CHEMISTRY 2120:

Chemistry for the Life Sciences II

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This version (version 2) has been revised and enriched by Dr. Ying Zheng.

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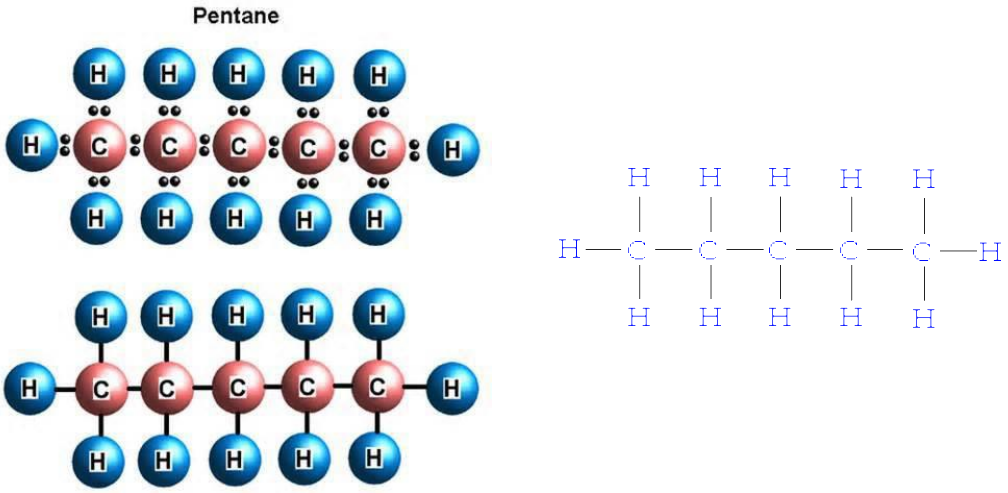
TOPIC 1: REPRESENTATIVE HYDROCARBONS

SATURATED HYDROCARBONS

The simplest hydrocarbon is methane, CH_4, with only one carbon atom and four single-bonded hydrogens. The carbon atom in methane satisfies its need for an octet with four single covalent bonds. Hydrocarbons with only singles bonds are called **saturated hydrocarbons**. The pentane molecule, C_5H_{12}, is an example of saturated hydrocarbon where all bonds with carbon are single bonds.

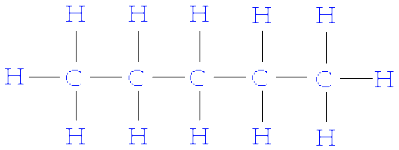
How do we show the bonding pattern in pentane on paper? We can do it by one of the following three kinds of Lewis representations.



Structural Formula (SF), Condensed SF, and Molecular Formula (MF)

Structural formulas show the connection between different atoms that are in a molecule

SF:



Condensed SF:

$CH_3CH_2CH_2CH_2CH_3$

or

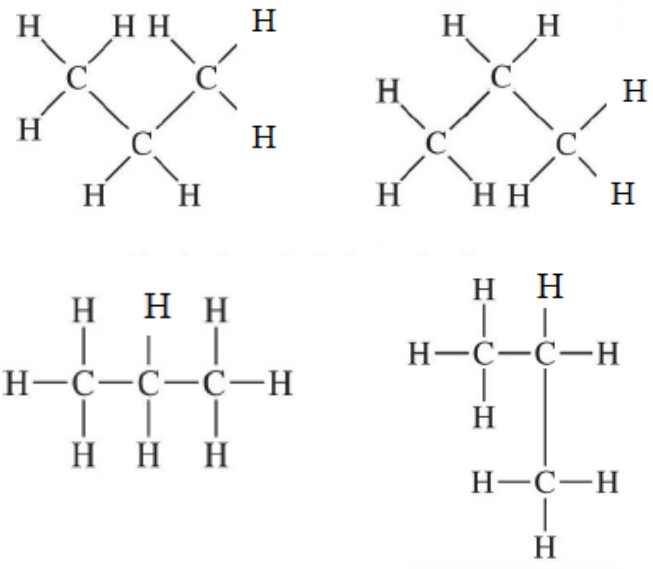
$CH_3(CH_2)_3CH_3$

MF:

C_5H_{12}

You should be able to convert one to the other with ease. Sometimes, one molecular formula might correspond to several structural formulas. For example, *how many ways can you "dash" propane?*

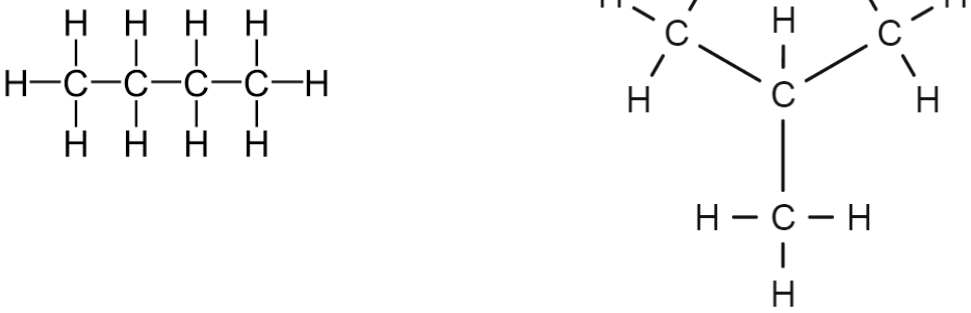
Equivalent Dash Formulas



There is relatively free rotation around the single bonds, so all four dash structures here are equivalent.

One thing to keep in mind is that dash formulas do not represent the 3D nature of molecules. The dash formulas of propane appear to have 90 degree angles for carbons, which actually have tetrahedral bond angles (109.5 degrees).

How many ways can you "dash" butane?



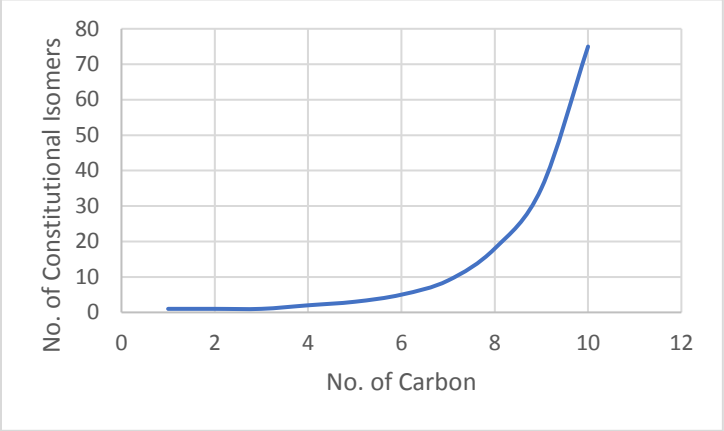
Are the two dash formulas above equivalent? No, even though they are all C_4H_{10}.

Constitutional Isomers

Constitutional Isomers have the same molecular formula, but *different connectivity*.

How many constitutional isomers are there for hexane? Try dash them out.

The number of constitutional isomers possible for a given saturated hydrocarbon molecule increases rapidly with the number of carbons in the carbon chain, as shown by the graph on the next page.

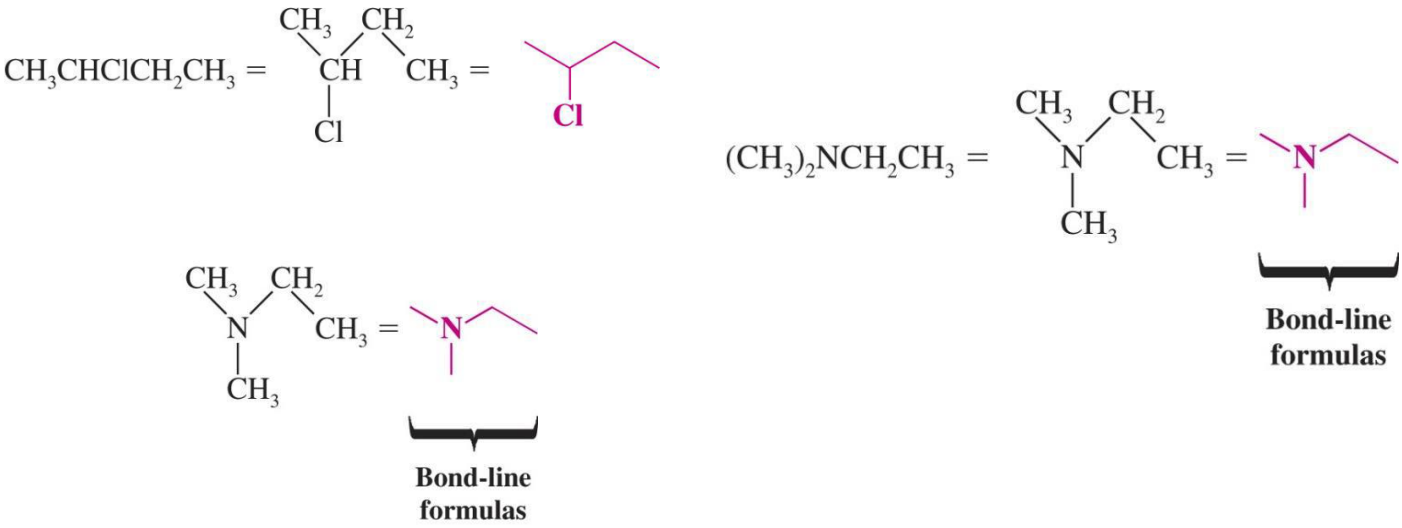


It would be a daunting task to dash out all the constitutional isomers for a given hydrocarbon with more than, say, eight carbons, in the carbon chain. Therefore, easier ways to draw out structural formulas are commonly used.

