heptagon irregularities in the hexagon graphene framework (often associated with bends in the tubes). All these functionalizations are exohedral derivatizations. Taking the hollow structure of nanotubes into consideration, endohedral functionalization of SWNTs is possible, i.e., the filling of the tubes with atoms or small molecules. It is important to note that covalent functionalization methods have one problem in common: extensive covalent functionalization modifies SWNT properties by disrupting the continuous π–system of SWNTs.

Various applications of nanotubes require different, specific modification to achieve desirable physical and chemical properties of nanotubes. In this regard, covalent functionalization provides a higher degree of fine-tuning the chemistry and physics of SWNTs than non-covalent functionalization. Until now, a variety of methods have been used to achieve the functionalization of nanotubes (Figure 16.5.9).

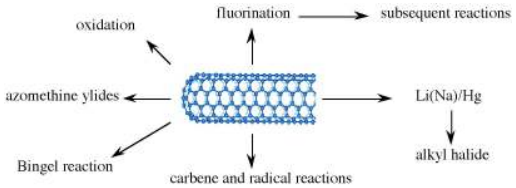


Figure 16.5.9: Schematic description of various covalent functionalization strategies for SWNTs.

Taking chemistry developed for C_{60}, SWNTs may be functionalized using 1,3 dipolar addition of azomethine ylides. The functionalized SWNTs are soluble in most common organic solvents. The azomethine ylide functionalization method was also used for the purification of SWNTs. Under electrochemical conditions, aryl diazonium salts react with SWNTs to achieve functionalized SWNTs, alternatively the diazonium ions may be generated *in-situ* from the corresponding aniline, while a solvent free reaction provides the best chance for large-scale functionalization this way. In each of these methods it is possible to control the amount of functionalization on the tube by varying reaction times and the reagents used; functionalization as high as 1 group per every 10 - 25 carbon atoms is possible.

Organic functionalization through the use of alkyl halides, a radical pathway, on tubes treated with lithium in liquid ammonia offers a simple and flexible route to a range of functional groups. In this reaction, functionalization occurs on every 17 carbons. Most success has been found when the tubes are dodecylated. These tubes are soluble in chloroform, DMF, and THF.

The addition of oxygen moieties to SWNT sidewalls can be achieved by treatment with acid or wet air oxidation, and ozonolysis. The direct epoxidation of SWNTs may be accomplished by the direct reaction with a peroxide reagent, or catalytically. Catalytic de-epoxidation (Figure 16.5.10) allows for the quantitative analysis of sidewall epoxide and led to the surprising result that previously assumed "pure" SWNTs actually contain *ca*. 1 oxygen per 250 carbon atoms.

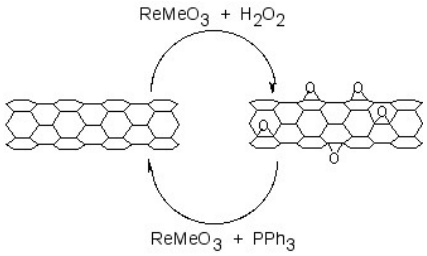


Figure 16.5.10: Catalytic oxidation and de-epoxidation of SWNTs.

One of the easiest functionalization routes, and a useful synthon for subsequent conversions, is the fluorination of SWNTs, using elemental fluorine. Importantly, a C:F ratios of up to 2:1 can be achieved without disruption of the tubular structure. The fluorinated SWNTs (F-SWNTs) proved to be much more soluble than pristine SWNTs in alcohols (1 mg/mL in *iso*-propanol), DMF and other selected organic solvents. Scanning tunneling microscopy (STM) revealed that the fluorine formed bands of approximately 20 nm, while calculations using DFT revealed 1,2 addition is more energetically preferable than 1,4 addition, which has been confirmed by solid state ^{13}C NMR. F-SWNTs make highly flexible synthons and subsequent elaboration has been performed with organo lithium, Grignard reagents, and amines.

Functionalized nanotubes can be characterized by a variety of techniques, such as atomic force microscopy (AFM), transmission electron microscopy (TEM), UV-vis spectroscopy, and Raman spectroscopy. Changes in the Raman spectrum of a nanotube sample can indicate if functionalization has occurred. Pristine tubes exhibit two distinct bands. They are the radial breathing mode (230 cm^{-1}) and the tangential mode (1590 cm^{-1}). When functionalized, a new band, called the disorder band, appears at *ca.*1350 cm^{-1}. This band is attributed to sp^3-hybridized carbons in the tube. Unfortunately, while the presence of a significant D mode is consistent with sidewall functionalization and the relative intensity of D (disorder) mode versus the tangential G mode (1550 – 1600 cm^{-1}) is often used as a measure of the level of substitution. However, it has been shown that Raman is an unreliable method for determination of the extent of functionalization since the relative intensity of the D band is also a function of the substituents distribution as well as concentration. Recent studies suggest that solid state ^{13}C NMR are possibly the only definitive method of demonstrating covalent attachment of particular functional groups.

Coating carbon nanotubes: creating inorganic nanostructures

Fullerenes, nanotubes and nanofibers represent suitable substrates for the seeding other materials such as oxides and other minerals, as well as semiconductors. In this regard, the carbon nanomaterial acts as a seed point for the growth as well as a method of defining unusual aspect ratios. For example, silica fibers can be prepared by a number of methods, but it is only through coating SWNTs that silica nano-fibers with of micron lengths with tens of nanometers in diameter may be prepared.

While C_{60} itself does not readily seed the growth of inorganic materials, liquid phase deposition of oxides, such as silica, in the presence of fullerenol, $C_{60}(OH)_n$, results in the formation of uniform oxide spheres. It appears the fullerenol acts as both a reagent and a physical point for subsequent oxide growth, and it is C_{60}, or an aggregate of C_{60}, that is present within the spherical particle. The addition of fullerenol alters the morphology and crystal phase of $CaCO_3$ precipitates from aqueous solution, resulting in the formation of spherical features, 5-pointed flower shaped clusters, and triangular crystals as opposed to the usual rhombic crystals. In addition, the meta-stable vaterite phase is observed with the addition of $C_{60}(OH)_n$.

As noted above individual SWNTs may be obtained in solution when encased in a cylindrical micelle of a suitable surfactant. These individualized nanotubes can be coated with a range of inorganic materials. Liquid phase deposition (LPD) appears to have significant advantages over other methods such as incorporating surfacted SWNTs into a preceramic matrix, *in situ* growth of the SWNT in an oxide matrix, and sol-gel methods. The primary advantage of LPD growth is that individual SWNTs may be coated rather than bundles or ropes. For example, SWNTs have been coated with silica by liquid phase deposition (LPD) using a silica/H_2SiF_6 solution and a surfactant-stabilized solution of SWNTs. The thickness of the coating is dependent on the reaction mixture concentration and the reaction time. The SWNT core can be removed by thermolysis under oxidizing conditions to leave a silica nano fiber. It is interesting to note that the use of a surfactant is counter productive when using MWNTs and VGFs, in this case surface activation of the nanotube offers the suitable growth initiation. Pre-oxidation of the MWNT or VGF allows for uniform coatings to be deposited. The coated SWNTs, MWNTs, and VGFs can be subsequently reacted with suitable surface reagents to impart miscibility in aqueous solutions, guar gels, and organic matrixes. In addition to simple oxides, coated nanotubes have been prepared with minerals such as carbonates and semiconductors.

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Graphene

Introduction

Graphene is a one-atom-thick planar sheet of sp^2-bonded carbon atoms that are densely packed in a honeycomb crystal lattice (Figure 16.5.11). The name comes from "graphite" and "alkene"; graphite itself consists of many graphene sheets stacked together.

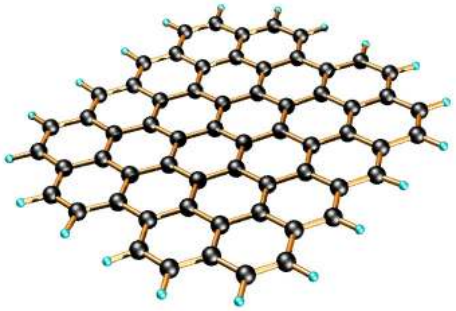


Figure 16.5.11: Idealized structure of a single graphene sheet.

Single-layer graphene nanosheets were first characterized in 2004, prepared by mechanical exfoliation (the "scotch-tape" method) of bulk graphite. Later graphene was produced by epitaxial chemical vapor deposition on silicon carbide and nickel substrates. Most recently, graphene nanoribbons (GNRs) have been prepared by the oxidative treatment of carbon nanotubes and by plasma etching of nanotubes embedded in polymer films.

Physical properties of graphene

Graphene has been reported to have a Young's modulus of 1 TPa and intrinsic strength of 130 GP; similar to single walled carbon nanotubes (SWNTs). The electronic properties of graphene also have some similarity with carbon nanotubes. Graphene is a zero-bandgap semiconductor. Electron mobility in graphene is extraordinarily high (15,000 cm^2/V.s at room temperature) and ballistic electron transport is reported to be on length scales comparable to that of SWNTs. One of the most promising aspects of graphene involves the use of GNRs. Cutting an individual graphene layer into a long strip can yield semiconducting materials where the bandgap is tuned by the width of the ribbon.

While graphene's novel electronic and physical properties guarantee this material will be studied for years to come, there are some fundamental obstacles yet to overcome before graphene based materials can be fully utilized. The aforementioned methods of graphene preparation are effective; however, they are impractical for large-scale manufacturing. The most plentiful and inexpensive source of graphene is bulk graphite. Chemical methods for exfoliation of graphene from graphite provide the most realistic and scalable approach to graphene materials.

Graphene layers are held together in graphite by enormous van der Waals forces. Overcoming these forces is the major obstacle to graphite exfoliation. To date, chemical efforts at graphite exfoliation have been focused primarily on intercalation, chemical derivatization, thermal expansion, oxidation-reduction, the use of surfactants, or some combination of these.

Graphite oxide

Probably the most common route to graphene involves the production of graphite oxide (GO) by extremely harsh oxidation chemistry. The methods of Staudenmeier or Hummers are most commonly used to produce GO, a highly exfoliated material that is dispersible in water. The structure of GO has been the subject of numerous studies; it is known to contain epoxide functional groups along the basal plane of sheets as well as hydroxyl and carboxyl moieties along the edges (Figure 16.5.12). In contrast to other methods for the synthesis of GO, the the *m*-peroxybenzoic acid (*m*-CPBA) oxidation of microcrystalline synthetic graphite at room temperature yields graphite epoxide in high yield, without significant additional defects.

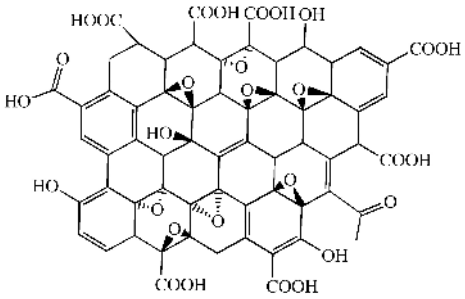


Figure 16.5.12: Idealized structure proposed for graphene oxide (GO). Adapted from C. E. Hamilton, PhD Thesis, Rice University (2009).

As graphite oxide is electrically insulating, it must be converted by chemical reduction to restore the electronic properties of graphene. Chemically converted graphene (CCG) is typically reduced by hydrazine or borohydride. The properties of CCG can never fully match those of graphene for two reasons:

1. Oxidation to GO introduces defects.
2. Chemical reduction does not fully restore the graphitic structure.

As would be expected, CCG is prone to aggregation unless stabilized. Graphene materials produced from pristine graphite avoid harsh oxidation to GO and subsequent (incomplete) reduction; thus, materials produced are potentially much better suited to electronics applications.

A catalytic approach to the removal of epoxides from fullerenes and SWNTs has been applied to graphene epoxide and GO. Treatment of oxidized graphenes with methyltrioxorhenium ($MeReO_3$, MTO) in the presence of PPh_3 results in the oxygen transfer, to form $O{=}PPh_3$ and allow for quantification of the C:O ratio.

Homogeneous graphene dispersions

An alternate approach to producing graphene materials involves the use of pristine graphite as starting material. The fundamental value of such an approach lies in its avoidance of oxidation to GO and subsequent (incomplete) reduction, thereby preserving the desirable electronic properties of graphene. There is precedent for exfoliation of pristine graphite in neat organic solvents without oxidation or surfactants. It has been reported that *N*,*N*-dimethylformamide (DMF) dispersions of graphene are possible, but no detailed characterization of the dispersions were reported. In contrast, Coleman and coworkers reported similar dispersions using *N*-methylpyrrolidone (NMP), resulting in individual sheets of graphene at a concentration of ≤0.01 mg/mL. NMP and DMF are highly polar solvents, and not ideal in cases where reaction chemistry requires a nonpolar medium. Further, they are hygroscopic, making their use problematic when water must be excluded from reaction mixtures. Finally, DMF is prone to thermal and chemical decomposition.

Recently, dispersions of graphene has been reported in *ortho*-dichlorobenzene (ODCB) using a wide range of graphite sources. The choice of ODCB for graphite exfoliation was based on several criteria:

1. ODCB is a common reaction solvent for fullerenes and is known to form stable SWNT dispersions.
2. ODCB is a convenient high-boiling aromatic, and is compatible with a variety of reaction chemistries.
3. ODCB, being aromatic, is able to interact with graphene *via* π-π stacking.
4. It has been suggested that good solvents for graphite exfoliation should have surface tension values of 40 – 50 mJ/m^2. ODCB has a surface tension of 36.6 mJ/m^2, close to the proposed range.

Graphite is readily exfoliated in ODCB with homogenization and sonication. Three starting materials were successfully dispersed: microcrystalline synthetic, thermally expanded, and highly ordered pyrolytic graphite (HOPG). Dispersions of microcrystalline

synthetic graphite have a concentration of 0.03 mg/mL, determined gravimetrically. Dispersions from expanded graphite and HOPG are less concentrated (0.02 mg/mL).

High resolution transmission electron microscopy (HRTEM) shows mostly few-layer graphene (n < 5) with single layers and small flakes stacked on top (Figure 16.5.13). Large graphitic domains are visible; this is further supported by selected area electron diffraction (SAED) and fast Fourier transform (FFT) in selected areas. Atomic force microscope (AFM) images of dispersions sprayed onto silicon substrates shows extremely thin flakes with nearly all below 10 nm. Average height is 7 - 10 nm. The thinnest are less than 1 nm, graphene monolayers. Lateral dimensions of nanosheets range from 100 – 500 nm.

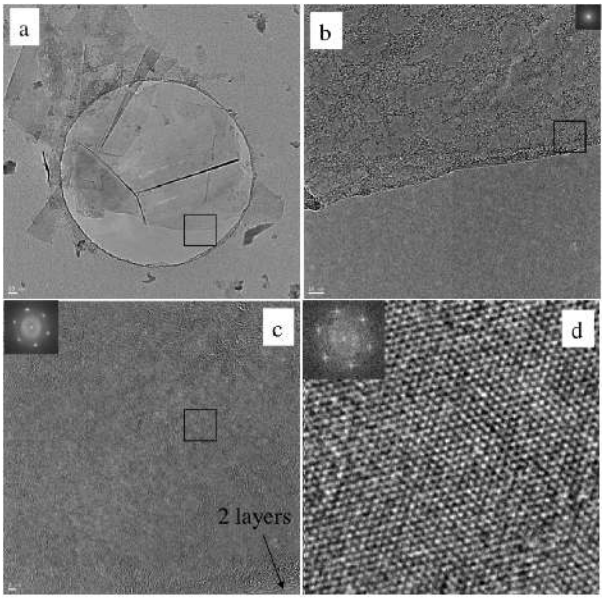


Figure 16.5.13: TEM images of single layer graphene from HOPG dispersion. (a) monolayer and few layer of graphene stacked with smaller flakes; (b) selected edge region from (a), (c) selected area from (b) with FFT inset, (d) HRTEM of boxed region in (c) showing lattice fringes with FFT inset. Adapted from C. E. Hamilton, PhD Thesis, Rice University (2009).