Line-Angle (Bond-Line) Formulas

All structures are drawn as zig-zag lines, with the bond angles reflecting the tetrahedral shape of the carbon center (recall the VSEPR theory).

1. Each vertex and line end is a "hidden" carbon center.
2. Each carbon center is saturated by "hidden" hydrogen atoms, meeting the requirement of "octet" for the carbon center.
3. Other atoms and their hydrogens are drawn in explicitly, as shown below.



Nomenclature

As organic chemistry grew and developed, many compounds were given trivial names, which are now commonly used and recognized. Some examples are:

Name	Methane	Butane	Acetone	Toluene	Acetylene	Ethyl Alcohol
Formula	CH_4	C_4H_{10}	CH_3COCH_3	$CH_3C_6H_5$	C_2H_2	C_2H_5OH

Such **common names** often have their origin in the history of the science and the natural sources of specific compounds, but the relationship of these names to each other is arbitrary, and no rational or systematic principles underlie their assignments.

The IUPAC Nomenclature System

A rational nomenclature system should do at least two things. First, it should indicate how the carbon atoms of a given compound are bonded together in a characteristic lattice of chains and rings. Second, it should identify and locate any functional groups present in the compound. Since hydrogen is such a common component of organic compounds, its amount and locations can be assumed from the tetravalency of carbon, and need not be specified in most cases.

Established by the **International Union of Pure and Applied Chemistry (IUPAC)**, the IUPAC nomenclature system is a set of logical rules devised and used by organic chemists to circumvent problems caused by arbitrary nomenclature. Knowing these rules and given a structural formula, one should be able to write a unique name for every distinct compound. Likewise, given an IUPAC name, one should be able to write a structural formula. In general, an IUPAC name will have three essential features:

- A root or base indicating a major chain or ring of carbon atoms found in the molecular structure.
- A suffix or other element(s) designating functional groups that may be present in the compound.
- Names of substituent groups, other than hydrogen, that complete the molecular structure.

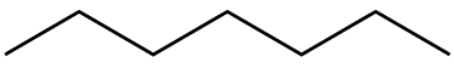
As an introduction to the IUPAC nomenclature system, we shall first consider compounds that have no specific functional groups: the alkanes.

Nomenclature: Alkanes

Alkanes are found in natural gas and petroleum. Smaller alkanes (≤ 4 carbons) are gases at room temperature. Alkanes are saturated hydrocarbons composed only of carbon and hydrogen atoms bonded together by single bonds. There are no double or triple bonded atoms. Alkanes are non-polar molecules. Due to London forces (change linearly with molar mass), a small number of carbons result in molecules that are gaseous (natural gases), while a large amount of carbons result in molecules that are solid (waxes) at room temperature.

Linear alkanes are named according to their chain length.

Butane = 

Heptane = 

The table on the next page gives the IUPAC name for the first ten linear alkanes.

# of Carbons	Molecular Formula	IUPAC Name
1	CH_4	Methane
2	C_2H_6	Ethane
3	C_3H_8	Propane
4	C_4H_{10}	Butane
5	C_5H_{12}	Pentane
6	C_6H_{14}	Hexane
7	C_7H_{16}	Heptane
8	C_8H_{18}	Octane
9	C_9H_{20}	Nonane
10	$C_{10}H_{22}$	Decane

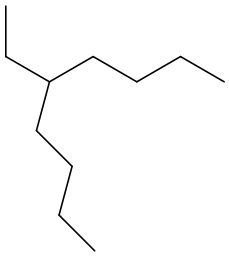
General formula for saturated hydrocarbons: C_nH_{2n+2}, where n = the number of carbons.

Higher alkanes have constitutional isomers that are not linear. This means that a molecule can have branches at various vertexes in a molecule. For branched alkanes, we use the longest continuous chain as the main chain, then call the remaining branch(es) **substituents**. This main chain is named as a linear alkane. The following general rules apply.

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. The prefixes di, tri, tetra etc., used to designate several groups of the same kind, are not considered when alphabetizing.

For example, the compound with the following structural formula is given the name 5-ethylnonane. At the first glance you might think that the main chain is the horizontal one with seven carbons and the branch is the vertical one with four carbons. However, if you followed rule No. 1 above, you should count the longest continuous carbon chain which contains nine carbons.



A C_9 main chain, where an ethyl group (C_2) branches off the 5th carbon of the nonane.

Substituents are named ahead of the main chain. Since the more carbons mean the more possible constitutional isomers, the location of the substituent(s) must be clearly written out in the correct IUPAC format. In the case of the above structure, the position of the ethyl group is right in the middle of the carbon chain, therefore you can start numbering the carbon atoms from either end of the carbon chain. In other cases, you should follow rule No. 3.

When the branch (substituent) is an alkane, they are called alkyl groups. They are formed by removing one hydrogen from the corresponding alkane. Where that hydrogen is no longer, that is where the substituent is attached to the main chain.

Alkyl groups are named based on their length, and the suffix is renamed from –ane to –yl. Using the above example, since the branch contains two carbons, the corresponding alkane is *ethane* and the substituent is called *ethyl*. The table below lists the ten alkyl groups derived from the first ten linear alkanes.

# of Carbons	Molecular Formula	IUPAC Name
1	CH_4	Methyl
2	C_2H_6	Ethyl
3	C_3H_8	Propyl
4	C_4H_{10}	Butyl
5	C_5H_{12}	Pentyl
6	C_6H_{14}	Hexyl
7	C_7H_{16}	Heptyl
8	C_8H_{18}	Octyl
9	C_9H_{20}	Nonyl
10	$C_{10}H_{22}$	Decyl

When there is more than one substituent

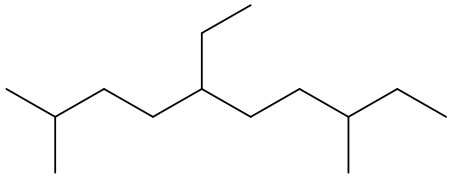
By default, if there are more than one substituent, they are listed alphabetically with their location on the main chain. If there are more than one of the same substituents (e.g. 2 methyl substituents), the prefix is altered.

1 methyl = methyl
2 methyls = dimethyl
3 methyls = trimethyl
4 methyls = tetramethyl

Additional punctuation

- The name of the entire molecule is written as one word
- Use commas to separate numbers
- Use hyphens to separate numbers from letters

e.g. 5-ethyl-2,8-dimethyldecane

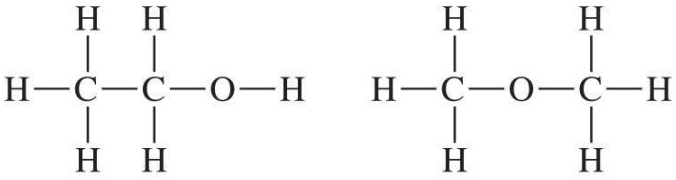


Naming conflicts

- If there are two or more main-chain options, choose the chain with the most branches/substituents.
- For possible branches with the same location, give the lower number to the lower alphabetical branch.

More on Constitutional Isomers

Consider two compounds with the molecular formula: C_2H_6O. The two compounds differ in the *connectivity* of their atoms. Due to that difference, the written name of the molecules can differ greatly. The chemical and physical properties of the molecules are also very different.



Ethyl alcohol **Dimethyl ether**

Classifying Carbons and Their Hydrogens

Carbon centers are classified as follows:

- **Primary (1°)** - carbons that are connected to only one other carbon
- **Secondary (2°)** - carbons that are connected to two other carbons
- **Tertiary (3°)** - carbons that are connected to three other carbons
- **Quaternary (4°)** - carbons are connected to four other carbons

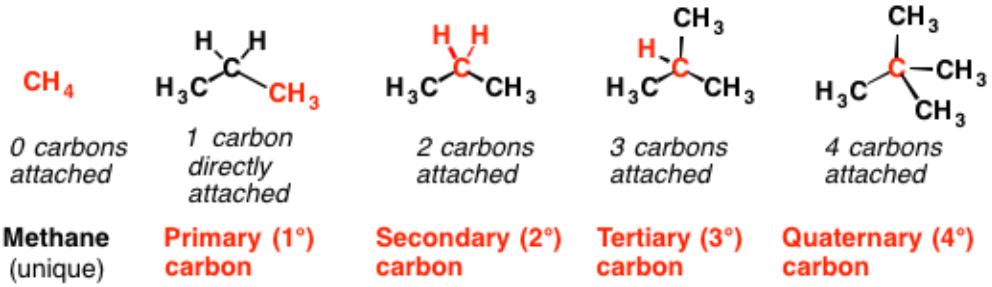


Figure 1. https://www.masterorganicchemistry.com/2010/06/16/1°-2°-3°-4°/

How to Recognize an Alkyl Group

Alkane		Alkyl Group	Abbreviation
CH_4 Methane	Removing one hydrogen	CH_3— Methyl group	Me—
CH_3CH_3 Ethane		CH_3CH_2— or C_2H_5— Ethyl group	Et—

Note that the "ane" suffix is replaced by "**yl**" in naming groups. The symbol **R** is used to designate a generic (unspecified) alkyl group.

Removing H from Different Carbons May Lead to Different Alkyl Groups

Are the eight hydrogens in propane C_3H_8 equivalent?

No. 6 are bonded to a primary carbon. 2 are bonded to a secondary carbon.
Removing an H from a primary carbon in propane gives a *propyl* group.
Removing an H from a secondary carbon in propane gives an *isopropyl* group. Isopropyl is considered the common name for the substituent, while the formal IUPAC name is 1-methylethyl.