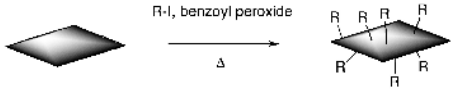
As-deposited films cast from ODCB graphene show poor electrical conductivity, however, after vacuum annealing at 400 °C for 12 hours the films improve vastly, having sheet resistances on the order of 60 Ω/sq. By comparison, graphene epitaxially grown on Ni has a reported sheet resistance of 280 Ω/sq.

Covalent functionalization of graphene and graphite oxide

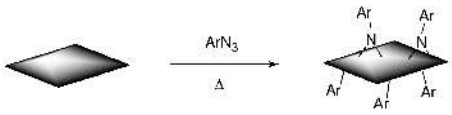
The covalent functionalization of SWNTs is well established. Some routes to covalently functionalized SWNTs include esterification/ amidation, reductive alkylation (Billups reaction), and treatment with azomethine ylides (Prato reaction), diazonium salts, or nitrenes. Conversely, the chemical derivatization of graphene and GO is still relatively unexplored.

Some methods previously demonstrated for SWNTs have been adapted to GO or graphene. GO carboxylic acid groups have been converted into acyl chlorides followed by amidation with long-chain amines. Additionally, the coupling of primary amines and amino acids via nucleophilic attack of GO epoxide groups has been reported. Yet another route coupled isocyanates to carboxylic acid groups of GO. Functionalization of partially reduced GO by aryldiazonium salts has also been demonstrated. The Billups reaction has been performed on the intercalation compound potassium graphite (C_8K), as well as graphite fluoride, and most recently GO. Graphene alkylation has been accomplished by treating graphite fluoride with alkyllithium reagents.

ODCB dispersions of graphene may be readily converted to covalently functionalize graphene. Thermal decomposition of benzoyl peroxide is used to initiate radical addition of alkyl iodides to graphene in ODCB dispersions.



Additionally, functionalized graphene with nitrenes generated by thermal decomposition of aryl azides



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16.6: Transmission Electron Microscopy

TEM: An Overview

Transmission electron microscopy (TEM) is a form of microscopy which in which a beam of electrons transmits through an extremely thin specimen, and then interacts with the specimen when passing through it. The formation of images in a TEM can be explained by an optical electron beam diagram in Figure 16.6.1. TEMs provide images with significantly higher resolution than visible-light microscopes (VLMs) do because of the smaller de Broglie wavelength of electrons. These electrons allow for the examination of finer details, which are several thousand times higher than the highest resolution in a VLM. Nevertheless, the magnification provide in a TEM image is in contrast to the absorption of the electrons in the material, which is primarily due to the thickness or composition of the material.

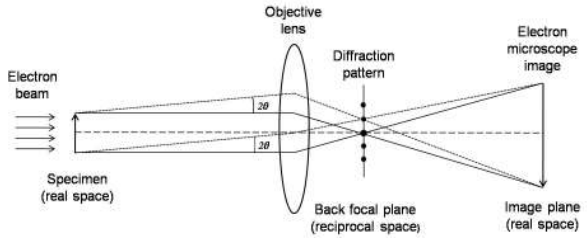


Figure 16.6.1 The optical electron beam diagram of TEM.

When a crystal lattice spacing (d) is investigated with electrons with wavelength λ, diffracted waves will be formed at specific angles 2θ, satisfying the Bragg condition, 16.6.1.

$$2dsin\theta = \lambda \tag{16.6.1}$$

The regular arrangement of the diffraction spots, the so-called diffraction pattern (DP), can be observed. While the transmitted and the diffracted beams interfere on the image plane, a magnified image (electron microscope image) appears. The plane where the DP forms is called the reciprocal space, which the image plane is called the real space. A Fourier transform can mathematically transform the real space to reciprocal space.

By adjusting the lenses (changing their focal lengths), both electron microscope images and DP can be observed. Thus, both observation modes can be successfully combined in the analysis of the microstructures of materials. For instance, during investigation of DPs, an electron microscope image is observed. Then, by inserting an aperture (selected area aperture), adjusting the lenses, and focusing on a specific area that we are interested in, we will get a DP of the area. This kind of observation mode is called a selected area diffraction. In order to investigate an electron microscope image, we first observe the DP. Then by passing the transmitted beam or one of the diffracted beams through a selected aperture and changing to the imaging mode, we can get the image with enhanced contrast, and precipitates and lattice defects can easily be identified.

Describing the resolution of a TEM in terms of the classic Rayleigh criterion for VLMs, which states that the smallest distance that can be investigated, δ, is given approximately by 16.6.2, where λ is the wavelength of the electrons, μ is the refractive index of the viewing medium, and β is the semi-angle of collection of the magnifying lens.

$$\delta = \frac{0.61\lambda}{\mu\, sin\beta} \tag{16.6.2}$$

ccording to de Broglie's ideas of the wave-particle duality, the particle momentum p is related to its wavelength λ through Planck's constant h, 16.6.3.

$$\lambda = \frac{h}{p} \tag{16.6.3}$$

Momentum is given to the electron by accelerating it through a potential drop, V, giving it a kinetic energy, eV. This potential energy is equal to the kinetic energy of the electron, 16.6.4.

$$eV = \frac{m_o u^2}{2} \tag{16.6.4}$$

Based upon the foregoing, we can equate the momentum (p) to the electron mass (mo), multiplied by the velocity (v) and substituting for v from 16.6.5 i.e., 16.6.6.

$$p = m_o u = (2m_o eV)^{\frac{1}{2}} \tag{16.6.5}$$

These equations define the relationship between the electron wavelength, λ, and the accelerating voltage of the electron microscope (V), Eq. However, we have to consider about the relative effects when the energy of electron more than 100 keV. So in order to be exact we must modify 16.6.6 to give 16.6.7.

$$\lambda = \frac{h}{(2m_o eV)^{\frac{1}{2}}} \tag{16.6.6}$$

$$\lambda = \frac{h}{[2m_o eV(1 + \frac{eV}{2m_o e^2})]^{\frac{1}{2}}} \tag{16.6.7}$$

From 16.6.2 and 16.6.3, if a higher resolution is desired a decrease in the electron wavelength is accomplished by increasing the accelerating voltage of the electron microscope. In other words, the higher accelerating rating used, the better resolution obtained.

Why the Specimen Should be Thin

The scattering of the electron beam through the material under study can form different angular distribution (Figure 16.6.2) and it can be either forward scattering or back scattering. If an electron is scattered < 90o, then it is forward scattered, otherwise, it is backscattered. If the specimen is thicker, fewer electrons are forward scattered and more are backscattered. Incoherent, backscattered electrons are the only remnants of the incident beam for bulk, non-transparent specimens. The reason that electrons can be scattered through different angles is related to the fact that an electron can be scattered more than once. Generally, the more times of scattering happen, the greater the angle of scattering.

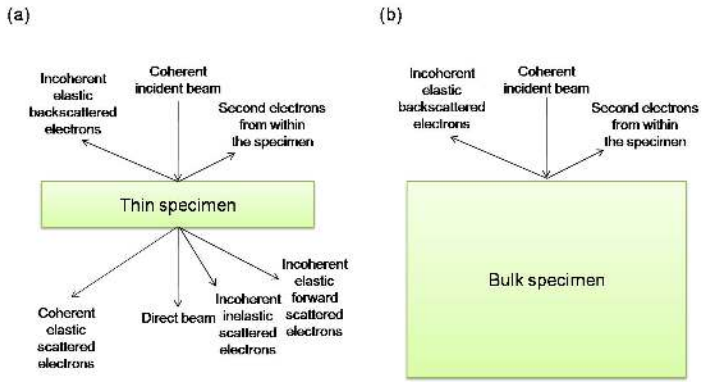


Figure 16.6.2 Two different kinds of electron scattering form (a) a thin specimen and (b) a bulk specimen.

All scattering in the TEM specimen is often approximated as a single scattering event since it is the simplest process. If the specimen is very thin, this assumption will be reasonable enough. If the electron is scattered more than once, it is called 'plural scattering.' It is generally safe to assume single scattering occurs, unless the specimen is particularly thick. When the times of scattering increase, it is difficult to predict what will happen to the electron and to interpret the images and DPs. So, the principle is 'thinner is better', i.e., if we make thin enough specimens so that the single-scattering assumption is plausible, and the TEM research will be much easier.

In fact, forward scattering includes the direct beam, most elastic scattering, refraction, diffraction, particularly Bragg diffraction, and inelastic scattering. Because of forward scattering through the thin specimen, a DP or an image would be showed on the viewing screen, and an X-ray spectrum or an electron energy-loss spectrum can be detected outside the TEM column. However, backscattering still cannot be ignored, it is an important imagine mode in the SEM.

Limitations of TEM

Interpreting Transmission Images

One significant problem that might encounter when TEM images are analyzed is that the TEM present us with 2D images of a 3D specimen, viewed in transmission. This problem can be illustrated by showing a picture of two rhinos side by side such that the

head of one appears attached to the rear of the other (Figure 16.6.3).

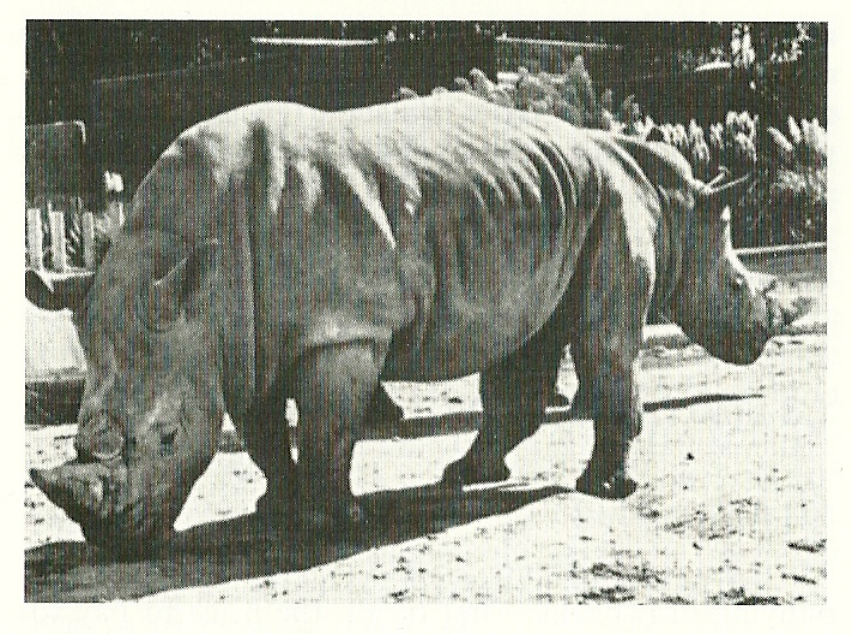


Figure 16.6.3 In projection, this photograph of two rhinos appears as one two-headed beast, because sometimes people have difficulty to translate a 2D image to a 3D image. Adapted from D. B. Williams and C. B. Carter, Transmission Electron Microscopy: A Textbook for Material Science, 2nd Ed., Springer, New York (2009).

One aspect of this particular drawback is that a single TEM images has no depth sensitivity. There often is information about the top and bottom surfaces of the specimen, but this is not immediately apparent. There has been progress in overcoming this limitation, by the development of electron tomography, which uses a sequence of images taken at different angles. In addition, there has been improvement in specimen-holder design to permit full 360o rotation and, in combination with easy data storage and manipulation; nanotechnologists have begun to use this technique to look at complex 3D inorganic structures such as porous materials containing catalyst particles.

Electron Beam Damage

A detrimental effect of ionizing radiation is that it can damage the specimen, particularly polymers (and most organics) or certain minerals and ceramics. Some aspects of beam damage made worse at higher voltages. Figure 16.6.4 shows an area of a specimen damaged by high-energy electrons. However, the combination of more intense electron sources with more sensitive electron detectors, and the use computer enhancement of noisy images, can be used to minimize the total energy received by the sample.

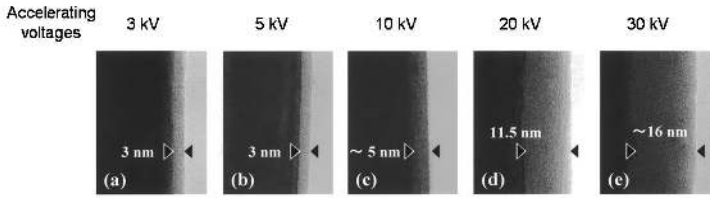


Figure 16.6.4 High-resolution TEM images at the slit edge of the GaAs samples prepared by slit focused ion beam. GaAs samples prepared at (a) 3 kV, (b) 5 kV, (c) 10 kV, (d) 20 kV, and (e) 30 kV. The thickness of the amorphous layer produced by focused ion beam is shown in each image. Adapted from Y. Yabuuchi, S. Tametou, T. Okano, S. Inazato, S. Sadayamn, and Y. Tamamoto, *J. Electron Micros.*, 2004, **53**, 5.

Sample Preparation

The specimens under study have to be thin if any information is to be obtained using transmitted electrons in the TEM. For a sample to be transparent to electrons, the sample must be thin enough to transmit sufficient electrons such that enough intensity falls on the screen to give an image. This is a function of the electron energy and the average atomic number of the elements in the sample. Typically for 100 keV electrons, a specimen of aluminum alloy up to ~ 1 µm would be thin, while steel would be thin up to about several hundred nanometers. However, thinner is better and specimens < 100 nm should be used wherever possible.

The method to prepare the specimens for TEM depends on what information is required. In order to observe TEM images with high resolution, it is necessary to prepare thin films without introducing contamination or defects. For this purpose, it is important to select an appropriate specimen preparation method for each material, and to find an optimum condition for each method.

Crushing

A specimen can be crushed with an agate mortar and pestle. The flakes obtained are suspended in an organic solvent (e.g., acetone), and dispersed with a sonic bath or simply by stirring with a glass stick. Finally, the solvent containing the specimen flakes is dropped onto a grid. This method is limited to materials which tend to cleave (e.g., mica).

Electropolishing

Slicing a bulk specimen into wafer plates of about 0.3 mm thickness by a fine cutter or a multi-wire saw. The wafer is further thinned mechanically down to about 0.1 mm in thickness. Electropolishing is performed in a specific electrolyte by supplying a direct current with the positive pole at the thin plate and the negative pole at a stainless steel plate. In order to avoid preferential polishing at the edge of the specimen, all the edges are cover with insulating paint. This is called the window method. The electropolishing is finished when there is a small hole in the plate with very thin regions around it (Figure 16.6.5). This method is mainly used to prepare thin films of metals and alloys.

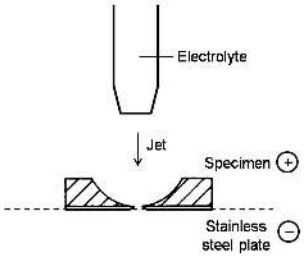


Figure 16.6.5 Principle of jet electropolishing method. The specimen and the stainless steel plate is electronic positive and negative, respectively.

Chemical Polishing

Thinning is performed chemically, i.e., by dipping the specimen in a specific solution. As for electropolishing, a thin plate of 0.1~0.2 mm in thickness should be prepared in advance. If a small dimple is made in the center of the plate with a dimple grinder, a hole can be made by etching around the center while keeping the edge of the specimen relatively thick. This method is frequently used for thinning semiconductors such as silicon. As with electro-polishing, if the specimen is not washed properly after chemical etching, contamination such as an oxide layer forms on the surface.

Ultramicrotomy

Specimens of thin films or powders are usually fixed in an acrylic or epoxy resin and trimmed with a glass knife before being sliced with a diamond knife. This process is necessary so that the specimens in the resin can be sliced easily by a diamond knife. Acrylic resins are easily sliced and can be removed with chloroform after slicing. When using an acrylic resin, a gelatin capsule is used as a vessel. Epoxy resin takes less time to solidify than acrylic resins, and they remain strong under electron irradiation. This method has been used for preparing thin sections of biological specimens and sometimes for thin films of inorganic materials which are not too hard to cut.

Ion Milling

A thin plate (less than 0.1 mm) is prepared from a bulk specimen by using a diamond cutter and by mechanical thinning. Then, a disk 3 mm in diameter is made from the plate using a diamond knife or a ultrasonic cutter, and a dimple is formed in the center of the surface with a dimple grinder. If it is possible to thin the disk directly to 0.03 mm in thickness by mechanical thinning without using a dimple grinder, the disk should be strengthened by covering the edge with a metal ring. Ar ions are usually used for the sputtering, and the incidence angle against the disk specimen and the accelerating voltage are set as 10 - 20o and a few kilovolts, respectively. This method is widely used to obtain thin regions of ceramics and semiconductors in particular, and also for cross section of various multilayer films.

Focused Ion Beam (FIB)

This method was originally developed for the purpose of fixing semiconductor devices. In principle, ion beams are sharply focused on a small area, and the specimen in thinned very rapidly by sputtering. Usually Ga ions are used, with an accelerating voltage of about 30 kV and a current of about 10 A/cm2. The probe size is several tens of nanometers. This method is useful for specimens containing a boundary between different materials, where it may be difficult to homogeneously thin the boundary region by other methods such as ion milling.

Vacuum Evaporation

The specimen to be studied is set in a tungsten-coil or basket. Resistance heating is applied by an electric current passing through the coil or basket, and the specimen is melted, then evaporated (or sublimed), and finally deposited onto a substrate. The deposition process is usually carried under a pressure of 10-3-10-4 Pa, but in order to avoid surface contamination, a very high vacuum is necessary. A collodion film or cleaved rock salt is used as a substrate. Rock salt is especially useful in forming single crystals with a special orientation relationship between each crystal and the substrate. Salt is easily dissolved in water, and then the deposited films can be fixed on a grid. Recently, as an alternative to resistance heating, electron beam heating or an ion beam sputtering method has been used to prepare thin films of various alloys. This method is used for preparing homogeneous thin films of metals and alloys, and is also used for coating a specimen with the metal of alloy.

The Characteristics of the Grid

The types of TEM specimens that are prepared depend on what information is needed. For example, a self-supporting specimen is one where the whole specimen consists of one material (which may be a composite). Other specimens are supported on a grid or on a Cu washer with a single slot. Some grids are shown in Figure 16.6.6. Usually the specimen or grid will be 3 mm in diameter.

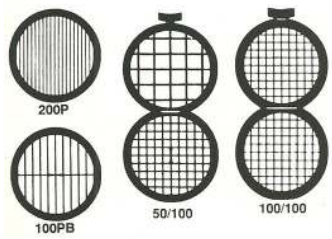


Figure 16.6.6 TEM sample support mesh grids. A diameter of a grid is usually 3.05 mm, however, some grids with diameters of 2.30 mm are also be used for earlier microscopes. Adapted from D. B. Williams and C. B. Carter, Transmission Electron Microscopy: A Textbook for Material Science, 2nd Ed., Springer, New York (2009).

TEM specimen stage designs include airlocks to allow for insertion of the specimen holder into the vacuum with minimal increase in pressure in other areas of the microscope. The specimen holders are adapted to hold a standard size of grid upon which the sample is placed or a standard size of self-supporting specimen. Standard TEM grid sizes is a 3.05 mm diameter ring, with a thickness and mesh size ranging from a few to 100 µm. The sample is placed onto the inner meshed area having diameter of approximately 2.5 mm. The grid materials usually are copper, molybdenum, gold or platinum. This grid is placed into the sample holder which is paired with the specimen stage. A wide variety of designs of stages and holders exist, depending upon the type of experiment being performed. In addition to 3.05 mm grids, 2.3 mm grids are sometimes, if rarely, used. These grids were particularly used in the mineral sciences where a large degree of tilt can be required and where specimen material may be extremely rare. Electron transparent specimens have a thickness around 100 nm, but this value depends on the accelerating voltage.

Once inserted into a TEM, the sample is manipulated to allow study of the region of interest. To accommodate this, the TEM stage includes mechanisms for the translation of the sample in the XY plane of the sample, for Z height adjustment of the sample holder, and usually at least one rotation degree of freedom. Most TEMs provide the ability for two orthogonal rotation angles of movement with specialized holder designs called double-tilt sample holders.

A TEM stage is required to have the ability to hold a specimen and be manipulated to bring the region of interest into the path of the electron beam. As the TEM can operate over a wide range of magnifications, the stage must simultaneously be highly resistant to mechanical drift as low as a few nm/minute while being able to move several µm/minute, with repositioning accuracy on the order of nanometers.

Transmission Electron Microscopy Image for Multilayer-Nanomaterials

Although, TEMs can only provide 2D analysis for a 3D specimen; magnifications of 300,000 times can be routinely obtained for many materials making it an ideal methodfor the study of nanomaterials. Besides from the TEM images, darker areas of the image show that the sample is thicker or denser in these areas, so we can observe the different components and structures of the specimen by the difference of color. For investigating multilayer-nanomaterials, a TEM is usually the first choice, because not only does it provide a high resolution image for nanomaterials but also it can distinguish each layer within a nanostructured material.

Observations of Multilayer-nanomaterials

TEM was been used to analyze the depth-graded W/Si multilayer films. Multilayer films were grown on polished, 100 mm thick Si wafers by magnetron sputtering in argon gas. The individual tungsten and silicon layer thicknesses in periodic and depth-graded multilayers are adjusted by varying the computer-controlled rotational velocity of the substrate platen. The deposition times required to produce specific layer thicknesses were determined from detailed rate calibrations. Samples for TEM were prepared by focused ion beam milling at liquid N2 temperature to prevent any beam heating which might result in re-crystallization and/or re-growth of any amorphous or fine grained polycrystalline layers in the film.

TEM measurements were made using a JEOL-4000 high-resolution transmission electron microscope operating at 400 keV; this instrument has a point-to-point resolution of 0.16 nm. Large area cross-sectional images of a depth-graded multilayer film obtained under medium magnification (~100 kX) were acquired at high resolution. A cross-sectional TEM image showed 150 layers W/Si film with the thickness of layers in the range of 3.33 ~ 29.6 nm (Figure 16.6.7shows a part of layers). The dark layers are tungsten and the light layers are silicon and they are separated by the thin amorphous W–Si interlayers (gray bands). By the high resolution of the TEM and the nature characteristics of the material, each layer can be distinguished clearly with their different darkness.

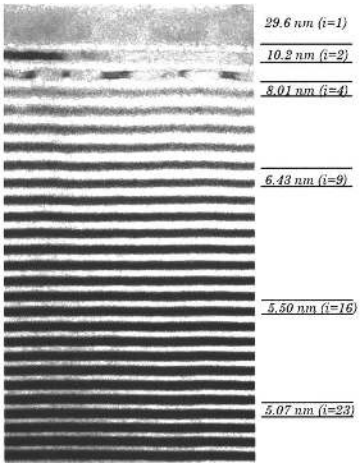


Figure 16.6.7 Cross-sectional transmission electron micrograph of the top portion of a depth-graded W/Si multilayer structure. Selected bilayer indices and thicknesses are indicated. The tungsten (dark bands) and silicon (light bands) layers are separated by thin amorphous W–Si interlayers (gray bands). The topmost silicon layer is not completely visible in this image. Adapted from D. L. Windt, F. E. Christensen, W. W. Craig, C. Hailey, F. A. Harrison, M. Jimenez-Garate, R. Kalyanaraman, and P. H. Mao, J. Appl. Phys., 2000, 88, 460.

Not all kinds of multilayer nanomaterials can be observed clearly under TEM. A materials consist of pc-Si:H multilayers were prepared by a photo-assisted chemical vapor deposition (photo-CVD) using a low-pressure mercury lamp as an UV light source to dissociate the gases. The pc-Si:H multilayer included low H2-diluted a-Si:H sublayers (SL's) and highly H2-diluted a-Si:H sublayers (SH's). Control of the CVD gas flow (H2|SiH4) under continuous UV irradiation resulted in the deposition of multilayer films layer by layer.

For a TEM measurement, a 20 nm thick undiluted a-Si:H film on a c-Si wafer before the deposition of multilayer to prevent from any epitaxial growth. Figure 16.6.8 shows a cross-sectional TEM image of a six-cycled pc-Si:H multilayer specimen. The white dotted lines are used to emphasize the horizontal stripes, which have periodicity in the TEM image. As can be seen, there are no significant boundaries between SL and SH could be observed because all sublayers are prepared in H2 gas. In order to get the more accurate thickness of each sublayer, other measurements might be necessary.

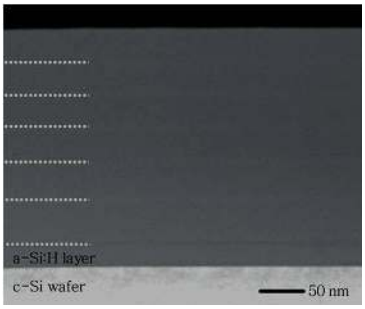


Figure 16.6.8 Cross-sectional TEM image of a 6-cycled pc-Si:H multilayer. Before the multilayer deposition, a 20 nm thick a-Si:H was deposited on a c-Si substrate. Adapted from S. W. Kwon, J. Kwak, S. Y. Myong, and K. S. Lim, *J. Non-Cryst. Solid*, 2006, **352**, 1132.

TEM Imaging of Carbon Nanomaterials

Transmission electron microscopy (TEM) is a form of microscopy that uses an high energy electron beam (rather than optical light). A beam of electrons is transmitted through an ultra thin specimen, interacting with the specimen as it passes through. The image (formed from the interaction of the electrons with the sample) is magnified and focused onto an imaging device, such as a photographic film, a fluorescent screen,or detected by a CCD camera. In order to let the electrons pass through the specimen, the specimen has to be ultra thin, usually thinner than 10 nm.

The resolution of TEM is significantly higher than light microscopes. This is because the electron has a much smaller de Broglie wavelength than visible light (wavelength of 400~700 nm). Theoretically, the maximum resolution, d, has been limited by λ, the wavelength of the detecting source (light or electrons) and NA, the numerical aperture of the system.

$$d = \frac{\lambda}{2n\ sin\alpha} \approx \frac{\lambda}{2NA} \tag{16.6.8}$$

For high speed electrons (in TEM, electron velocity is close to the speed of light, c, so that the special theory of relativity has to be considered), the λe:

$$\lambda_e = \frac{h}{\sqrt{2m_0E(1+E/2m_0c^2)}} \tag{16.6.9}$$

According to this formula, if we increase the energy of the detecting source, its wavelength will decrease, and we can get higher resolution. Today, the energy of electrons used can easily get to 200 keV, sometimes as high as 1 MeV, which means the resolution is good enough to investigate structure in sub-nanometer scale. Because the electrons is focused by several electrostatic and electromagnetic lenses, like the problems optical camera usually have, the image resolution is also limited by aberration, especially the spherical aberration called Cs. Equipped with a new generation of aberration correctors, transmission electron aberration-corrected microscope (TEAM) can overcome spherical aberration and get to half angstrom resolution.

Although TEAM can easily get to atomic resolution, the first TEM invented by Ruska in April 1932 could hardly compete with optical microscope, with only 3.6×4.8 = 14.4 magnification. The primary problem was the electron irradiation damage to sample in poor vacuum system. After World War II, Ruska resumed his work in developing high resolution TEM. Finally, this work brought him the Nobel Prize in physics 1986. Since then, the general structure of TEM hasn't changed too much as shown in Figure 16.6.9. The basic components in TEM are: electron gun, condenser system, objective lens (most important len in TEM which determines the final resolution), diffraction lens, projective lenses (all lens are inside the equipment column, between apertures), image recording system (used to be negative films, now is CCD cameras) and vacuum system.

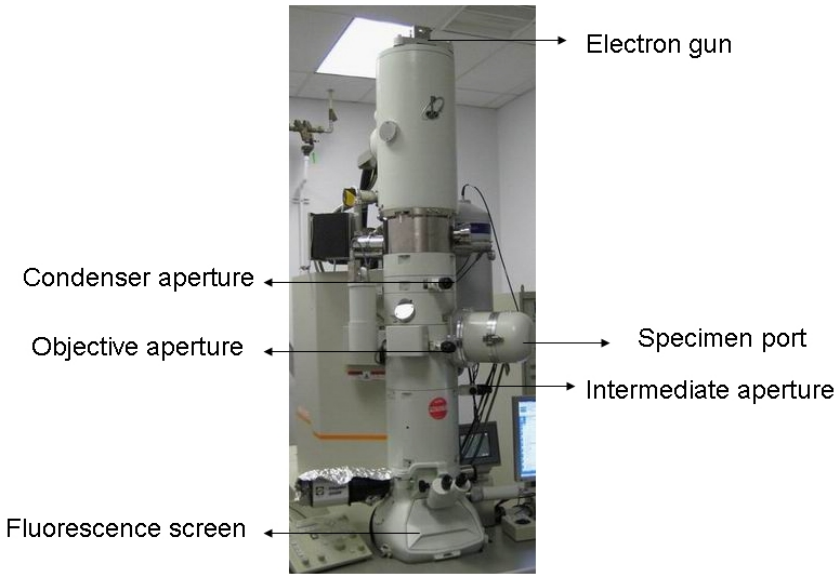


Figure 16.6.9 Position of the basic components in a TEM.

The Family of Carbon Allotropes and Carbon Nanomaterials

Common carbon allotropes include diamond, graphite, amorphrous C (a-C), fullerene (also known as buckyball), carbon nanotube (CNT, including single wall CNT and multi wall CNT), graphene. Most of them are chemically inert and have been found in nature. We can also define carbon as sp2 carbon (which is graphite), sp3 carbon (which is diamond) or hybrids of sp2 and sp3 carbon. As shown in Figure, (a) is the structure of diamond, (b) is the structure of graphite, (c) graphene is a single sheet of graphite, (d) is amorphous carbon, (e) is C60, and (f) is single wall nanotube. As for carbon nanomaterials, fullerene, CNT and graphene are the three most well investigated, due to their unique properties in both mechanics and electronics. Under TEM, these carbon nanomaterials will display three different projected images.

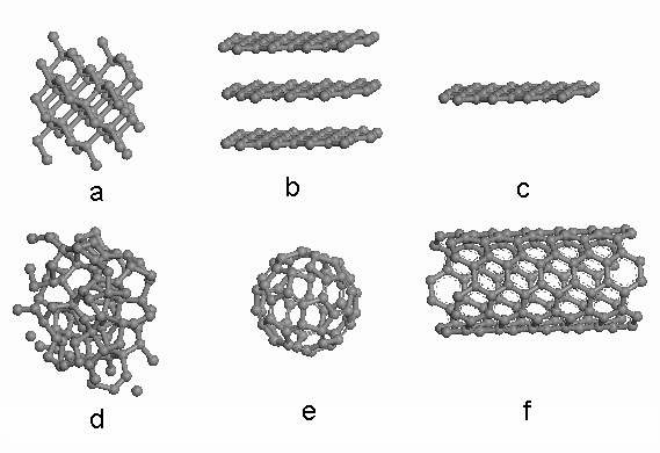


Figure 16.6.10 Six allotropes of carbon: a) diamond, b) graphite, c) graphene, d) amorphous carbon, e) C60 (Buckminsterfullerene or buckyball), f) single-wall carbon nanotube or buckytube.

Atomic Structure of Carbon Nanomaterials under TEM

All carbon naomaterials can be investigated under TEM. Howerver, because of their difference in structure and shape, specific parts should be focused in order to obtain their atomic structure.