Constitutional Isomers Can Give Even More Alkyl Groups

4-Carbon Alkane	One H Removed	Alkyl Group	Name
$CH_3CH_2CH_2CH_3$ Butane	From 1° C	$CH_3CH_2CH_2CH_2$— *butyl* group	IUPAC: butyl Common: butyl
	From 2° C	$CH_3CH_2CHCH_3$— *sec-butyl* group	IUPAC: 1-*methylpropyl* Common: *sec-butyl*
$CH_3(CH_3)CHCH_3$ 2-methylpropane or isobutane	From 1° C	$CH_3(CH_3)CHCH_2$— *iso-butyl group*	IUPAC: 2-methylpropyl Common: isobutyl
	From 3° C	$(CH_3)_3C$— *tert-butyl group*	IUPAC: 1,1-dimethylethyl Common: t-butyl

There are three Constitutional Isomers with this formula C_5H_{12}, each will give different substituent groups.

$CH_3CH_2CH_2CH_2CH_3$ – pentane

Remove H from the end 1° C → pentyl
Remove H from the first 2° C → 1-methylbutyl
Remove H from the middle (2°) C → 1-ethylpropyl

$CH_3(CH_3)CHCH_2CH_3$ – 2-methylbutane

How many alkyl groups can be obtained from this isomer? Try to figure out on your own.

$CH_3(CH_3)_2CCH_3$ – 2,2-dimethylpropane

Remove H from any 1° C → 2,2-dimethylpropyl (or *neopentyl*) group

Haloakanes

Substituting Hydrogen with Halogens Can Produce Haloalkanes

Such halogens are called substituents and their names are changed accordingly.

F → Fluoro-
Cl → Chloro-
Br → Bromo-
I → Iodo-

e.g. 5-chloro-3,3-diiodooctane, can you draw a line-bond structural formula for this compound?

Simple haloalkanes are commonly called **alkyl halides**.

Molecule:	**CH_3-Cl**	**CH_3-CH_2-Br**	**CH_3-CH-F-CH_3**
IUPAC:	Chloromethane	Bromoethane	2-fluoropropane
Common name:	Methyl chloride	Ethyl bromide	Isopropylflouride

Important: like with naming and ordering alkyl substituents, when molecules with different halogens are involved, their order is also done alphabetically.

E.g.: 1-bromo-3-chloro-hexane

Unsaturated Hydrocarbons: Alkenes & Alkynes

- Contain fewer than maximum number of hydrogens per carbon (as compared to the saturated hydrocarbons)
- Can react with H_2 to become saturated (aka hydrogentation)

Alkenes

Ethene (ethylene) and propene (propylene) are used heavily in industry.

Molecular formula of ethane: C_2H_4

Used in the production of ethanol and the polymer polyethylene
Degree of unsaturation = 1

Molecular formula of propene: C_3H_6

Used to make the polymer polypropylene and is the starting material for making acetone
Degree of unsaturation = 1

Can you give the structural formula for propene?
Does propene have any structural isomers?

Nomenclature for Alkenes with One Double Bond

# of Carbons	Molecular Formula	IUPAC Name
1	n/a	n/a
2	C_2H_4	Ethene
3	C_3H_6	Propene
4	C_4H_8	Butene
5	C_5H_{10}	Pentene
6	C_6H_{12}	Hexene
7	C_7H_{14}	Heptene
8	C_8H_{16}	Octene
9	C_9H_{18}	Nonene
10	$C_{10}H_{20}$	Decene

Note the general formula for 1 unit of unsaturated hydrocarbons: *2n*, where n = the number of carbons. One unit of saturation means there are two less hydrogens per unit.

Alkynes

Ethyne (acetylene) is used in welding torches because it burns at high temperatures.
The following reaction is a good example of making organic material from inorganic materials.

$$\mathbf{CaC_2 + 2H_2O \rightarrow C_2H_2 + Ca(OH)_2}$$

Molecular formula of ethyne: C_2H_2

Degree of unsaturation = 2

One triple bond equals 2 degrees of unsaturation; or one triple bond equals two double bonds.

Nomenclature for Alkenes with One Triple Bond

# of Carbons	Molecular Formula	IUPAC Name
1	n/a	n/a
2	C_2H_4	Ethyne
3	C_3H_6	Propyne

4	C_4H_8	Butyne
5	C_5H_{10}	Pentyne
6	C_6H_{12}	Hexyne
7	C_7H_{14}	Heptyne
8	C_8H_{16}	Octyne
9	C_9H_{18}	Nonyne
10	$C_{10}H_{20}$	Decyne

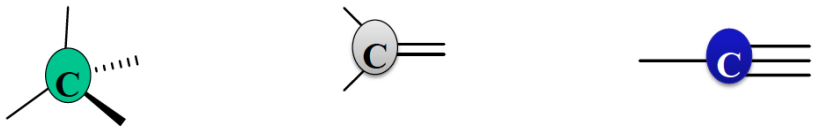
Note the general formula for 2 units of unsaturated hydrocarbons: *2n-2*, where n = the number of carbons. One unit of saturation means there are two less hydrogens per unit. Two units means there are *four* less hydrogens per unit.

Three-Dimensional Structural Formulas

The different bonding angles around each carbon center are:

- Four single bonds
- Two single bonds and one double bond
- One single bond and one triple bond

Using the VSEPR theory, the corresponding shape of each carbon center is, respectively:

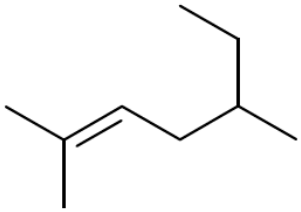


tetrahedral **Trigonal planar** **linear**

3D structural formulas are used to represent the bonding modes of the carbon centers.

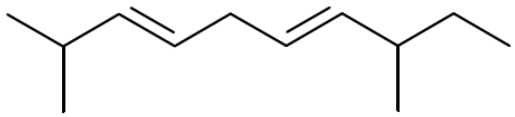
Nomenclature

The main chain should contain the double (or triple) bond. It is numbered to give the double bond the lowest number. In addition, if the molecule has more than one double bond, use IUPAC prefix rules (di, tri, etc.).



2,5-dimethyl-2-heptene, or 2,5-dimethylhept-2-ene

The IUPAC has introduced a new rule in 1993. The rule says that the number location where the double or triple bond is, now comes before suffix it is for.



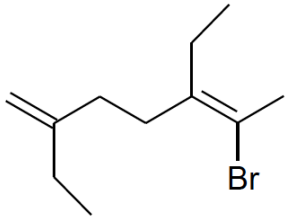
2,8-dimethyl-3,6-decadiene, or 2,8-dimethyldeca-3,6-diene

Note that the suffix adjustment to state the type of bond is also adjusted to include the prefix rule for the number of bonds it has. In this case, the "di" in "diene." The prefix rule is not just for substituents.

Additional Naming Adjustments

When altering names, especially within one, two consonants together are adjusted.

Example:



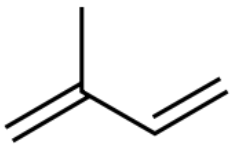
*6-bromo-2,5-diethyl-1,5-hept**a**diene, or 6-bromo-2,5-diethyl-hept**a**-1,5-diene*

Terpenes, Cyclic Alkanes, and Aromatic Compounds

Terpenes

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 5n5n carbon atoms (nn 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}



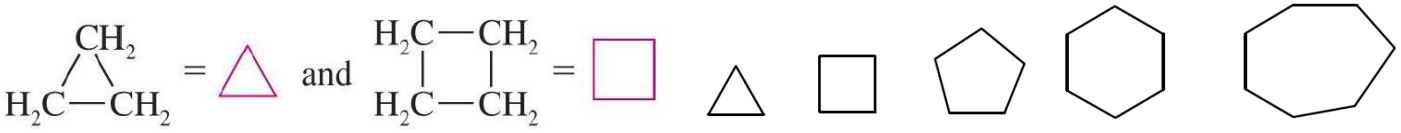
Terpenes connected in a head-to-tail manner.
Monoterpenes contain two isoprene units. 2 x 5 = 10 carbons.
Diterpenes contain four isoprene units. 20 carbons.

Unsaturated Hydrocarbons: Cyclic Alkanes

In a cyclic hydrocarbon, the ends of a hydrocarbon chain are connected to form a ring of covalently bonded carbon atoms. Cyclic hydrocarbons are named by attaching the prefix *cyclo-* to the name of the alkane, the

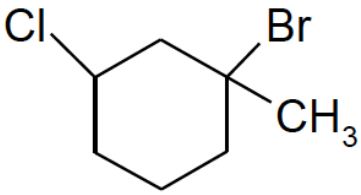
alkene, or the alkyne. The simplest cyclic alkanes are *cyclopropane* (C_3H_6) a flammable gas that is also a powerful anesthetic, and *cyclobutane* (C_4H_8). The most common way to draw the structures of cyclic alkanes is to sketch a polygon with the same number of vertices as there are carbon atoms in the ring; each vertex represents a CH_2 unit.

1 ring = 1 double bond = 1 unit of saturation



Naming Cycloalkanes

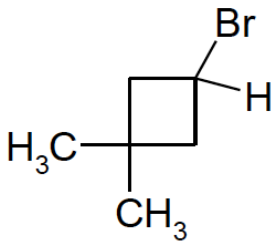
Simple cycloalkanes fit the general formula C_nH_{2n}.