For C60, which has a diameter of only 1 nm, it is relatively difficult to suspend a sample over a lacey carbon grid (a common kind of TEM grid usually used for nanoparticles). Even if the C60 sits on a thin a-C film, it also has some focus problems since the surface profile variation might be larger than 1 nm. One way to solve this problem is to encapsulate the C60 into single wall CNTs, which is known as nano peapods. This method has two benefits:

CNT helps focus on C60. Single wall is aligned in a long distance (relative to C60). Once it is suspended on lacey carbon film, it is much easier to focus on it. Therefore, the C60 inside can also be caught by minor focus changes.
The CNT can protect C60 from electron irradiation. Intense high energy electrons can permanently change the structure of the CNT. For C60, which is more reactive than CNTs, it can not survive after exposing to high dose fast electrons.
In studying CNT cages, C92 is observed as a small circle inside the walls of the CNT. While a majority of electron energy is absorbed by the CNT, the sample is still not irradiation-proof. Thus, as is seen in Figure 16.6.11, after a 123 s exposure, defects can be generated and two C92 fused into one new larger fullerene.

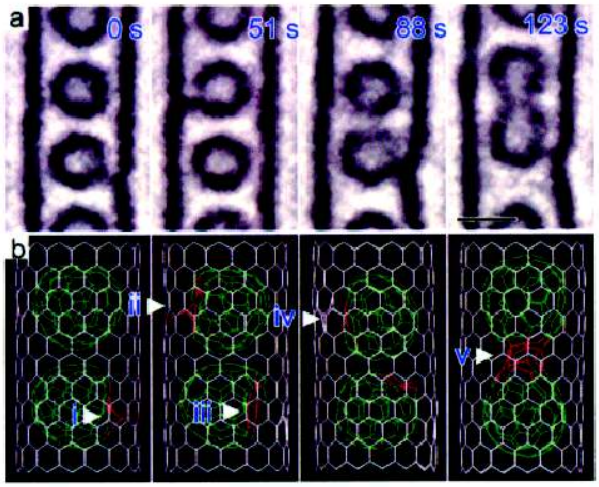


Figure 16.6.11 C_{92} encapsulated in SWNTs under different electron irradiation time. Courtesy of Dr. Kazutomo SUENAGA, adapted from K. Urita, Y. Sato, K. Suenaga, A. Gloter, A. Hasimoto, M. Ishida, T. Shimada, T. Shinohara, S. Iijima, *Nano Lett.*, 2004, **4**, 2451. Copyright American Chemical Society (2004).

Although, the discovery of C_{60} was first confirmed by mass spectra rather than TEM. When it came to the discovery of CNTs, mass spectra was no longer useful because CNTs shows no individual peak in mass spectra since any sample contains a range of CNTs with different lengths and diameters. On the other hand, HRTEM can provide a clear image evidence of their existence. An example is shown in Figure 16.6.12

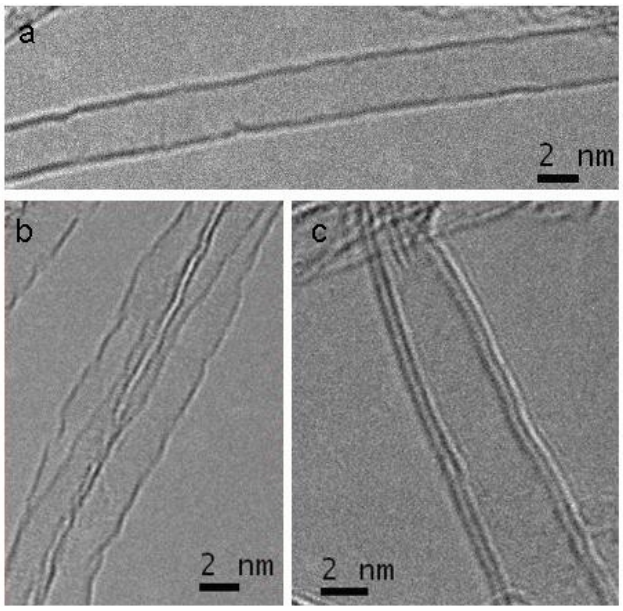


Figure 16.6.11 TEM images of SWNT and DWCNTs. Parallel dark lines corresponds to (002) lattice image of graphite. (a) and (b) SWNTs have 1 layer graphene sheet, diameter 3.2 nm. (c) DWCNT, diameter 4.0 nm.

Graphene is a planar fullerene sheet. Until recently, Raman, AFM and optical microscopy (graphene on 300 nm SiO2 wafer) were the most convenient methods to characterize samples. However, in order to confirm graphene's atomic structure and determine the

difference between mono-layer and bi-layer, TEM is still a good option. In Figure 16.6.13 a monolayer suspended graphene is observed with its atomic structure clearly shown. Inset is the FFT of the TEM image, which can be used as a filter to get an optimized structure image. High angle annular dark field (HAADF) image usually gives better contrast for different particles on it. It is also sensitive with changes of thickness, which allows a determination of the number of graphene layers.

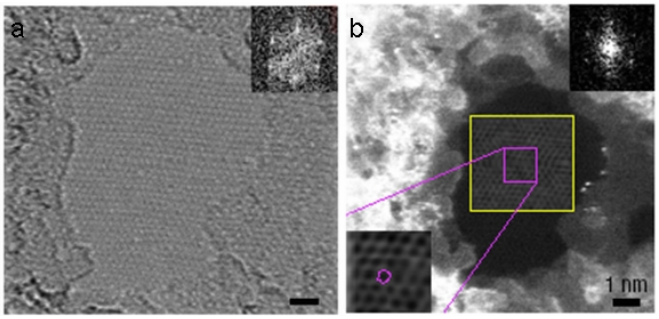


Figure 16.6.13 HRTEM of monolayer graphene. (a) Bright filed. (b) High Angle Annular Dark Field. Courtesy of Dr M. H. Gass, adapted from M. H. Gass, U. Bangert, A. L. Bleloch, P. Wang, R. R. Nair, and A. K. Geim, Nature Nanotechnol., 2008, 3, 676.

Graphene Stacking and Edges Direction

Like the situation in CNT, TEM image is a projected image. Therefore, even with exact count of edge lines, it is not possible to conclude that a sample is a single layer graphene or multi-layer. If folding graphene has AA stacking (one layer is superposed on the other), with a projected direction of [001], one image could not tell the thickness of graphene. In order to distinguish such a bilayer of graphene from a single layer of graphene, a series of tilting experiment must be done. Different stacking structures of graphene are shown in Figure 16.6.13a.

Theoretically, graphene has the potential for interesting edge effects. Based upon its sp2 structure, its edge can be either that of a zigzag or armchair configuration. Each of these possess different electronic properties similar to that observed for CNTs. For both research and potential application, it is important to control the growth or cutting of graphene with one specific edge. But before testing its electronic properties, all the edges have to be identified, either by directly imaging with STM or by TEM. Detailed information of graphene edges can be obtained with HRTEM, simulated with fast fourier transform (FFT). In Figure 16.6.14b, armchair directions are marked with red arrow respectively. A clear model in Figurec shows a 30 degree angle between zigzag edge and armchair edge.

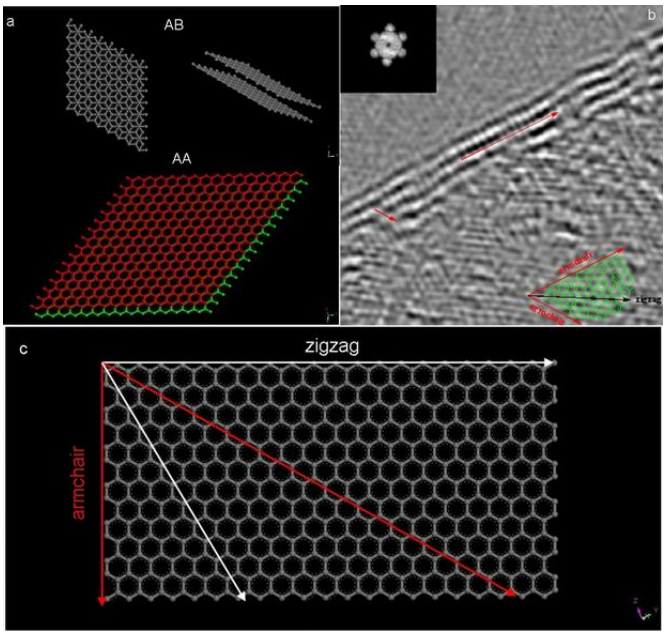


Figure 16.6.14 (a) Graphene stacking structure; (b) HRTEM image of graphene edges: zigzag and armchain (inset is FFT); (c) graphene edge model, a 30° angle between zigzag and armchair direction.

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Transmission Electron Energy Loss Spectroscopy

Electron energy loss spectroscopy (EELS) is a technique that measures electronic excitations within solid-state materials. When an electron beam with a narrow range of kinetic energy is directed at a material some electrons will be inelastically scattered, resulting in a kinetic energy loss. Electrons can be inelastically scattered from phonon excitations, plasmon excitations, interband transitions, or inner shell ionization. EELS measures the energy loss of these inelastically scattered electrons and can yield information on atomic composition, bonding, electronic properties of valance and conduction bands and surface properties. An example of atomic level composition mapping is shown in Figure 16.6.15a. EELS has even been used to measure pressure and temperature within materials.

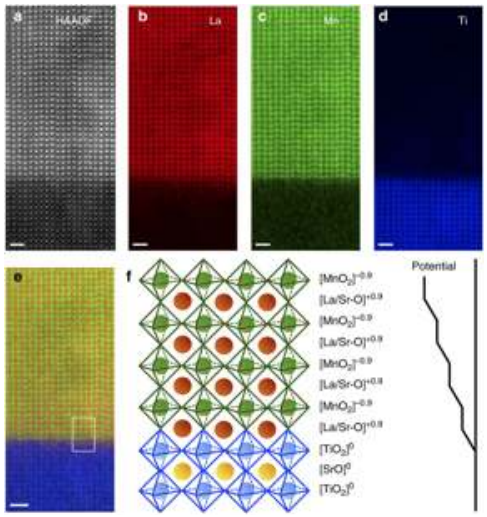


Figure 16.6.15 EEL Map showing atomic composition with atomic scale spatial resolution. (a) Shows a high angle annular dark field (HAADF) image with atomic resolution of a LaxSr1-xMnO3 film grow on TiO2. (b) La (c) Mn (d) Ti elemental data obtain from a STEM-EELS measurement. (e) Overlayed image of b-d showing relative positions of La, Mn, and Ti compared to atomic resolution imaging. (f) Model of theoretical packing in LaxSr1-xMnO3 film. Reproduced from J. A. Mundy, et al., Nat. Commun., 2014, 5, 3464. Copyright Nature Publishing Group 2015.

The EEl Spectrum

An idealized EEL spectrum is show in Figure 16.6.16 The most prominent feature of any EEL spectrum is the zero loss peak (ZLP). The ZLP is due to those electrons from the electron beam that do not inelastically scatter and reach the detector with their original kinetic energy; typically 100-300 keV. By definition the ZLP is set to 0 eV for further analysis and all signals arising from inelastically scatter electrons occur at >0 eV. The second largest feature is often the plasmon resonance - the collective excitation of conduction band electrons within a material. The plasmon resonance and other peaks attributed to weakly bound, or outer shell electrons, occur in the “low-loss” region of the spectrum. The low-loss regime is typically thought of as energy loss <50 eV, but this cut-off from low-loss to high-loss is arbitrary. Shown in the inset of Figure 16.6.16is an edge from atom core-loss and further fine structure. Inner shell ionizations, represented by the core-loss peaks, are useful in determining elemental compositions as these peaks can act as fingerprints for specific elements. For example, if there is a peak at 532 eV in a EEL spectrum, there is a high probability that the sample contains a considerable amount of oxygen because this is known to be the energy needed to remove an inner shell electron from oxygen. This idea is further explored by looking at sudden changes in the bulk plasmon for aluminum in different chemical environments as shown in Figure 16.6.16

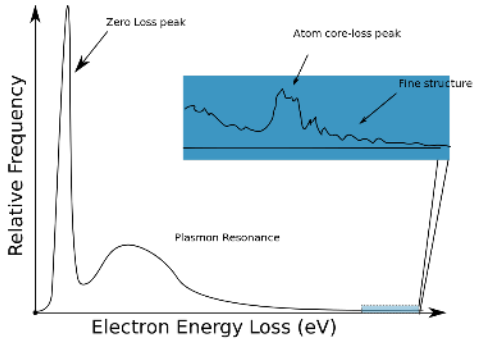


Figure 16.6.16 Idealized electron energy loss spectrum (EELS). Inset shows core loss and fine structure. This image is filed under the Creative Commons Attribution-Share Alike 3.0 Unported License. Original Author Hat'n'Coat.

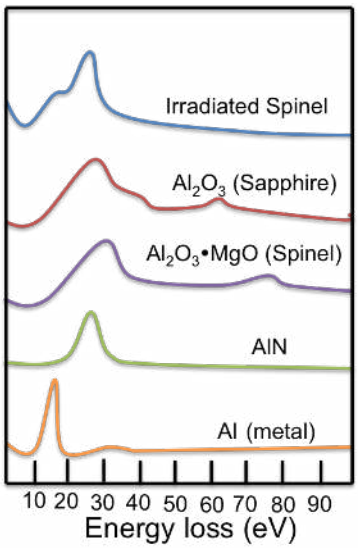


Figure 16.6.17 Slight shifts in the plasmon peak of pure Al, AlN, and various aluminum oxides. Slight shifts in peak shape and energy can allow EEL spectroscopists to determine slight variations in chemical and electron enviroments. Adapted from D.B. William, C.B. Carter. Transmission Electron Microscopy: A Textbook for Materials Science. Springer, New York, NY, 2nd Ed., 2009. 760p.

Of course, there are several other techniques available for probing atomic compositions many of which are covered in this text. These include Energy dispersive X-ray spectroscopy, X-ray photoelectron spectroscopy, and Auger electron spectroscopy. Please reference these chapters thorough introduction to these techniques.

Electron Energy Loss Spectroscopy Versus Energy Dispersive X-ray Spectroscopy

As a technique EELS is most frequently compared to energy dispersive X-ray spectroscopy (EDX) also known as energy dispersive spectroscopy (EDS). Energy dispersive X-ray detectors are commonly found as analytical probes on both scanning and transmission electron microscopes. The popularity of EDS can be understood by recognizing the simplicity of compositional analysis using this technique. However, EELS data can offer complementary compositional analysis while also generally yielding further insight into the solid-state physics and chemistry in a system at the cost of a steeper learning curve. EDS and EELS spectra are both derived from the electronic excitations of materials, however, EELS probes the initial excitation while EDS looks at X-ray emissions from the decay of this excited state. As a result, EEL spectra investigate energy ranges from 0-3 keV while EDS spectra analyze a wider energy range from 1-40 keV. The difference in ranges makes EDS suited particularly well for heavy elements while EELS complements measurement elements lighter than Zn.

History and Implementation

In the early 1940s, James Hillier (Figure 16.6.18) and R.F. Baker were looking to develop a method for pairing the size, shape, and structure available from electron microscopes to a convenient method for "determining the composition of individual particles in a mixed specimen". Their instrument, shown in Figure 16.6.19 reported in the Journal of Applied Physics in September 1994 was the first electron-optical instrument used to measure the velocity distribution in an electron beam transmitting through a sample.



Figure 16.6.18 Dr. James Hillier (August 22, 1915 – January 15, 2007) received his Ph.D. in Physics from the University of Toronto. He is recognized as a pioneer in the field of electron microscopy and as a graduate student in 1938 designed and built the first successful electron microscope in the western hemisphere. Dr. Hillier authored 150 papers on both technical subjects and management and held 41 patents for his inventions. He was inducted into the National Inventors Hall of Fame for the electron microscope in 1980.

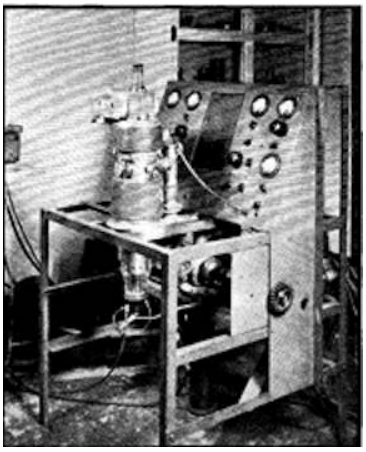


Figure 16.6.19 The first instrument capable of performing electron energy loss spectroscopy built by Hillier and Baker in 1944. Reproduced from J. Hillier and R. F. Baker, *J. Appl. Phys.*, 1944, **15**, 663–675. Copyright AIP Publishing LLC

The instrument was built from a repurposed transmission electron microscope (TEM). It consisted of an electron source and three electromagnetic focusing lenses, standard for TEMs at the time, but also incorporated a magnetic deflecting lenses, which when turned on, would redirect the electrons 180° into a photographic plate. The electrons with varying kinetic energies dispersed across the photographic plate and could be correlated to the energy loss of each peak depending on position. In this groundbreaking work, Hillier and Baker were able to find the discrete energy loss corresponding to the K levels of both carbon and oxygen.

The vast majority of EEL spectrometers are found as secondary analyzers in transmission electron microscopes. It wasn't until the 1990s when EELS became a widely used research tool because of advances in electron beam aberration correction and vacuum technologies. Today, EELS is capable of spatial resolutions down to the single atom level, and if the electron beam is monochromated energy resolution can be as low as 0.01eV. Figure 16.6.20depicts the typical layout of an EEL spectrometer at the base of a TEM.

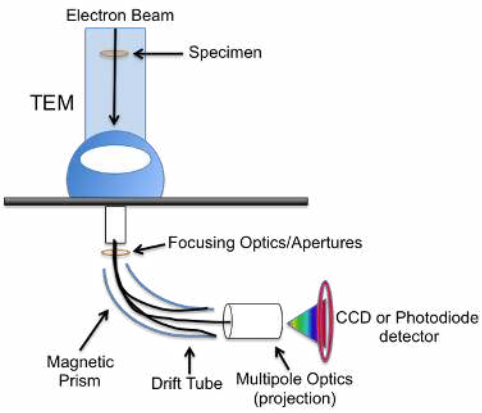


Figure 16.6.20 Schematic to show the simplified positions of standard EELS components in a standard TEM.

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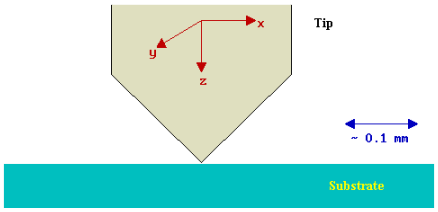
- **8.2: Transmission Electron Microscopy** by Pavan M. V. Raja & Andrew R. Barron is licensed CC BY 4.0. Original source: http://cnx.org/contents/ba27839d-5042-4a40-afcf-c0e6e39fb45425.2.

16.7: Scanning Probe Microscopy - STM and AFM

In the early 1980's two IBM scientists, Binnig & Rohrer, developed a new technique for studying surface structure - Scanning Tunneling Microscopy (STM). This invention was quickly followed by the development of a whole family of related techniques which, together with STM, may be classified in the general category of Scanning Probe Microscopy (SPM) techniques. Of these later techniques, the most important is Atomic Force Microscopy (AFM). The development of these techniques has without doubt been the most important event in the surface science field in recent times, and opened up many new areas of science and engineering at the atomic and molecular level.

Basic Principles of SPM Techniques

All of the techniques are based upon scanning a probe (typically called the *tip* in STM, since it literally is a sharp metallic tip) just above a surface whilst monitoring some interaction between the probe and the surface.



The interaction that is monitored in:

- **STM** - is the *tunnelling current* between a metallic tip and a conducting substrate which are in very close proximity but **not** actually in physical contact.
- **AFM** - is the van der Waals force between the tip and the surface; this may be either the short range repulsive force (in contact-mode) or the longer range attractive force (in non-contact mode).

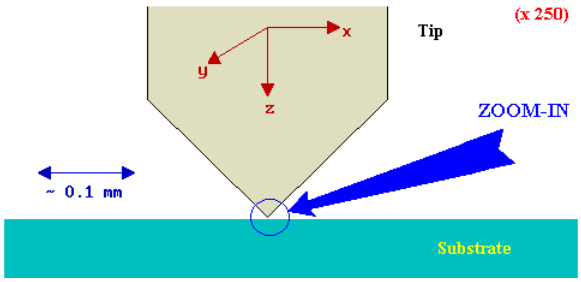
For the techniques to provide information on the surface structure at the atomic level (which is what they are capable of doing):

1. the position of the tip with respect to the surface must be very accurately controlled (to within about 0.1 Å) by moving either the surface or the tip.
2. the tip must be very sharp - ideally terminating in just a single atom at its closest point of approach to the surface.

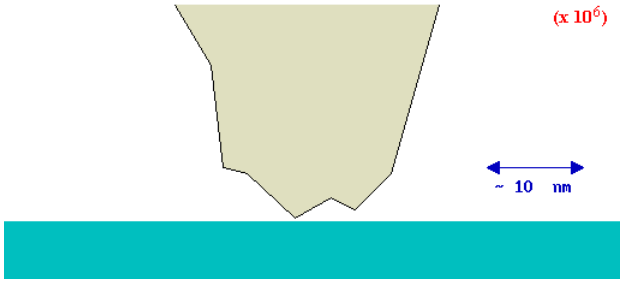
The attention paid to the first problem and the engineering solution to it is the difference between a good microscope and a not so good microscope - it need not worry us here, sufficient to say that it is possible to accurately control the relative positions of tip and surface by ensuring good vibrational isolation of the microscope and using sensitive piezoelectric positioning devices.

> Tip preparation is a science in itself - having said that, it is largely serendipity which ensures that one atom on the tip is closer to the surface than all others.

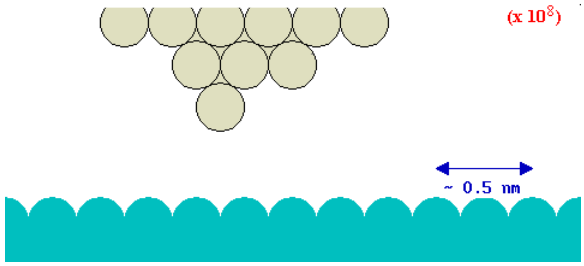
Let us look at the region where the tip approaches the surface in greater detail ....



... the end of the tip will almost invariably show a certain amount of structure, with a variety of crystal facets exposed ...



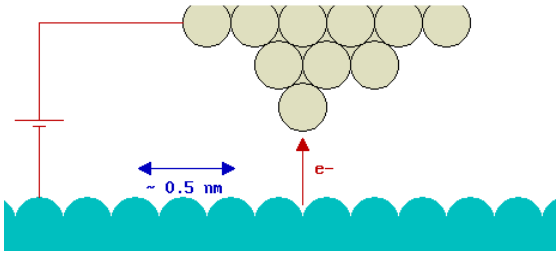
… and if we now go down to the atomic scale ....



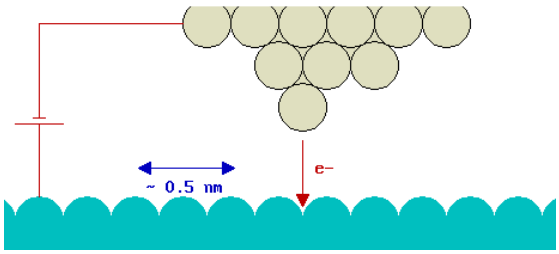
... there is a reasonable probability of ending up with a truly atomic tip.

If the tip is biased with respect to the surface by the application of a voltage between them then electrons can tunnel between the two, provided the separation of the tip and surface is sufficiently small - this gives rise to a *tunnelling current*.

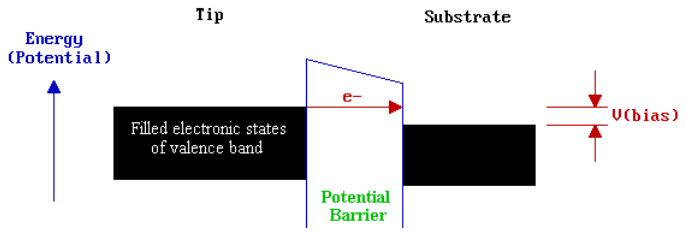
The direction of current flow is determined by the polarity of the bias.



If the sample is biased -ve with respect to the tip, then electrons will flow from the surface to the tip as shown above, whilst if the sample is biased +ve with respect to the tip, then electrons will flow from the tip to the surface as shown below.



The name of the technique arises from the quantum mechanical *tunnelling*-type mechanism by which the electrons can move between the tip and substrate. Quantum mechanical tunnelling permits particles to tunnel through a potential barrier which they could not surmount according to the classical laws of physics - in this case electrons are able to traverse the classically-forbidden region between the two solids as illustrated schematically on the energy diagram below.

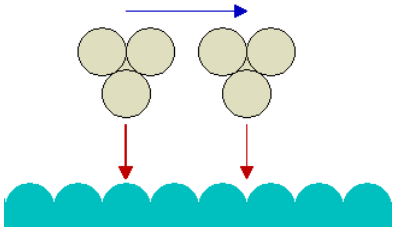


This is an over-simplistic model of the tunnelling that occurs in STM but it is a useful starting point for understanding how the technique works. In this model, the probability of tunnelling is exponentially-dependent upon the distance of separation between the tip and surface: the tunnelling current is therefore a very sensitive probe of this separation.

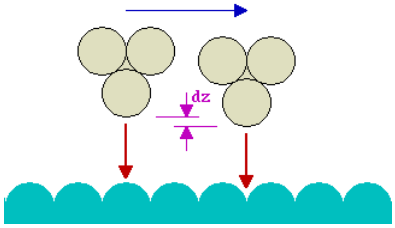
Imaging of the surface topology may then be carried out in one of two ways:

1. in constant height mode (in which the tunnelling current is monitored as the tip is scanned parallel to the surface)
2. in constant current mode (in which the tunnelling current is maintained constant as the tip is scanned across the surface)

If the tip is scanned at what is nominally a constant height above the surface, then there is actually a periodic variation in the separation distance between the tip and surface atoms. At one point the tip will be directly above a surface atom and the tunnelling current will be large whilst at other points the tip will be above hollow sites on the surface and the tunnelling current will be much smaller.



A plot of the tunnelling current v's tip position therefore shows a periodic variation which matches that of the surface structure - hence it provides a direct "image" of the surface (and by the time the data has been processed it may even look like a real picture of the surface !).



In practice, however, the normal way of imaging the surface is to maintain the tunnelling current constant whilst the tip is scanned across the surface. This is achieved by adjusting the tip's height above the surface so that the tunnelling current does not vary with the lateral tip position. In this mode the tip will move slightly upwards as it passes over a surface atom, and conversely, slightly in towards the surface as it passes over a hollow.

The image is then formed by plotting the tip height (strictly, the voltage applied to the z-piezo) v's the lateral tip position.

Summary

In summary, the development of the various scanning probe microscopy techniques has revolutionized the study of surface structure - atomic resolution images have been obtained not only on single crystal substrates in UHV but also on samples at atmospheric pressure and even under solution. Many problems still remain, however, and the interpretation of SPM data is not always as straightforward as it might at first seem. There is still very much a place for the more traditional surface structural techniques such as LEED.

This introduction to STM has concentrated on the non-invasive imaging applications of the technique, yet there is increasing interest in using such techniques as a tool for the actual modification of surfaces. At the moment this is still at the "gimmicky"

stage, but the longer term implications of being able to manipulate surface structure and molecules at the atomic level have yet to be fully appreciated: we can but await the future with interest !

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16.8: Scanning Tunneling Microscopy

Scanning tunneling microscopy (STM) is a powerful instrument that allows one to image the sample surface at the atomic level. As the first generation of scanning probe microscopy (SPM), STM paves the way for the study of nano-science and nano-materials. For the first time, researchers could obtain atom-resolution images of electrically conductive surfaces as well as their local electric structures. Because of this milestone invention, Gerd Binnig (Figure 16.8.1) and Heinrich Rohrer (Figure 16.8.2) won the Nobel Prize in Physics in 1986.



Figure 16.8.1 German physicist Gerd Binnig (1947 -).

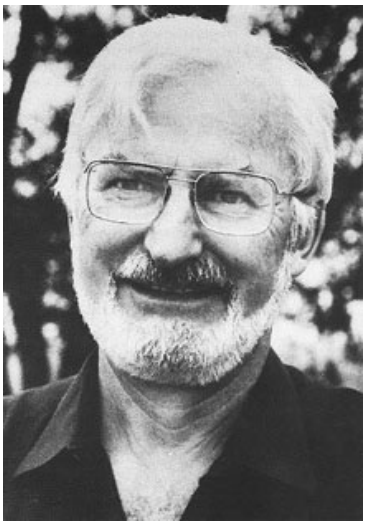


Figure 16.8.2 Swiss physicist Heinrich Rohrer (1933 -)

Principles of Scanning Tunneling Microscopy

The key physical principle behind STM is the tunneling effect. In terms of their wave nature, the electrons in the surface atoms actually are not as tightly bonded to the nucleons as the electrons in the atoms of the bulk. More specifically, the electron density is not zero in the space outside the surface, though it will decrease exponentially as the distance between the electron and the surface increases (Figure 16.8.3 a). So, when a metal tip approaches to a conductive surface within a very short distance, normally just a few Å, their perspective electron clouds will starting to overlap, and generate tunneling current if a small voltage is applied between them, as shown in Figure \(\PageIndex{3}) b.

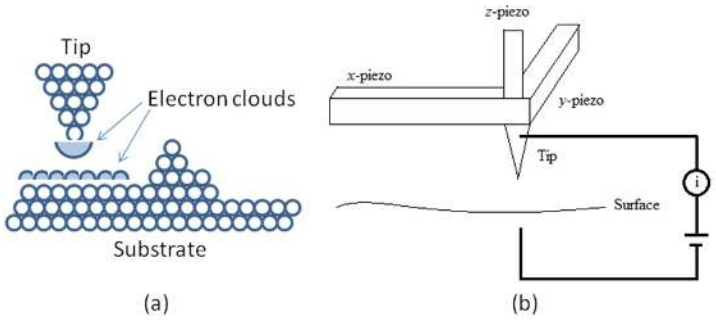


Figure 16.8.3 Schematic diagram of the principles of AFM showing (a) the interactions between tip and surface and (b) the tunneling current generated from tip and surface is measured and used as feedback to control the movement of the tip.

When we consider the separation between the tip and the surface as an ideal one-dimensional tunneling barrier, the tunneling probability, or the tunneling current I, will depend largely on s, the distance between the tip and surface, 16.8.1, where m is the electron mass, e the electron charge, h the Plank constant, ϕ the averaged work function of the tip and the sample, and V the bias voltage.

$$I \propto e^{-2s\,[2m/h^2(<\phi> - e|V|/2)]^{1/2}} \tag{16.8.1}$$

A simple calculation will show us how strongly the tunneling current is affected by the distance (s). If s is increased by Δs = 1 Å, 16.8.2 and 16.8.3.

$$\Delta I = e^{-2k_0\Delta s} \tag{16.8.2}$$

$$k_0 = [2m/h^2(<\phi> - e|V|/2)]^{1/2} \tag{16.8.3}$$

Usually (<ϕ> −e|V|/2) is about 5 eV, which k_0 about 1 Å^{-1}, then ΔI/I = $^1/_8$. That means, if *s* changes by 1 Å, the current will change by one order of the magnitude. That's the reason why we can get atom-level image by measuring the tunneling current between the tip and the sample.

In a typical STM operation process, the tip is scanning across the surface of sample in *x*-*y* plain, the instrument records the *x*-*y* position of the tip, measures the tunneling current, and control the height of the tip via a feedback circuit. The movements of the tip in *x*, *y* and *z* directions are all controlled by piezo ceramics, which can be elongated or shortened according to the voltage applied on them.