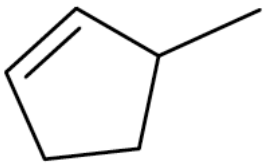
1-bromo-3-chloro-1-methylcyclohexane

3-bromo-1,1-dimethylcyclobutane

This is not 1-bromo-3,3-dimethylcyclobutane, because the lower of location numbers is preferred.

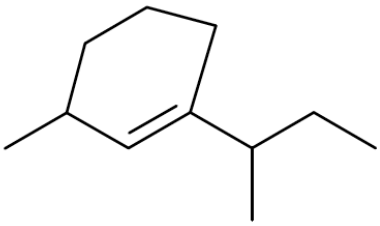


Cycloalkenes are numbered to give the double bond 1 and 2, and then the substituents the lowest number.



3-methylcyclopentene

1-sec-butyl-3-methylcyclohexene



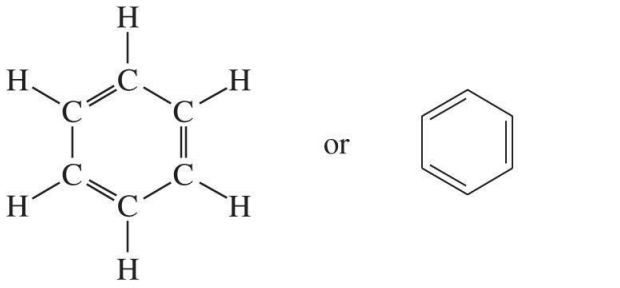
Unsaturated Hydrocarbons: Aromatic Compounds

Alkanes, alkenes, alkynes, and cyclic hydrocarbons are generally called aliphatic hydrocarbons. The name comes from the Greek *aleiphar*, meaning "oil," because the first examples were extracted from animal fats.

In contrast, the first examples of aromatic hydrocarbons, also called *arenes*, were obtained by the distillation and degradation of highly scented (thus *aromatic*) resins from tropical trees.

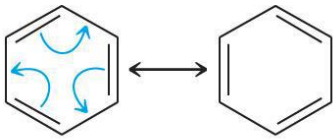
The simplest aromatic hydrocarbon is *benzene* (C_6H_6), which was first obtained from a coal distillate. The word *aromatic* now refers to benzene and structurally similar compounds.

The Kekulé structure (named after August Kekulé, who formulated it) is a six-membered ring with alternating double and single bonds.

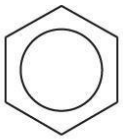


Kekulé structure for benzene **Bond-line representation of Kekulé structure**

It is possible to draw the structure of benzene in two different but equivalent ways, depending on which carbon atoms are connected by double bonds or single bonds.



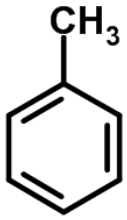
Two contributing Kekulé structures for benzene



A representation of the resonance hybrid

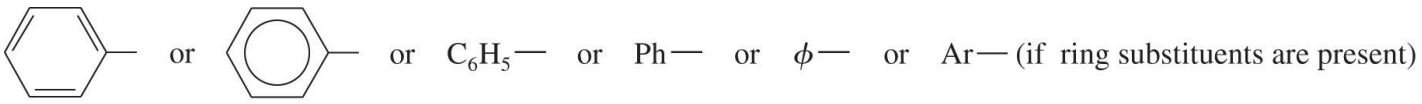
Toluene is similar to benzene, except that one hydrogen atom is replaced by a $–CH_3$ group; it has the formula C_7H_8.

The chemical behavior of aromatic compounds differs from the behavior of aliphatic compounds. Benzene and toluene are found in gasoline, and benzene is the starting material for preparing substances as diverse as aspirin and nylon.



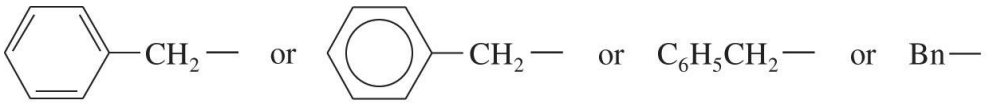
Benzene and Phenyl vs. Toluene and Benzyl

A benzene ring with a hydrogen removed is called *phenyl* and can be represented in various ways.



Ways of representing a phenyl group

Toluene (methylbenzene) with its methyl hydrogen removed is called a *benzyl group*.

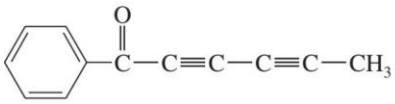


Ways of representing a benzyl group

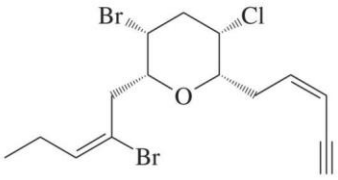
Nature has many unsaturated compounds…

The following are of biological interest.

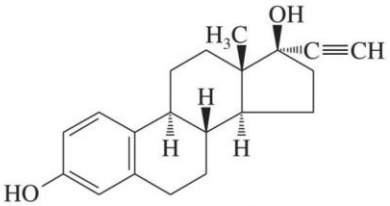
- Capillin is an anti-fungal agent found naturally.
- Dactylyne is a marine natural product.
- Ethinyl estradiol is a synthetic estrogen used in oral contraceptives.



Capillin



Dactylyne



Ethinyl estradiol
[17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol]

TOPIC 2: STEREOCHEMISTRY I

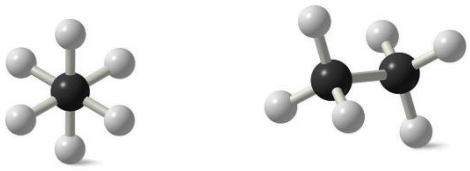
Conformations and Conformers

There is free rotation around any **single** carbon-carbon bond. Such rotation leads to the formation of many different conformations for a particular compound. Ethane has two **distinct** conformations (among other possibilities), they are called **conformational isomers** or **conformers**.

When using ball-and-stick models, if one allows the sticks to rotate in the holes, it will be found that for ethane, CH3−CH3CH3−CH3, an infinite number of different atomic orientations are possible, depending on the angular relationship (the so-called *torsional* angle) between the hydrogens on each carbon. Two extreme orientations or **conformations** are **staggered** and **eclipsed**.

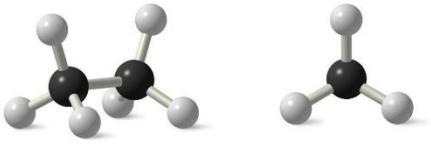
The *staggered* conformation has each of the hydrogens on the forward carbon set between each of the hydrogens on the back carbon. It has not been possible to obtain separate samples of ethane that correspond to these or intermediate orientations because actual ethane molecules appear to have essentially "free rotation" about the single bond joining the carbons. Free, or at least rapid, rotation is possible around all C−C *single* bonds, except when the carbons are part of a ring as in cyclopropane or cyclohexane.

Staggered



The eclipsed conformer has all C-H bonds on adjacent carbons directly on top of each other.

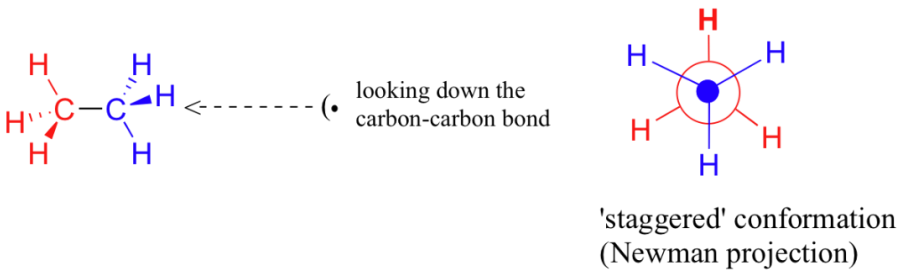
Eclipsed



For ethane and its derivatives, the staggered conformations are more stable than the eclipsed conformations. The reason for this in ethane is not wholly clear, but doubtless depends on the fact that, in the staggered conformation, the C−H bonding electrons are as far away from one another as possible and give the least *interelectronic* repulsion. With groups larger than hydrogen atoms substituted on ethane carbons, space-filling models usually show less interference (**steric hindrance**) for staggered conformations than for eclipsed conformations.

Newman Projection

In order to better visualize different conformations of a molecule, 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.



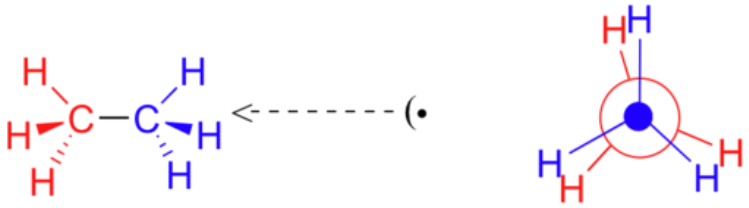
'staggered' conformation
(Newman projection)

The six carbon-hydrogen bonds are shown as solid lines protruding from the two carbons. Note that we do *not* draw bonds as solid or dashed wedges in a Newman projection.

Looking down the C-C bond in this way, the angle formed between a C-H bond on the front carbon and a C-H bond on the back carbon is referred to as a **dihedral angle**. (The dihedral angle between the hour hand and the minute hand on a clock is 0º at noon, 90º at 3:00, and so forth).

The lowest energy conformation of ethane, shown in the figure above, is called the '**staggered'** conformation: all of the dihedral angles are 60º, and the distance between the front and back C-H bonds is maximized.

If we now rotate the front CH_3 group 60° clockwise, the molecule is in the highest energy '**eclipsed**' conformation, where the dihedral angles are all 0º (we stagger the bonds slightly in our Newman projection drawing so that we can see them all).

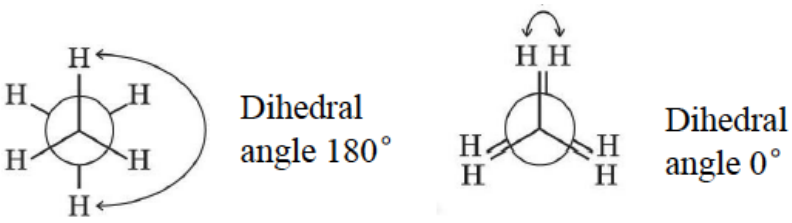


'eclipsed' conformation

Another 60° rotation returns the molecule to a second staggered 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 conformations in between these two extremes.

Dihedral Angle and Torsional Strain

Dihedral angles are the angle between two atoms 3-bonds apart.



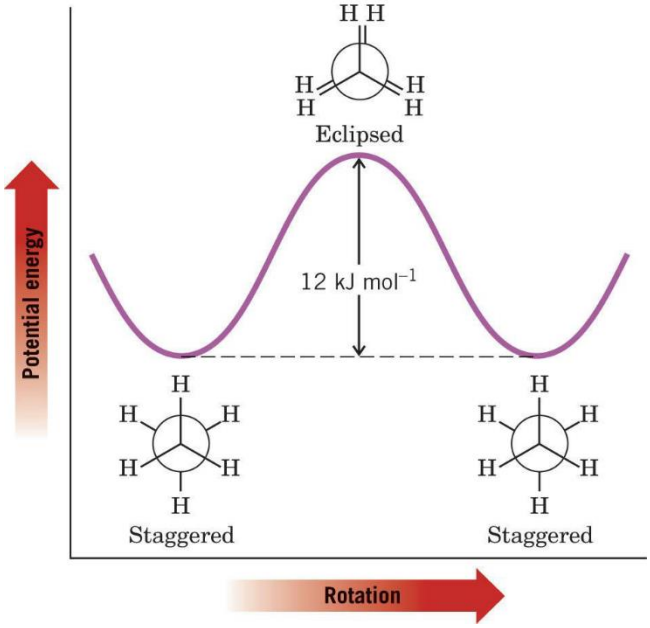
Atoms with smaller dihedral angles "run into each other," causing **torsional strain** in the molecule and gives the molecule a higher potential energy, destabilizing the molecule.

At a given temperature, a compound exists mainly in the most stable conformation.

Conformational analysis is the process of tracking the potential energy changes of some key conformers.

Conformational Analysis of Ethane

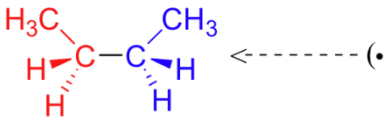
The potential energy diagram of the key conformers of ethane shows that the staggered conformers is more stable than the eclipsed one by 12 kJ mol^{-1}

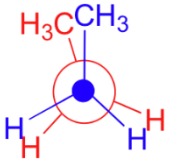


The eclipsed conformation is destabilized by **torsional strain**.

Conformation Analysis of Butane

Now let's consider butane, with its four-carbon chain. There are now three rotating carbon-carbon 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, with the two C-C bonds at a 0° dihedral angle.

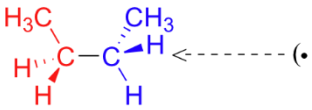


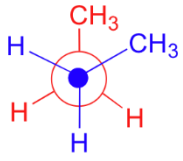


eclipsed (A)

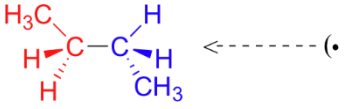
If we rotate the front, (blue) carbon by 60° clockwise, the butane molecule is now in a staggered conformation.

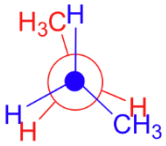
This is more specifically referred to as the **gauche** conformation of butane. Notice that although they are staggered, the two methyl groups are not as far apart as they could possibly be.





gauche

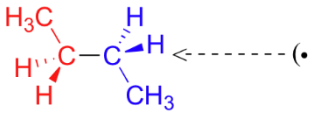


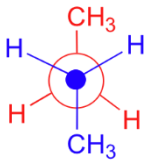


eclipsed (B)

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

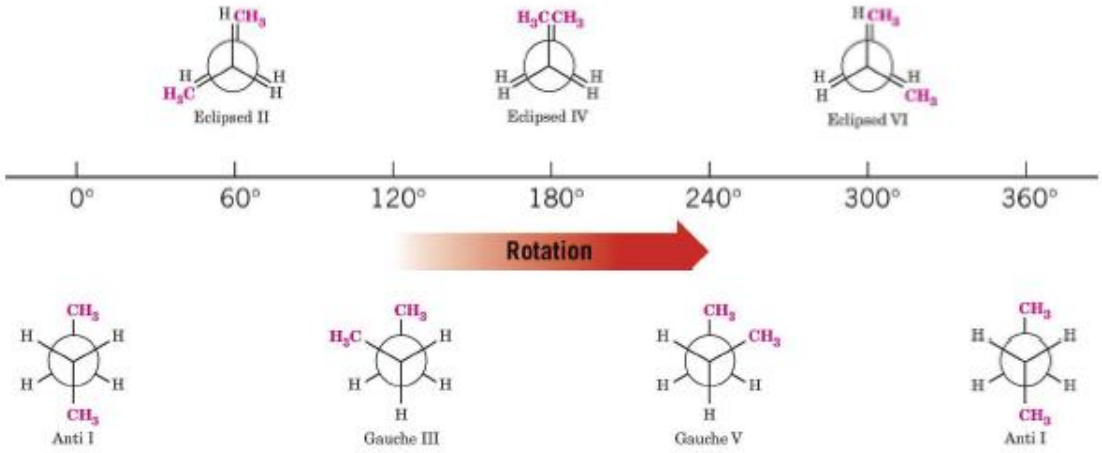
One more 60 rotation produces another staggered conformation called the **anti**-conformation, where the two methyl groups are positioned opposite each other (a dihedral angle of 180°).



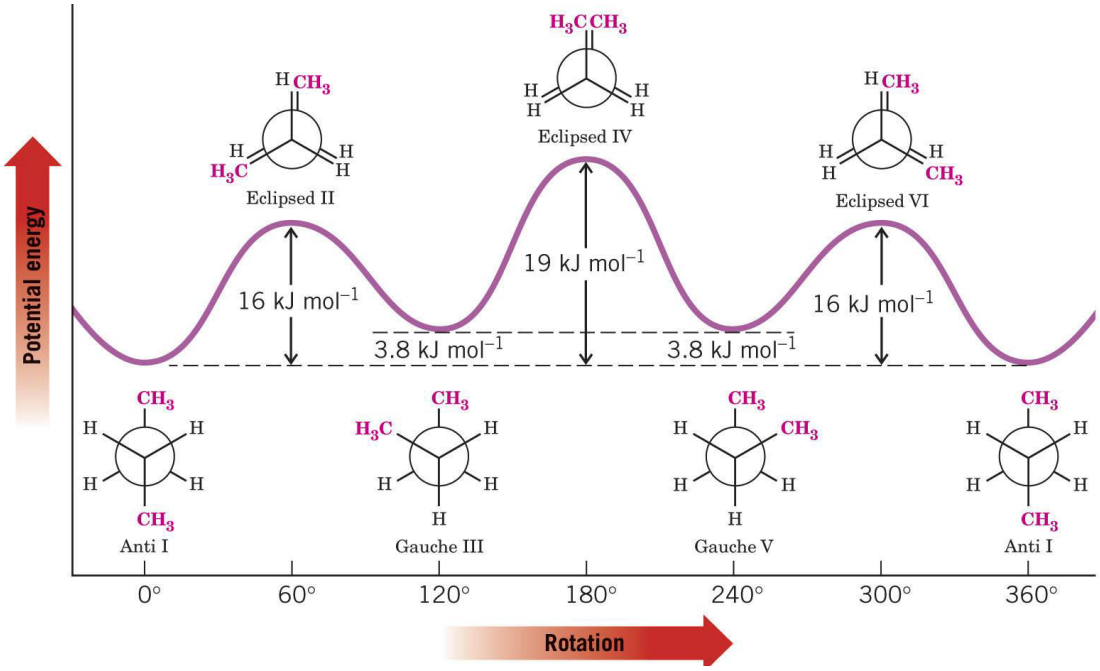


anti

Rotation of the front carbon (clockwise) around C_2-C_3 of butane gives six key conformations.



In the case of butane, we need to consider both torsional strain and steric strain (between two atoms four or more bonds apart). The following is the potential energy diagram for the key butane conformers.



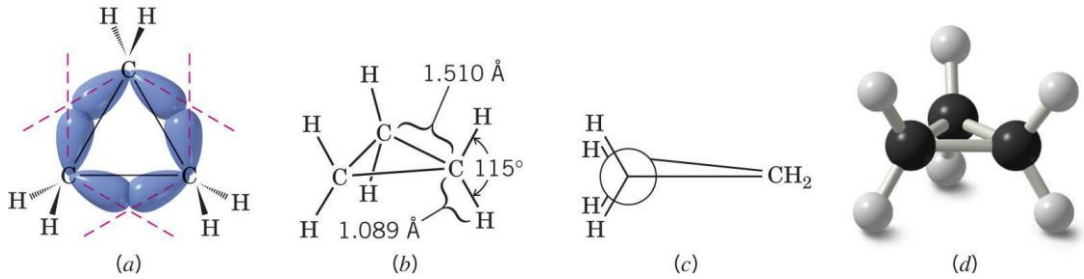
Ring Strain

Cycloalkanes tend to give off a very high and non-favorable energy, and the spatial orientation of the atoms is called the ring strain. When atoms are close together, their proximity is highly unfavorable and causes steric hindrance. The reason we do not want ring strain and steric hindrance is because heat will be released

due to an increase in energy; therefore, a lot of that energy is stored in the bonds and molecules, causing the ring to be unstable and reactive.