Normally, there are two modes of operation for STM, *constant height mode* and *constant current mode*. In constant height mode, the tip stays at a constant height when it scans through the sample, and the tunneling current is measured at different (*x*, *y*) position (Figure 16.8.4b). This mode can be applied when the surface of sample is very smooth. But, if the sample is rough, or has some large particles on the surface, the tip may contact with the sample and damage the surface. In this case, the constant current mode is applied. During this scanning process, the tunneling current, namely the distance between the tip and the sample, is settled to an unchanged target value. If the tunneling current is higher than that target value, that means the height of the sample surface is increasing, the distance between the tip and sample is decreasing. In this situation, the feedback control system will respond quickly and retract the tip. Conversely, if the tunneling current drops below the target value, the feedback control will have the tip closer to the surface. According to the output signal from feedback control, the surface of the sample can be imaged.

Comparison of Atomic Force Microscopy (AFM) and Scanning Tunneling Microscopy (STM)

Both AFM and STM are widely used in nano-science. According to the different working principles though, they have their own advantages and disadvantages when measuring specific properties of sample (Table 16.8.1). STM requires an electric circuit including the tip and sample to let the tunneling current go through. That means, the sample for STM must be conducting. In case of AFM however, it just measures the deflection of the cantilever caused by the van der Waals forces between the tip and sample. Thus, in general any kind of sample can be used for AFM. But, because of the exponential relation of the tunneling current and distance, STM has a better resolution than AFM. In STM image one can actually "see" an individual atom, while in AFM it's almost impossible, and the quality of AFM image is largely depended on the shape and contact force of the tip. In some cases, the measured signal would be rather complicated to interpret into morphology or other properties of sample. On the other side, STM can give straight forward electric property of the sample surface.

Table 16.8.1 Comparison of AFM and STM

	AFM	STM
Sample Requirement	-	Conducting
Work environment	Air, liquid	Vacuum
Lateral resolution	~1 nm	~0.1 nm
Vertical resolution	~0.05 nm	~0.05 nm
Working mode	Tapping, contact	Constant current, constant height

Applications of Scanning Tunneling Microscopy in Nanoscience

STM provides a powerful method to detect the surface of conducting and semi-conducting materials. Recently STM can also be applied in the imaging of insulators, superlattice assemblies and even the manipulation of molecules on surface. More importantly, STM can provide the surface structure and electric property of surface at atomic resolution, a true breakthrough in the development of nano-science. In this sense, the data collected from STM could reflect the local properties even of single molecule and atom. With these valuable measurement data, one could give a deeper understanding of structure-property relations in nanomaterials.

An excellent example is the STM imaging of graphene on Ru(0001), as shown in Figure 16.8.4 Clearly seen is the superstructure with a periodicity of ~30 Å , coming from the lattice mismatch of 12 unit cells of the graphene and 11 unit cells of the underneath Ru(0001) substrate. This so-called moiré structure can also be seen in other systems when the adsorbed layers have strong chemical bonds within the layer and weak interaction with the underlying surface. In this case, the periodic superstructure seen in graphene tells us that the formed graphene is well crystallized and expected to have high quality.

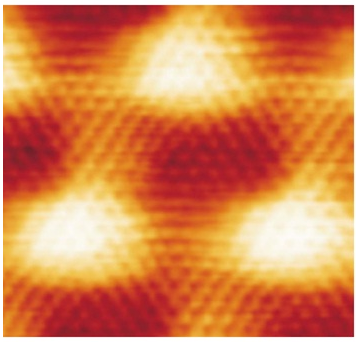


Figure 16.8.4 Atomically resolved image of the graphene overlayer. The scanning area is 40 x 40 Å, the operation mode is constant current mode, I_t is l nA, V_{Bias} is -0.05 V. Adapted with permission from S. Marchini, S. Gunther, and J. Wintterlin, *Phys. Rev. B*, 2007, **76**, 075429. Copyrighted by the American Physical Society.

Another good example is shown to see that the measurement from STM could tell us the bonding information in single-molecular level. In thiol- and thiophene-functionalization of single-wall carbon nanotubes (SWNTs), the use of Au nanoparticles as chemical markers for AFM gives misleading results, while STM imaging could give correct information of substituent location. From AFM image, Au-thiol-SWNT (Figure 16.8.6a) shows that most of the sidewalls are unfunctionalized, while Au-thiophene-SWNT (Figure 16.8.6c)shows long bands of continuous functionalized regions on SWNT. This could lead to the estimation that thiophene is better functionalized to SWNT than thiol. Yet, if we look up to the STM image (Figure 16.8.6b and d), in thiol-SWNTs the multiple functional groups are tightly bonded in about 5 - 25 nm, while in thiophene-SWNTs the functionalization is spread out uniformly along the whole length of SWNT. This information indicates that actually the functionalization levels of thiol- and thiophene-SWNTs are comparable. The difference is that, in thiol-SWNTs, functional groups are grouped together and each group is bonded to a single gold nanoparticle, while in thiophene-SWNTs, every individual functional group is bonded to a nanoparticle.

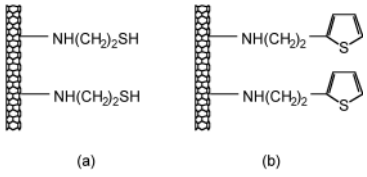


Figure 16.8.5 Structure of (a) thiol-functionalized SWNTs and thiophene-functionalized SWNTs.

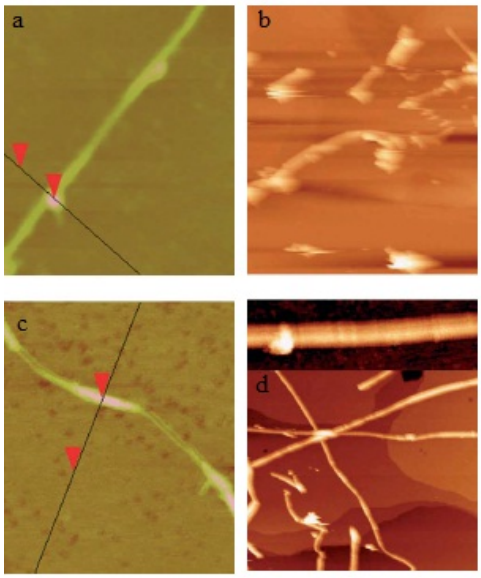


Figure 16.8.6 Difference between AFM and STM images of functionalized SWNTs. (a) and (c) are tapping mode AFM images and height profiles of thiol- and thiophene-SWNTs. (b) and (d) are STM images of thiol-SWNTs (scanning area is 4560 x 4000 Å, the operation mode is constant current mode, I_t is 3.25 pA, V_{Bias} is -0.5 V) and thiophene-SWNTs (scanning area is 4560 x 4000 Å, the operation mode is constant current mode, I_t is 5.66 pA, V_{Bias} is -0.8 V). Inset in (d) is a higher resolution image of the local defects on thiophene-SWNT (500 x 140 Å, the operation mode is constant current mode, I_t is 25.5 pA, V_{Bias} is -0.8 V). Adapted from L. Zhang, J. Zhang, N. Schmandt, J. Cratty, V. N. Khabashesku, K. F. Kelly, and A. R. Barron, *Chem. Commun.*, 2005, 5429 (http://dx.doi.org/10.1039/b509257d). Reproduced by permission of The Royal Society of Chemistry.

Adaptations to Scanning Tunneling Microscopy

Scanning tunneling microscopy (STM) is a relatively recent imaging technology that has proven very useful for determining the topography of conducting and semiconducting samples with angstrom (Å) level precision. STM was invented by Gerd Binnig (Figure 16.8.7) and Heinrich Rohrer (Figure 16.8.8), who both won the 1986 Nobel Prize in physics for their technological advances.



Figure 16.8.7 German physicist Gerd Binnig (1947 -).

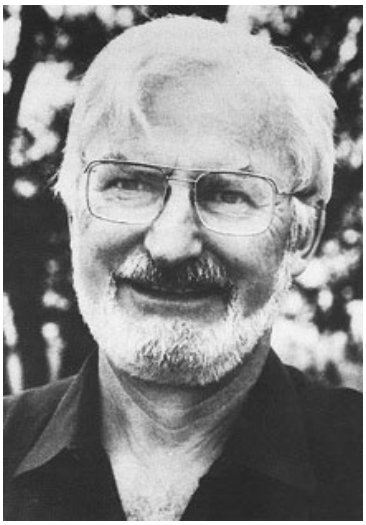


Figure 16.8.8 Swiss physicist Heinrich Rohrer (1933 -).

The main component of a scanning tunneling microscope is a rigid metallic probe tip, typically composed of tungsten, connected to a piezodrive containing three perpendicular piezoelectric transducers (Figure 16.8.9). The tip is brought within a fraction of a nanometer of an electrically conducting sample. At close distances, the electron clouds of the metal tip overlap with the electron clouds of the surface atoms (Figure 16.8.9 inset). If a small voltage is applied between the tip and the sample a tunneling current is generated. The magnitude of this tunneling current is dependent on the bias voltage applied and the distance between the tip and the surface. A current amplifier can covert the generated tunneling current into a voltage. The magnitude of the resulting voltage as compared to the initial voltage can then be used to control the piezodrive, which controls the distance between the tip and the surface (i.e., the *z* direction). By scanning the tip in the *x* and *y* directions, the tunneling current can be measured across the entire sample. The STM system can operate in either of two modes: Constant height or constant current

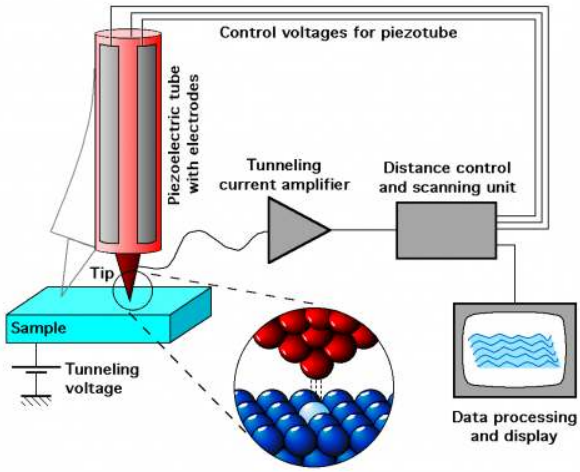


Figure 16.8.9 Schematic drawing of a STM apparatus.

In constant height mode, the tip is fixed in the *z* direction and the change in tunneling current as the tip changes in the *x*,*y* direction is collected and plotted to describe the change in topography of the sample. This method is dangerous for use in samples with fluctuations in height as the fixed tip might contact and destroy raised areas of the sample. A common method for non-uniformly smooth samples is constant current mode. In this mode, a target current value, called the set point, is selected and the tunneling current data gathered from the sample is compared to the target value. If the collected voltage deviates from the set point, the tip is moved in the *z* direction and the voltage is measured again until the target voltage is reached. The change in the *z* direction required to reach the set point is recorded across the entire sample and plotted as a representation of the topography of the sample. The height data is typically displayed as a gray scale image of the topography of the sample, where lighter areas typically indicate raised sample areas and darker spots indicate protrusions. These images are typically colored for better contrast.

The standard method of STM, described above, is useful for many substances (including high precision optical components, disk drive surfaces, and buckyballs) and is typically used under ultrahigh vacuum to avoid contamination of the samples from the surrounding systems. Other sample types, such as semiconductor interfaces or biological samples, need some enhancements to the traditional STM apparatus to yield more detailed sample information. Three such modifications, spin-polarized STM (SP-STM), ballistic electron emission microscopy (BEEM) and photon STM (PSTM) are summarized in Table 16.8.2 and in described in detail below.

Table 16.8.2 Comparison of conventional and altered STM types

Name	Alterations to Conventional STM	Sample Types	Limitations
STM	None	Conducting surface	Rigidity of probe
SP-STM	Magnetized STM tip	Magnetic	Needs to be overlaid with STM, magnetized tip type
BEEM	Three-terminal with base electrode and current collector	Interfaces	Voltage, changes due to barrier height
PSTM	Optical fiber tip	Biological	Optical tip and psrim manufacture

Spin Polarized STM

Spin-polarized scanning tunneling microscopy (SP-STM) can be used to provide detailed information of magnetic phenomena on the single-atom scale. This imaging technique is particularly important for accurate measurement of superconductivity and high-density magnetic data storage devices. In addition, SP-STM, while sensitive to the partial magnetic moments of the sample, is not a field-sensitive technique and so can be applied in a variety of different magnetic fields.

Device setup and sample preparation

In SP-STM, the STM tip is coated with a thin layer of magnetic material. As with STM, voltage is then applied between tip and sample resulting in tunneling current. Atoms with partial magnetic moments that are aligned in the same direction as the partial magnetic moment of the atom at the very tip of the STM tip show a higher magnitude of tunneling current due to the interactions between the magnetic moments. Likewise, atoms with partial magnetic moments opposite that of the atom at the tip of the STM tip demonstrate a reduced tunneling current (Figure 16.8.10). A computer program can then translate the change in tunneling current to a topographical map, showing the spin density on the surface of the sample.

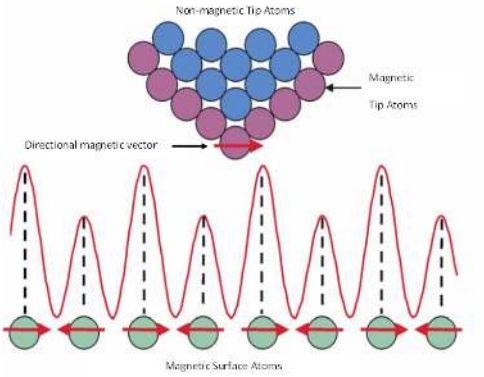


Figure 16.8.10 Schematic illustration of magnetized tip for SP-STM.

The sensitivity to magnetic moments depends greatly upon the direction of the magnetic moment of the tip, which can be controlled by the magnetic properties of the material used to coat the outermost layer of the tungsten STM probe. A wide variety of magnetic materials have been studied as possible coatings, including both ferromagnetic materials, such as a thin coat of iron or of gadolinium, and antiferromagnetic materials such as chromium. Another method that has been used to make a magnetically sensitive probe tip is irradiation of a semiconducting GaAs tip with high energy circularly polarized light. This irradiation causes a splitting of electrons in the GaAs valence band and population of the conduction band with spin-polarized electrons. These spin-

polarized electrons then provide partial magnetic moments which in turn influence the tunneling current generated by the sample surface.

Sample preparation for SP-STM is essentially the same as for STM. SP-STM has been used to image samples such as thin films and nanoparticle constructs as well as determining the magnetic topography of thin metallic sheets such as in Figure 16.8.11. The upper image is a traditional STM image of a thin layer of cobalt, which shows the topography of the sample. The second image is an SP-STM image of the same layer of cobalt, which shows the magnetic domain of the sample. The two images, when combined provide useful information about the exact location of the partial magnetic moments within the sample.

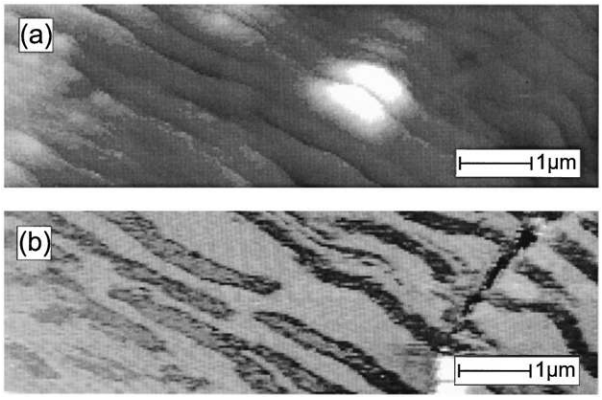


Figure 16.8.11 A thin layer of Co(0001) as imaged by (a) STM, showing the topography, and (b) SP-STM, showing the magnetic domain structure. Image adapted from W. Wulfhekel and J. Kirschner, Appl. Phys. Lett., 1999, 75, 1944.

Limitations

One of the major limitations with SP-STM is that both distance and partial magnetic moment yield the same contrast in a SP-STM image. This can be corrected by combination with conventional STM to get multi-domain structures and/or topological information which can then be overlaid on top of the SP-STM image, correcting for differences in sample height as opposed to magnetization.

The properties of the magnetic tip dictate much of the properties of the technique itself. If the outermost atom of the tip is not properly magnetized, the technique will yield no more information than a traditional STM. The direction of the magnetization vector of the tip is also of great importance. If the magnetization vector of the tip is perpendicular to the magnetization vector of the sample, there will be no spin contrast. It is therefore important to carefully choose the coating applied to the tungsten STM tip in order to align appropriately with the expected magnetic moments of the sample. Also, the coating makes the magnetic tips more expensive to produce than standard STM tips. In addition, these tips are often made of mechanically soft materials, causing them to wear quickly and require a high cost of maintenance.

Ballistic Electron Emission Microscopy

Ballistic electron emission microscopy (BEEM) is a technique commonly used to image semiconductor interfaces. Conventional surface probe techniques can provide detailed information on the formation of interfaces, but lack the ability to study fully formed interfaces due to inaccessibility to the surface. BEEM allows for the ability to obtain a quantitative measure of electron transport across fully formed interfaces, something necessary for many industrial applications.

Device Setup and Sample Preparation

BEEM utilizes STM with a three-electrode configuration, as seen in Figure 16.8.12 In this technique, ballistic electrons are first injected from a STM tip into the sample, traditionally composed of at least two layers separated by an interface, which rests on three indium contact pads that provide a connection to a base electrode (Figure 16.8.12). As the voltage is applied to the sample, electrons tunnel across the vacuum and through the first layer of the sample, reaching the interface, and then scatter. Depending on the magnitude of the voltage, some percentage of the electrons tunnel through the interface, and can be collected and measured as a current at a collector attached to the other side of the sample. The voltage from the STM tip is then varied, allowing for measurement of the barrier height. The barrier height is defined as the threshold at which electrons will cross the interface and are measurable as a current in the far collector. At a metal/n-type semiconductor interface this is the difference between the conduction band minimum and the Fermi level. At a metal/p-type semiconductor interface this is the difference between the valence band maximum of the semiconductor and the metal Fermi level. If the voltage is less than the barrier height, no electrons will cross the

interface and the collector will read zero. If the voltage is greater than the barrier height, useful information can be gathered about the magnitude of the current at the collector as opposed to the initial voltage.

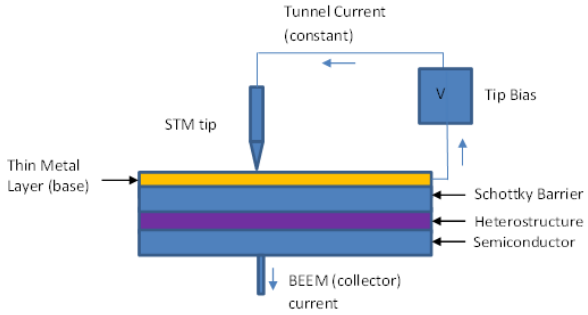


Figure 16.8.12 Diagram of a STM/BEEM system. The tip is maintained at the tunneling voltage, V, and the tunneling current, It = VI/RF, is held constant by the STM feedback circuit. The sample base layer is grounded and current into the semiconductor is measured by a virtual ground current amplifier.

Samples are prepared from semiconductor wafers by chemical oxide growth-strip cycles, ending with the growth of a protective oxide layer. Immediately prior to imaging the sample is spin-etched in an inert environment to remove oxides of oxides and then transferred directly to the ultra-high vacuum without air exposure. The BEEM apparatus itself is operated in a glove box under inert atmosphere and shielded from light.

Nearly any type of semiconductor interface can be imaged with BEEM. This includes both simple binary interfaces such as Au/n-Si(100) and more chemically complex interfaces such as Au/n-GaAs(100), such as seen in Figure 16.8.13

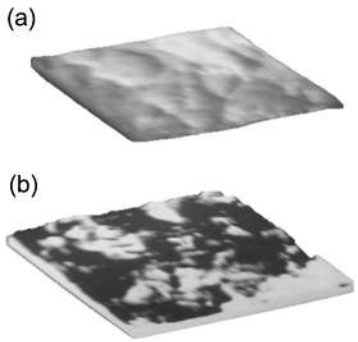


Figure 16.8.13 Images of Au/n-GaAs(100) layer (image area 510 Å x 390 Å) showing (a) the topography of the Au surface and (b) the BEEM grey-scale interface image. Image adapted from M. H. Hecht, L. D. Bell, W. J. Kaiser, and F. J. Grunthaner, Appl. Phys. Lett., 1989, 55, 780.

Limitations

Expected barrier height matters a great deal in the desired setup of the BEEM apparatus. If it is necessary to measure small collector currents, such as with an interface of high-barrier-height, a high-gain, low-noise current preamplifier can be added to the system. If the interface is of low-barrier-height, the BEEM apparatus can be operated at very low temperatures, accomplished by immersion of the STM tip in liquid nitrogen and enclosure of the BEEM apparatus in a nitrogen-purged glove box.

Photon STM

Photon scanning tunneling microscopy (PSTM) measures light to determine more information about characteristic sample topography. It has primarily been used as a technique to measure the electromagnetic interaction of two metallic objects in close proximity to one another and biological samples, which are both difficult to measure using many other common surface analysis techniques.

Device Setup and Sample Preparation

This technique works by measuring the tunneling of photons to an optical tip. The source of these photons is the evanescent field generated by the total internal reflection (TIR) of a light beam from the surface of the sample (Figure 16.8.14). This field is characteristic of the sample material on the TIR surface, and can be measured by a sharpened optical fiber probe tip where the light intensity is converted to an electrical signal (Figure 16.8.15). Much like conventional STM, the force of this electrical signal

modifies the location of the tip in relation to the sample. By mapping these modifications across the entire sample, the topography can be determined to a very accurate degree as well as allowing for calculations of polarization, emission direction and emission time.

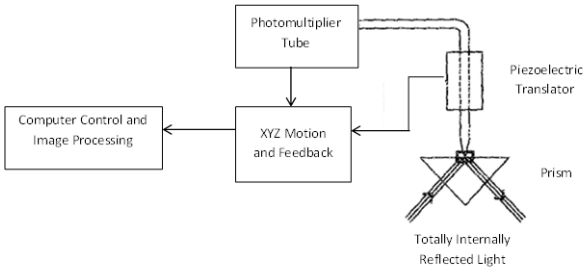


Figure 16.8.14 A schematic of a PSTM system

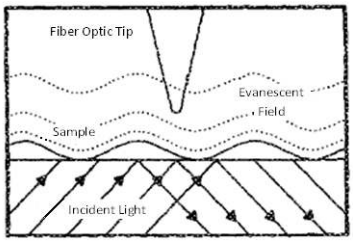


Figure 16.8.15 A TIR light beam generates an evanescent field which is modulated by the sample. A sharpened fiber optic probe tip receives light from the evanescent field and spatial variations in evanescent field intensity form the basis for imaging.

In PSTM, the vertical resolution is governed only by the noise, as opposed to conventional STM where the vertical resolution is limited by the tip dimensions. Therefore, this technique provides advantages over more conventional STM apparatus for samples where subwavelength resolution in the vertical dimension is a critical measurement, including fractal metal colloid clusters, nanostructured materials and simple organic molecules.

Samples are prepared by placement on a quartz or glass slide coupled to the TIR face of a triangular prism containing a laser beam, making the sample surface into the TIR surface (Figure 16.8.16). The optical fiber probe tips are constructed from UV grade quartz optical fibers by etching in HF acid to have nominal end diameters of 200 nm or less and resemble either a truncated cone or a paraboloid of revolution (Figure 16.8.16).

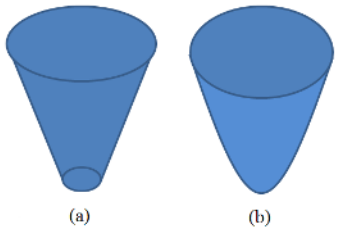


Figure 16.8.16 Possible optical fiber tip configurations: (a) truncated cone and (b) paraboloid of rotation.

PSTM shows much promise in the imaging of biological materials due to the increase in vertical resolution and the ability to measure a sample within a liquid environment with a high index TIR substrate and probe tip. This would provide much more detailed information about small organisms than is currently available.

Limitations

The majority of the limitations in this technique come from the materials and construction of the optical fibers and the prism used in the sample collection. The sample needs to be kept at low temperatures, typically around 100K, for the duration of the imaging and therefore cannot decompose or be otherwise negatively impacted by drastic temperature changes.

Conclusion

Scanning tunneling microscopy can provide a great deal of information into the topography of a sample when used without adaptations, but with adaptations, the information gained is nearly limitless. Depending on the likely properties of your sample surface, SP-STM, BEEM and PSTM can provide much more accurate topographical pictures than conventional forms of STM

(Table 16.8.2). All of these adaptations to STM have their limitations and all work within relatively specialized categories and subsets of substances, but they are very strong tools that are constantly improving to provide more useful information about materials to the nanometer scale.

Scanning Transmission Electron Microscope- Electron Energy Loss Spectroscopy (STEM-EELS)

History

STEM-EELS is a terminology abbreviation for scanning transmission electron microscopy (STEM) coupled with electron energy loss spectroscopy (EELS). It works by combining two instruments, obtaining an image through STEM and applying EELS to detect signals on the specific selected area of the image. Therefore, it can be applied for many research, such as characterizing morphology, detecting different elements, and different valence state. The first STEM was built by Baron Manfred von Arden (Figure 16.8.17) in around 1983, since it was just the prototype of STEM, it was not as good as transmission electron microscopy (TEM) by that time. Development of STEM was stagnant until the field emission gun was invented by Albert Crewe (Figure 16.8.18) in 1970s; he also came with the idea of annular dark field detector to detect atoms. In 1997, its resolution increased to 1.9 Å, and further increased to 1.36 Å in 2000. 4D STEM-EELS was developed recently, and this type of 4D STEM-EELS has high brightness STEM equipped with a high acquisition rate EELS detector, and a rotation holder. The rotation holder plays quite an important role to achieve this 4D aim, because it makes observation of the sample in 360° possible, the sample could be rotated to acquire the sample's thickness. High acquisition rate EELS enables this instrument the acquisition of the pixel spectrum in a few minutes.



Figure 16.8.17 German physicist and inventor Baron Manfred von Arden (1907–1997).



Figure 16.8.18 British physicist Albert Crewe (1927–2009).

Basics of STEM-EELS

Interaction between Electrons and Sample

When electrons interact with the samples, the interaction between those two can be classified into two types, namely, elastic and inelastic interactions (Figure 16.8.19). In the elastic interaction, if electrons do not interact with the sample and pass through it, these electrons will contribute to the direct beam. The direct beam can be applied in STEM. In another case, electrons' moving direction in the sample is guided by the Coulombic force; the strength of the force is decided by charge and the distance between

electrons and the core. In both cases, these is no energy transfer from electrons to the samples, that's the reason why it is called elastic interaction. In inelastic interaction, energy transfers from incident electrons to the samples, thereby, losing energy. The lost energy can be measured and how many electrons amounted to this energy can also be measured, and these data yield the electron energy loss spectrum (EELS).

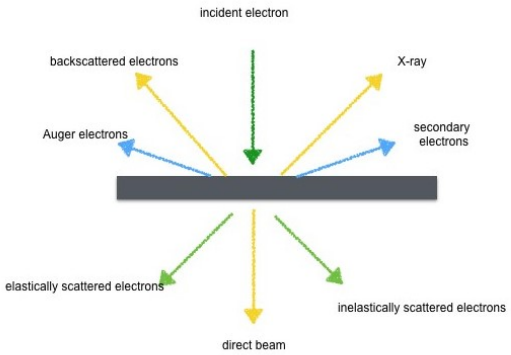


Figure 16.8.19 Demonstration of interaction between sample and electrons. Adapted from http://www.microscopy.ethz.ch/downlo...teractions.pdf

How do TEM, STEM and STEM-EELS work?

In transmission electron microscopy (TEM), a beam of electrons is emitted from tungsten source and then accelerated by electromagnetic field. Then with the aid of lens condenser, the beam will focus on and pass through the sample. Finally, the electrons will be detected by a charge-coupled device (CCD) and produce images, Figure 16.8.20 STEM works differently from TEM, the electron beam focuses on a specific spot of the sample and then raster scans the sample pixel by pixel, the detector will collect the transmitted electrons and visualize the sample. Moreover, STEM-EELS allows to analyze these electrons, the transmitted electrons could be characterized by adding a magnetic prism, the more energy the electrons lose, the more they will be deflected. Therefore, STEM-EELS can be used to characterize the chemical properties of thin samples.

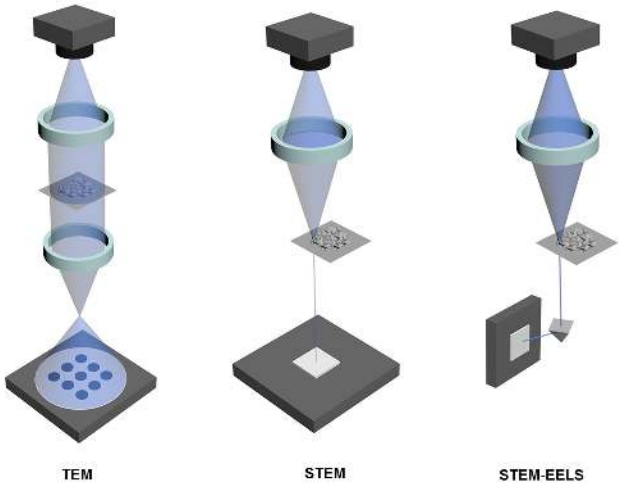


Figure 16.8.20 Scheme of TEM, STEM and STEM-EELS experiments. Adapted from http://toutestquantique.fr/en/scanning-electron/.

Principles of STEM-EELS

A brief illustration of STEM-EELS is displayed in Figure 16.8.21 The electron source provides electrons, and it usually comes from a tungsten source located in a strong electrical field. The electron field will provide electrons with high energy. The condenser and the object lens also promote electrons forming into a fine probe and then raster scanning the specimen. The diameter of the probe will influence STEM's spatial resolution, which is caused by the lens aberrations. Lens aberration results from the refraction difference between light rays striking the edge and center point of the lens, and it also can happen when the light rays pass through

with different energy. Base on this, an aberration corrector is applied to increase the objective aperture, and the incident probe will converge and increase the resolution, then promote sensitivity to single atoms. For the annular electron detector, the installment sequence of detectors is a bright field detector, a dark field detector and a high angle annular dark field detector. Bright field detector detects the direct beam that transmits through the specimen. Annular dark field detector collects the scattered electrons, which only go through at an aperture. The advantage of this is that it will not influence the EELS to detect signals from direct beam. High angle annular dark field detector collects electrons which are Rutherford scattering (elastic scattering of charged electrons), and its signal intensity is related with the square of atomic number (Z). So, it is also named as Z-contrast image. The unique point about STEM in acquiring image is that the pixels in image are obtained in a point by point mode by scanning the probe. EELS analysis is based on the energy loss of the transmitted electrons, so the thickness of the specimen will influence the detecting signal. In other words, if the specimen is too thick, the intensity of plasmon signal will decrease and may cause difficulty distinguishing these signals from the background.

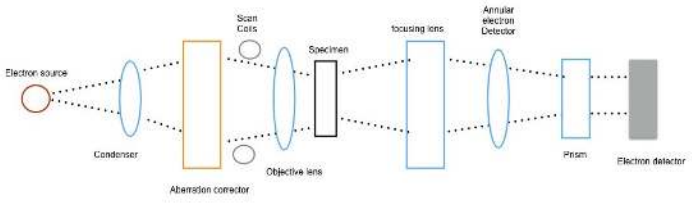


Figure 16.8.21 Schematic representation of STEM-EELS.

Typical features of EELS Spectra

As shown in Figure 16.8.22, a significant peak appears at energy zero in EELS spectra and is therefore called zero-loss peak. Zero-loss peak represents the electrons which undergo elastic scattering during the interaction with specimen. Zero-loss peak can be used to determine the thickness of specimen according to 16.8.4, where t stands for the thickness, λ_{inel} is inelastic mean free path, It stands for the total intensity of the spectrum and IZLP is the intensity of zero loss peak.