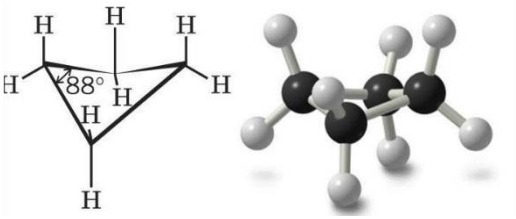
Ring strain is the sum of angle strain and torsional strain. Angle strain is caused by bond angles different from 109.5°. Torsional strain is caused by eclipsing C-H bonds on adjacent carbons. The smaller the angle, the greater the ring strain.

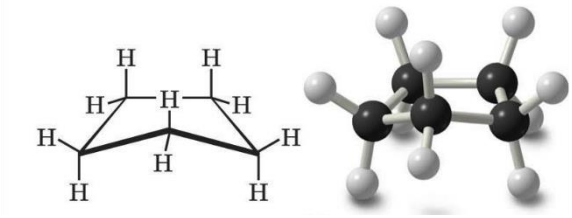
Cyclopropane is destabilized by ring strain, since there are only three sides to the cycloalkane. Cyclopropane has the highest angle and torsional strain.



Ring Strain in Cyclobutane and Cyclopentane: Angle Strain and Torsional Strain

Cyclobutane has considerable angle strain. It bends to relieve some torsional strain.





Cyclopentane has little angle strain in the planar form but bends to relieve some torsional strain.

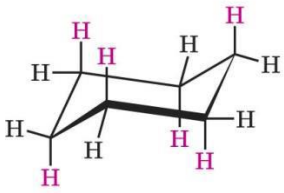
Another reason we try to avoid ring strain is because it will affect the structures and the conformational function of the smaller cycloalkanes. One way to determine the presence of ring strain is by its heat of combustion. By comparing the heat of combustion with the value measured for the straight chain molecule, we can determine the stability of the ring. There are two types of strain, which are eclipsing/torsional strain and bond angle strain. Bond angle strain causes a ring to have a poor overlap between the atoms, resulting in weak and reactive C-C bonds. An eclipsed spatial arrangement of the atoms on the cycloalkanes results in high energy.

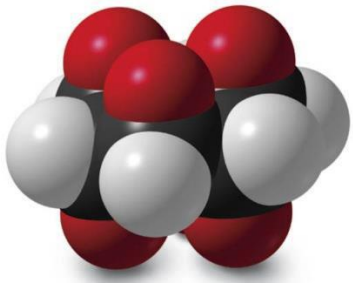
Experimental evidence of ring strain can be found in the following data. Compared to unbranched alkanes (no ring strain), cyclohexane has the least ring strain among the small cycloalkanes (n <10). Cyclopropane has the greatest ring strain.

Cycloalkane $(CH_2)_n$	*n*	Heat of Combustion per CH_2 Group (kJ mol^{-1})
Cyclopropane	3	697.0
Cyclobutane	4	686.0
Cyclopentane	5	664.0
Cyclohexane	6	658.7
Cycloheptane	7	662.4
Cyclooctane	8	663.8
Cyclononane	9	664.6
Cyclodecane	10	663.6
Cyclopentadecane	15	659.0
Unbranched alkane	—	658.6

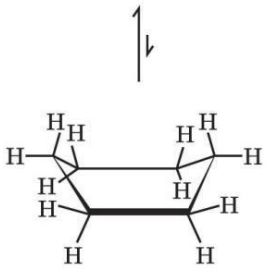
Nature Prefers 6-Membered Rings

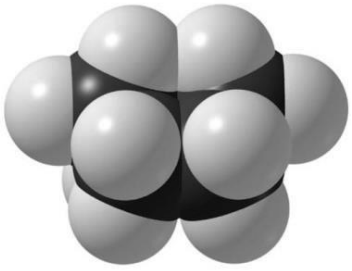
Cyclohexane (n = 6) has the lowest energy, measured at 658.7 kJ mol^{-1}. There are several conformations of cyclohexane. The 'chair' conformation is the most stable, as it has the least amount of ring strain. All bonds are 109.5° (minimizing angle strain) and all hydrogens are perfectly staggered (minimizing torsional strain).





The *boat* conformation is the least stable because of flagpole interactions and torsional strain along the bottom of the boat.

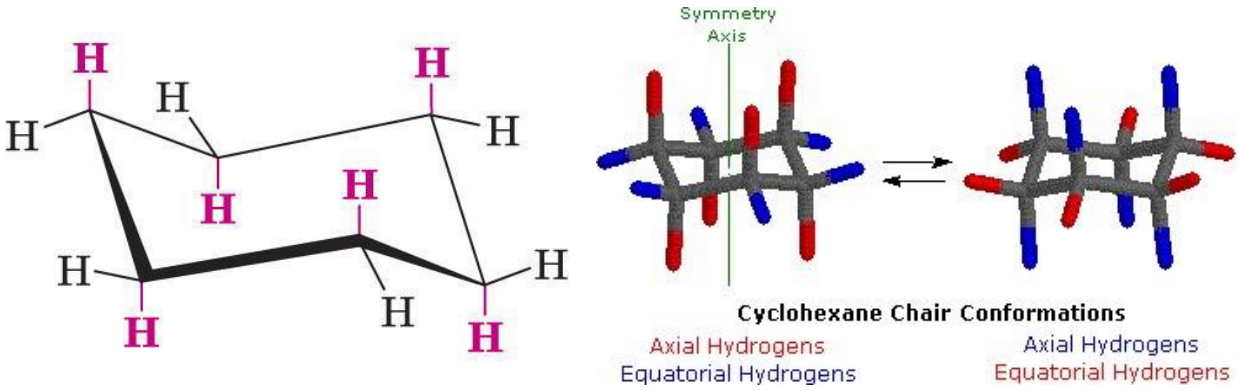




The twist conformation is intermediate stable.

Two Kinds of Hydrogen of Cyclohexane

In the chair conformation, hydrogen atoms are labeled according to their location. Those hydrogens which exist above or below the plane of the molecule are called **axial**. Those hydrogens which exist in the plane of the molecule are called **equatorial**.



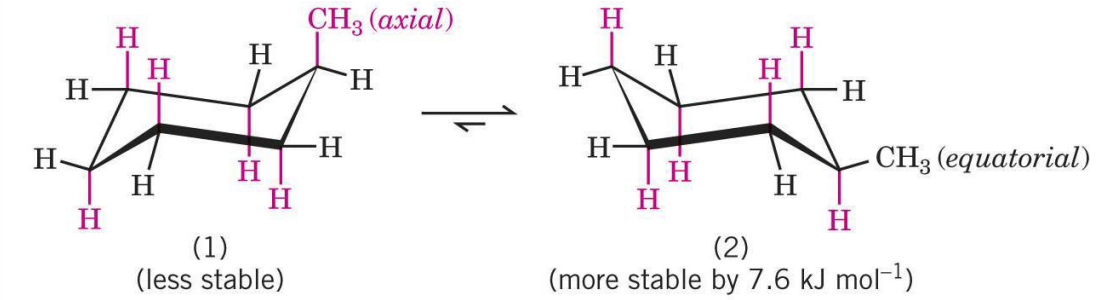
Although the chair conformation is the most stable conformation that cyclohexane can adopt, there is enough thermal energy for it to also pass through less favorable conformations before returning to a different chair conformation. When it does so, the axial and equatorial substituents change places. The passage of cyclohexane from one chair conformation to another, during which the axial substituents switch places with the equatorial substituents, is called a **ring flip** (shown later in this chapter).

If an H is replaced by a methyl group, does it prefer to lie down or stand up?

Substituents Prefer Equatorial Position in Cyclohexane

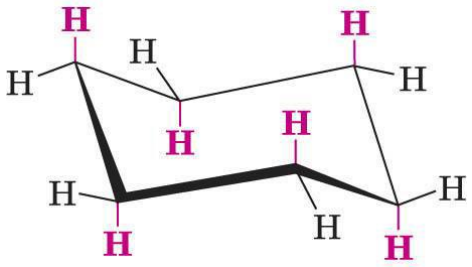
Methylcyclohexane is cyclohexane in which one hydrogen atom is replaced with a methyl group substituent. Methylcyclohexane can adopt two basic chair conformations: one in which the methyl group is axial, and one in which it is equatorial. Methylcyclohexane strongly prefers the equatorial conformation. In the axial conformation, the methyl group comes in close proximity to the axial hydrogens, an energetically unfavorable effect known as a **1,3-diaxial interaction.** Thus, the equatorial conformation is preferred for the methyl group. In most cases, if the cyclohexane ring contains a substituent, the substituent will prefer the equatorial conformation.

An axial methyl group is similar to the steric strain in the gauche conformation seen in the butane molecule earlier (see Newman Projections). Steric strain is increase even more so, the larger the substituent.