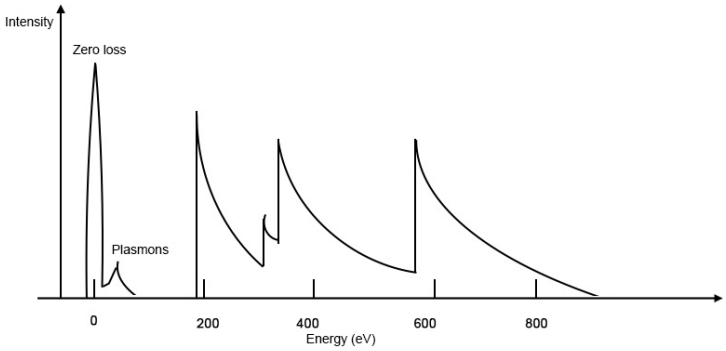


Figure 16.8.22 Typical features of EELS spectra. Adapted from http://www.mardre.com/homepage/mic/t...ls/sld001.html.

$$t = \lambda_{inel}\, ln[I_t/I_{ZLP}] \tag{16.8.4}$$

The low loss region is also called valence EELS. In this region,valence electrons will be excited to the conduction band. Valence EELS can provide the information about band structure, bandgap, and optical properties. In the low loss region, plasmon peak is the most important. Plasmon is a phenomenon originates from the collective oscillation of weakly bound electrons. Thickness of the sample will influence the plasmon peak. The incident electrons will go through inelastic scattering several times when they interact with a very thick sample, and then result in convoluted plasmon peaks. It is also the reason why STEM-EELS favors sample with low thickness (usually less than 100 nm).

The high loss region is characterized by the rapidly increasing intensity with a gradually falling, which called ionization edge. The onset of ionization edges equals to the energy that inner shell electron needs to be excited from the ground state to the lowest unoccupied state. The amount of energy is unique for different shells and elements. Thus, this information will help to understand the bonding, valence state, composition and coordination information.

Energy resolution affects the signal to background ratio in the low loss region and is used to evaluate EELS spectrum. Energy resolution is based on the full width at half maximum of zero-loss peak.

Background signal in the core-loss region is caused by plasmon peaks and core-loss edges, and can be described by the following power law, 16.8.5, where IBG stands for the background signal, E is the energy loss, A is the scaling constant and r is the slope exponent:

$$I_{BG} = AE^{-r} \tag{16.8.5}$$

Therefore, when quantification the spectra data, the background signal can be removed by fitting pre-edge region with the above-mentioned equation and extrapolating it to the post-edge region.

Advantages and Disadvantages of STEM-EELS

STEM-EELS has advantages over other instruments, such as the acquisition of high resolution of images. For example, the operation of TEM on samples sometimes result in blurring image and low contrast because of chromatic aberration. STEM-EELS equipped with aberration corrector, will help to reduce the chromatic aberration and obtain high quality image even at atomic resolution. It is very direct and convenient to understand the electron distributions on surface and bonding information. STEM-EELS also has the advantages in controlling the spread of energy. So, it becomes much easier to study the ionization edge of different material.

Even though STEM-EELS does bring a lot of convenience for research in atomic level, it still has limitations to overcome. One of the main limitation of STEM-EELS is controlling the thickness of the sample. As discussed above, EELS detects the energy loss of electrons when they interact with samples and the specimen, then the thickness of samples will impact on the energy lost detection. Simplify, if the sample is too thick, then most of the electrons will interact with the sample, signal to background ratio and edge visibility will decrease. Thus, it will be hard to tell the chemical state of the element. Another limitation is due to EELS needs to characterize low-loss energy electrons, which high vacuum condition is essential for characterization. To achieve such a high vacuum environment, high voltage is necessary. STEM-EELS also requires the sample substrates to be conductive and flat.

Application of STEM-EELS

STEM-EELS can be used to detect the size and distribution of nanoparticles on a surface. For example, CoO on MgO catalyst nanoparticles may be prepared by hydrothermal methods. The size and distribution of nanoparticles will greatly influence the catalytic properties, and the distribution and morphology change of CoO nanoparticles on MgO is important to understand. Co L3/L2 ratios display uniformly around 2.9, suggesting that Co2+ dominates the electron state of Co. The results show that the ratios of O:(Co+Mg) and Mg:(Co+Mg) are not consistence, indicating that these three elements are in a random distribution. STEM-EELS mapping images results further confirm the non-uniformity of the elemental distribution, consistent with a random distribution of CoO on the MgO surface (Figure 16.8.23).

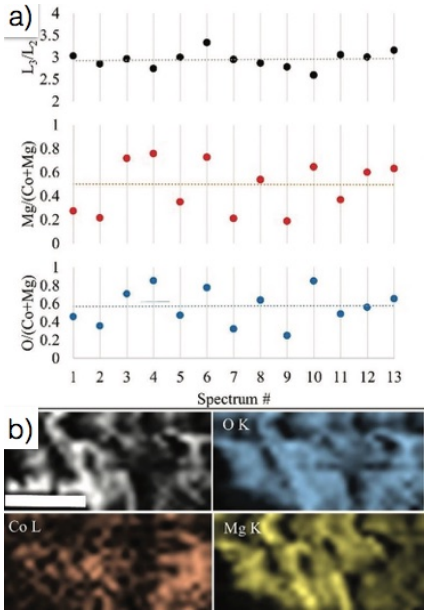


Figure 16.8.23 EELS data for a CoO/MgO sample. (a) EELS signal ratio of Co L3/L2, and O and Mg EELS signals relative to combined Co + Mg signals. (b) STEM image and EELS maps acquired at O K, Co L and Mg K edges. Reproduced from S. Alayoglu, D. J. Rosenberg, and M. Ahmed, Dalton Trans., 2016, 45, 9932 with permission of The Royal Society of Chemistry.

Figure 16.8.24 shows the K-edge absorption of carbon and transition state information could be concluded. Typical carbon based materials have the features of the transition state, such that 1s transits to π* state and 1s to σ* states locate at 285 and 292 eV, respectively. The two-transition state correspond to the electrons in the valence band electrons being excited to conduction state. Epoxy exhibits a sharp peak around 285.3 eV compared to GO and GNPs. Meanwhile, GNPs have the sharpest peak around 292 eV, suggesting the most C atoms in GNPs are in 1s to σ* state. Even though GO is in oxidation state, part of its carbon still behaves 1s transits to π*.

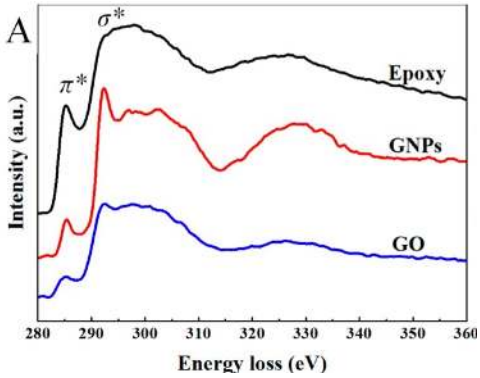


Figure 16.8.24 EELS spectrum of graphene nanoplatelets (GNPs), graphene oxide (GO) in comparison with an epoxide resin. Reprinted with permission from Y. Liu, A. L. Hamon, P. Haghi-Ashtiani, T. Reiss, B. Fan, D. He, and J. Bai, ACS Appl. Mater. Inter., 2016, 8, 34151). Copyright (2017) American Chemical Society.

The annular dark filed (ADF) mode of STEM provides information about atomic number of the elements in a sample. For example, the ADF image of La1.2Sr1.8Mn2O7 (Figure 16.8.25a and b) along [010] direction shows bright spots and dark spots, and even for bright spots (p and r), they display different levels of brightness. This phenomenon is caused by the difference in atomic numbers. Bright spots are La and Sr, respectively. Dark spots are Mn elements. O is too light to show on the image. EELS result shows the core-loss edge of La, Mn and O (Figure 16.8.25c), but the researchers did not give information on core-loss edge of Sr, Sr has N2,3 edge at 29 eV and L3 edge at 1930 eV and L2 edge at 2010 eV.

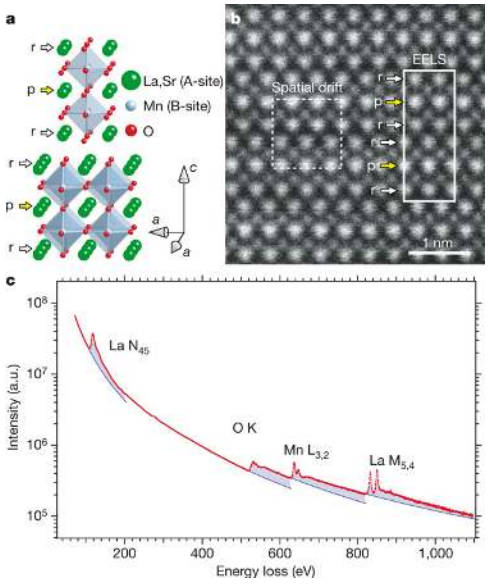


Figure 16.8.25 (a) Crystal structure of La1.2Sr21.8Mn2O7, (b) the ADF image of the specimen observed along the [010] direction , and (c) STEM-EELS data of La1.2Sr21.8Mn2O7 obtained from rectangular area of (b) and the blue area equals the core-loss of each element. Reproduced from K. Kimoto, T. Asaka, T. Nagai, M. Saito, Y. Matsui, K. Ishizuka, Nature, 2007, 450, 702. Copyright © 2007, Rights Managed by Nature Publishing Group

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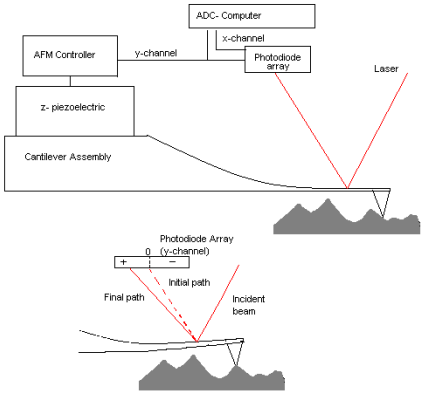
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16.9: Atomic Force Microscopy

Atomic force microscopy utilizes a microscale probe to produce three dimensional image of surfaces at sub nanometer scales. The atomic force microscope obtains images by measurement of the attractive and repulsive forces acting on a microscale probe interacting with the surface of a sample. Ideally the interaction occurs at an atomically fine probe tip being attracted and repulsed by the atoms of the surface giving atomically resolved surface images.

Introduction

The atomic force microscope (AFM) probe is mounted onto a flexible cantilever that is manipulated by a vertical piezoelectric into interacting with the sample. The piezoelectric expands and exerts a force on the cantilever proportional to the potential voltage. The force is balanced by those acting on the probe by its interaction with the surface and the stain on the cantilever.



The flexible cantilever will bend proportionally to the force acting upon it in accordance to Hooke's law. By measuring the reflection of a laser source on the cantilever it is possible to determine the degree of the bend and by a feedback loop control the force exerted by the cantilever. By using the strain as a restoring force, a piezoelectric element can be used to drive the probe as a mechanical oscillator with a calculable resonate frequency, allowing for tapping mode microscopy. The laser acts on a photodiode array to give measurement of the deflection both horizontally and vertically. Using the deflection it is possible to calculate the quantity of force acting on the probe in both the horizontal and vertical directions. From the force applied by the vertical piezoelectric and the force acting on the probe it is possible to obtain a measure of the relative height of the probe.

As the probe encounters a feature, it raises with the feature, causing a deflection measured by the photodiode and a change in the force on the vertical piezoelectric. The potential may be adjusted to minimize the deflection, by feedback from the photodiode array, knowing the expansion rate of the vertical piezoelectric allows for a direct computation of the height, this is the z-sensor. By computation from the total deflection and thus strain on the cantilever, it is also possible to obtain the relative height of the feature given a known spring constant of the cantilever.

The probe is scanned across the surface, with either the probe or the sample being moved by piezoelectric elements. This allows for the measure of the interaction of the forces across the entire sample, allowing the surface to be rendered as a three dimensional image. The force exerted by the probe has the potential to alter the surface by etching or simply moving loosely bound surface features. As such, this microscopy technique can be potentially used to write (etch) as well as read, atomic scale surface features. The strain on the probe tip may cause deformation that leads to loss in resolution due to flattening or the generation of artifacts due to secondary tips.

The probe tip is idealized to be an atomically perfect spherical surface with a nanoscopic radius of curvature, leading to a single point of contact between the probe tip and the surface. Tips however may have multiple points of contact, leading to image artifacts such as doubled images or shadowing. Alternatively tips may be flattened or event indented, causing a lower resolution as smaller surface features are passed over. Significant error may arise from the expansion of the piezoelectric materials as they become heated. This problem is typically mitigated by attempting to maintain an isothermal environment. Drift may be measured and accounted for by repeat measurement of a known point and normalizing the data from that known height.

Modes of Operation

There are mutiple methods of imaging a surface using an atomic force microscope, these imaginging modes uniquely utilize the probe and its interaction with the surface to obtain data.

Contact

If a constant potential is maintained for the vertical piezoelectric, the probe will maintain continuous contact with the surface. It is then possible to use deflection and z-sensor to yield accurate height information of surface features.

Friction

When the probe is in contact with the sample the resistance acting on the probe's horizontal motion causes it to be strained horizontally. This strain is proportional to the resistance, friction, allowing for a direct measurement of the friction of the sample and probe surface.

Adhesion

Also known as non-contact mode, this method utilizes the attractive forces acting on the probe. To measure this, the probe is pulled from the sample by the vertical piezoelectric with a set force, as a feature is encountered the attractive force acting on the probe increases causing it to deflect downward. The downward deflection is counteracted by the vertical piezoelectric in a similar manner to contact mode, reaching the same equilibrium of forces acting on the cantilever.

Tapping

By using a piezoelectric device it is possible to use the cantilever as a harmonic oscillator with a resonance frequency proportional to the known spring constant. The probe then moves with an amplitude proportional to the driving force which is controlled and a frequency which is proportional to the spring constant. When the probe tip contact the surface the effective restoring force increases, increasing the frequency.

The total change in frequency is proportional to the feature's height, and vertical piezoelectric can then be used to raise the cantilever and restore the frequency to the original giving additional data from the z-sensor regarding the feature's height.

Additionally, as the probe contacts the surface it acts as a driving force, deforming the surface which is restored by the internal stress (that acts on the probe to repel it). The phenomenon is proportional to the Young's modulus of compressibility of the sample and will case a phase shift between the oscillation of the piezoelectric driver of the probe and the probe itself.

Other uses of AFM

Use of specialized probes allows a further expansion of atomic force microscopy's role in nanoscience. By alterations in probe design it is possible to: directly obtain data about the surface interaction with other functional groups, alter the surface by etching or causing chemical change, or deposit substrates onto a surface; all at the nanoscopic scale.

Chemical Force Microscopy

Functionalizing a probe can be accomplished by binding a protein or functional groups to the probe tip surface. The probe now takes direct measure of the iteration between the surface and the functional group. This technique is particularly useful for biological application, e.g. affinity of a protein to the binding site of a membrane.

Etching

The strain exerted by the tip on the surface has the potential to manipulate or alter the surface features, allowing for the mechanical etching of the system. By using specialized thermal tips, it becomes possible to heat the surface. Either technique can be used to precisely carve into or otherwise alter a surface at the scales necessary for many nanotechnologic advances.

Depositing

Use of a special tip similar to a fountain pen head, it is possible to deposit units of a substrate onto a surface. Precise deposition allows for building very precise surface structures, e.g. protien binding sites, onto an atomically flat surface.

Data recording

AFM has been demonstrated as a potential means of data storage by the IBM corperation. By using a heated tip it is possible to alter a polymer surface by a reversible polymerization reaction. The indentation created may be read by contact or tapping mode allowing for written data to be read. Data may be erased by use of the thermal tip to cause a polymerization on the surface, sealing the indentation.

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