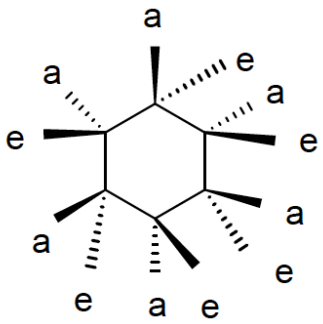


Two visual representations of cyclohexane:

Chair



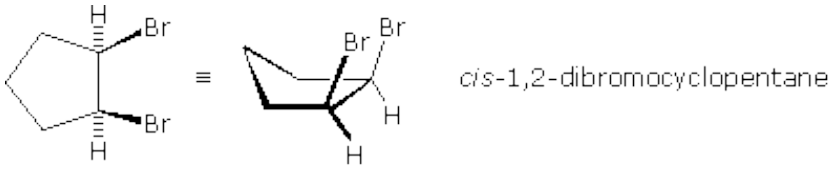
Planar



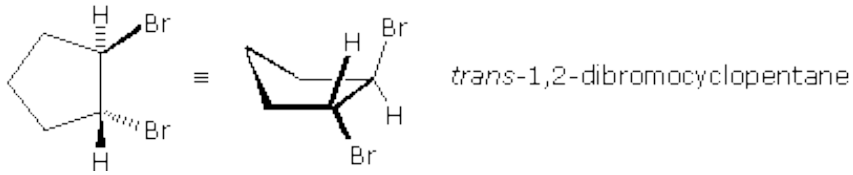
Planar does not differentiate axial or equatorial. It is arbitrary; however, it is important to note that the axial and equatorial designation alternate wedge/dash alignment across sequential carbons. An axial wedge in one carbon is an axial dash on the next carbon.

Disubstituted Cycloalkanes

Stereoisomers are also observed in certain disubstituted (and higher substituted) cyclic compounds. Unlike the relatively flat molecules of alkenes, substituted cycloalkanes must be viewed as three-dimensional configurations in order to appreciate the spatial orientations of the substituents. By agreement, chemists use heavy, **wedge-shaped** bonds to indicate a substituent located above the average plane of the ring (note that cycloalkanes larger than three carbons are not planar), and a **hatched line** for bonds to atoms or groups located below the ring. As in the case of the 2-butene stereoisomers, disubstituted cycloalkane stereoisomers may be designated by nomenclature prefixes such as **cis** and **trans**. The stereoisomeric 1,2-dibromocyclopentanes shown below is an example.



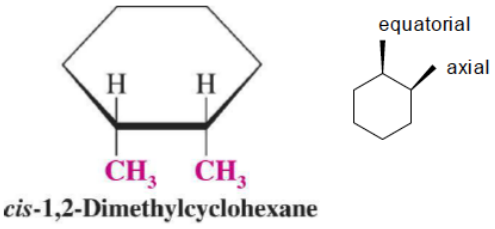
Cis: groups on the same side of the ring



Trans: groups on the opposite side of the ring

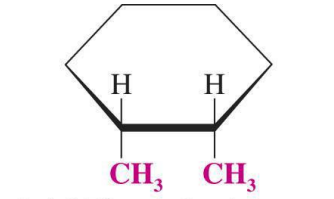
Many of the stereochemical concepts we have covered are illustrated nicely by looking at disubstituted cyclohexanes. We will now examine several dichlorocyclohexanes.

The 1,1-dichloro isomer has no centers of chirality. The 1,2- and 1,3-dichlorocyclohexanes each have two centers of chirality, bearing the same set of substituents. The cis & trans-1,4-dichlorocyclohexanes do not have any chiral centers, since the two ring groups on the substituted carbons are identical.

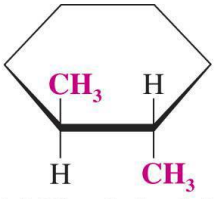


cis-1,2-Dimethylcyclohexane

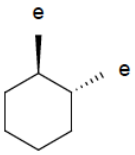
The molecule is drawn based on the planar visual. Again, note that the wedge alignment of one carbon is equatorial, meaning the wedge of the next carbon is axial.

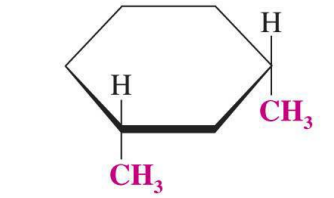


cis-1,2-Dimethylcyclohexane

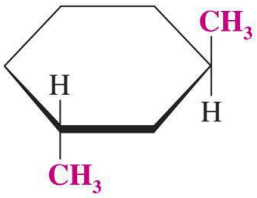


trans-1,2-Dimethylcyclohexane

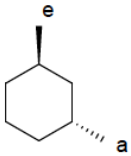


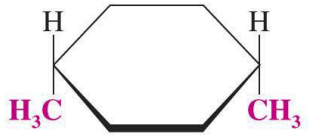


cis-1,3-Dimethylcyclohexane

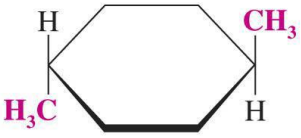


trans-1,3-Dimethylcyclohexane

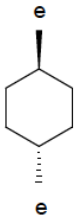




cis-1,4-Dimethylcyclohexane

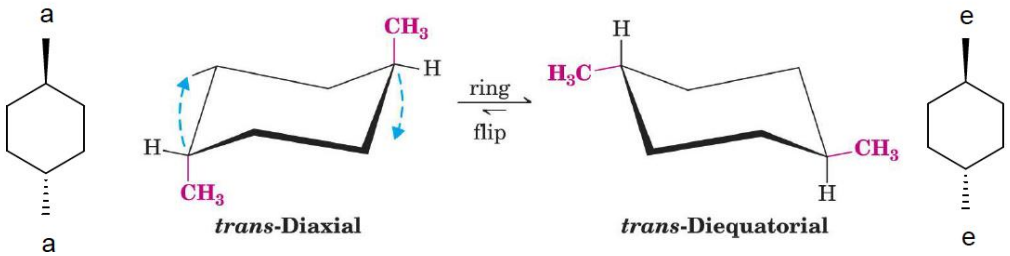


trans-1,4-Dimethylcyclohexane



Conformational Preference of Disubstituted Cyclohexanes

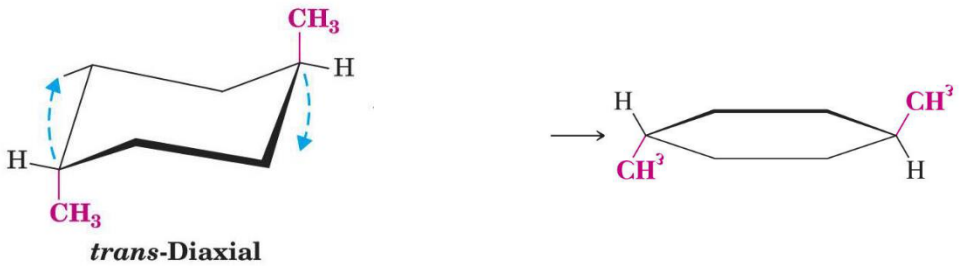
With CH3 being larger than H, two CH_3 on an axial orientation (trans) will result in a ring flip so the cyclohexane will be flip from trans-diaxial to a trans-diequatorial.



trans-Diaxial *trans*-Diequatorial

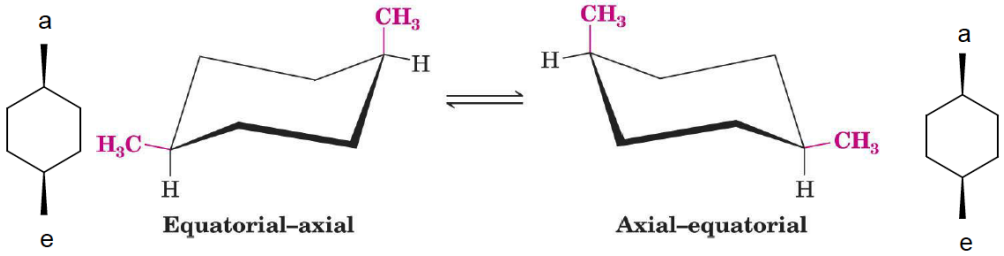
a* becomes *e

An alternative view:

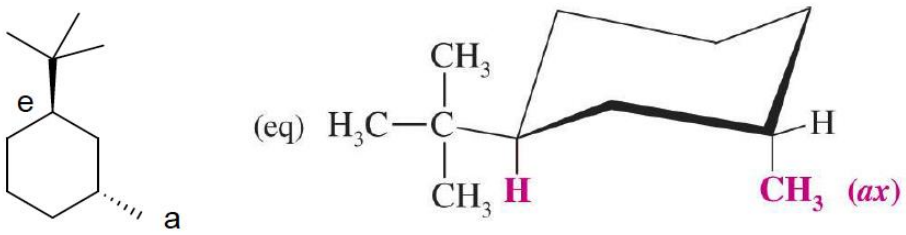


trans-Diaxial

For cis-1,4-dimethylcyclohexane, however, a **ring flip** would not make a difference.



For the following trans compound, the more stable conformation has the very large tert-butyl group on the *e* position.



The larger substituent gets the *e* priority.

Cyclopentane, because it is nearly flat, doesn't need to do a ring flip.

TOPIC 3: FAMILIES OF ORGANIC COMPOUNDS

What is Functional Group?

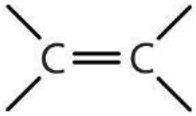
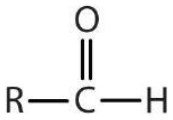
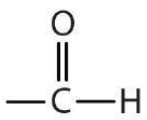
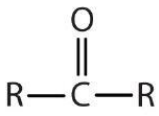
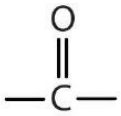
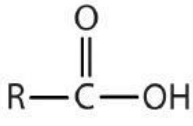
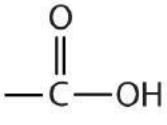
A functional group is the site of most chemical reactivity of a molecule. Alkanes do not have a functional group. C—C and C—H single bonds are generally very unreactive.

Previously, we considered several kinds of hydrocarbons. Now we examine some of the many organic compounds that contain functional groups. We first introduced the idea of the functional group, a specific structural arrangement of atoms or bonds that imparts a characteristic chemical reactivity to the molecule. If you understand the behavior of a particular functional group, you will know a great deal about the general properties of that class of compounds. In this chapter, we make a brief yet systematic study of some of organic compound families. Each family is based on a common, simple functional group that contains an oxygen atom or a nitrogen atom.

Nomenclature

In the IUPAC system of nomenclature, functional groups are normally designated in one of two ways. The presence of the function may be indicated by a characteristic suffix and a location number. This is common for the carbon-carbon double and triple bonds which have the respective suffixes **ene** and **yne**. Halogens, on the other hand, do not have a suffix and are named as substituents, for example: $(CH_3)_2C{=}CHCHClCH_3$ is 4-chloro-2-methyl-2-pentene.

Many compounds have a common name, as well as a formal name that follows the IUPAC naming system (e.g. ethyl alcohol and ethanol). Many common names are still recognized by the IUPAC.

Name of Family	General Formula	Functional Group	Suffix*
alkane	RH	none	*-ane*
alkene	R2C=CR2		*-ene*
alkyne	RC≡CR	–C≡C–	*-yne*
alcohol	ROH	–OH	*-ol*
thiol	RSH	–SH	*-thiol*
ether	ROR	–O–	ether
aldehyde			*-al*
ketone			*-one*
carboxylic acid			*-oic acid*

**Ethers do not have a suffix in their common name; all ethers end with the word ether.*

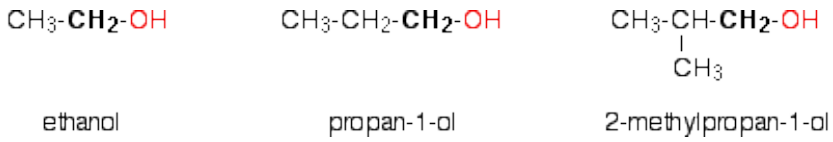
Naming Priorities

1	Acid
2	Ester
3	Amide
4	Nitrile
5	Aldehyde
6	Ketone
7	Alcohol
8	Phenol
9	Thiol
10	Amine
11	Ether
12	Alkene
13	Alkyne
14	Akyl, aryl, halides

Alcohols

Primary alcohols

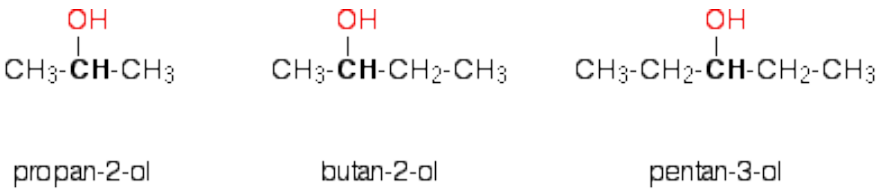
In a primary (1°) alcohol, the carbon which carries the -OH group is only attached to one alkyl group. Some examples of primary alcohols include:



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.

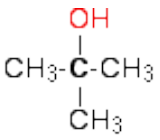
Secondary alcohols

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:

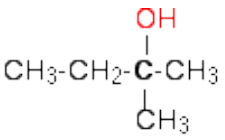


Tertiary alcohols

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:



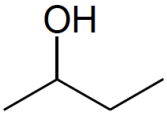
2-methylpropan-2-ol



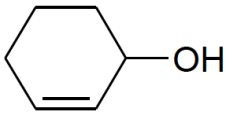
2-methylbutan-2-ol

Alcohols are usually named by the first procedure and are designated by an ***-ol*** suffix, as in ethanol, CH_3CH_2OH (note that a locator number is not needed on a two-carbon chain). On longer chains the location of the hydroxyl group determines chain numbering. For example: $(CH_3)_2C{=}CHCH(OH)CH_3$ is 4-methyl-3-penten-2-ol.

Naming Priority



butan-2-ol
or 2-butanol

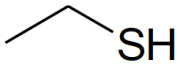


cyclohex-2-en-1-ol

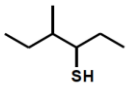
—OH takes priority over double bonds. Because it takes priority, it also means that it is position number 1 when naming, making the double bond position number 2.

Thiols

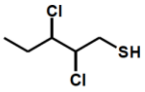
Thiols are very similar to alcohols. The only difference is that instead of oxygen (—OH), it is sulfur (—SH). Instead of ending with *-ol*, they end with *-thiol*.



ethanethiol

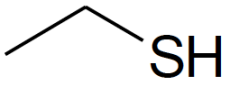


4-methylhexane-3-thiol

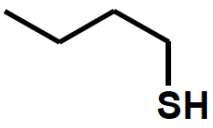


2,3-dichloropentane-1-thiol

The Smell of Thiols
The smell added to natural gas or propane is ethanethiol.



The odour that is a defensive strategy by skunks, detectable at 10 ppb, is butanethiol.



Removal of a thiol smell can be done by using H_2O_2 or Cl_2 bleach.

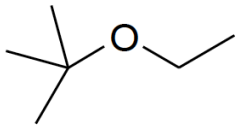
Ethers

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.

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 oxygen. 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.

Another example: 2-ethoxy-2-methlypropane

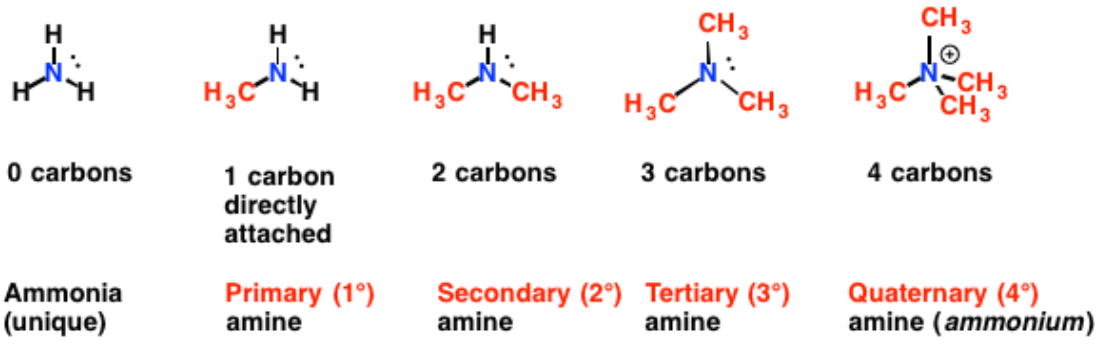


Ethoxy on the right, methylpropane on the left.

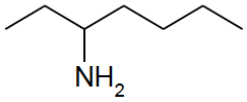
Lacking an R—OH group, the properties of ethers are in sharp contrast to those of alcohols. Diethyl ether, for example, has a lower boiling point (34.5°C) than ethanol, CH_3CH_2OH (78.3°C), and is only slightly soluble in water.

Amines

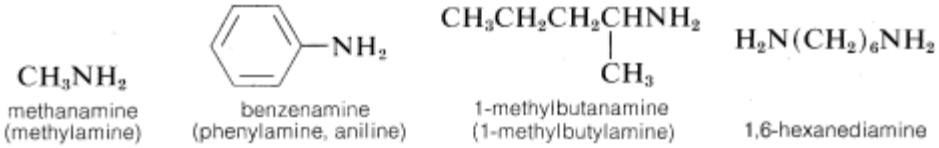
The word "amine" is derived from *ammonia*, and the class of compounds known as amines therefore are commonly named as substituted ammonias. In this system, **primary** amines (RNH_2), having only one substituent on nitrogen, are named with the substituent as a prefix.



More systematic nomenclature appends -*amine* to the longest chain, as for alcohols. For primary amines, the IUPAC standard nomenclature is to take the alkane name, drop the ending *e* and add –*amine* at the end.

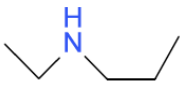


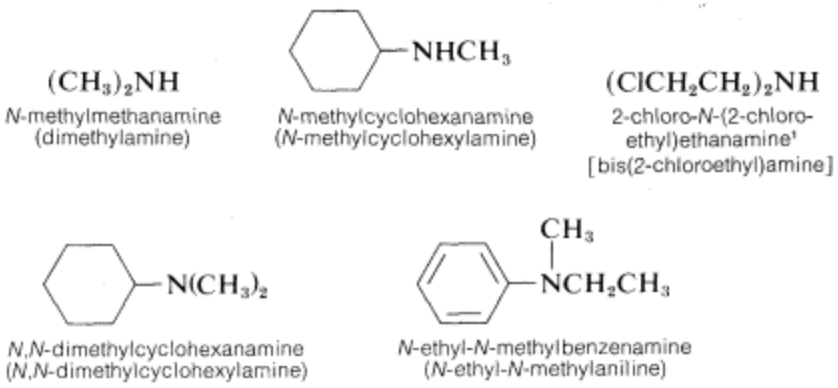
3-Heptanamine



Secondary (*R_2NH*) and **tertiary** amines (*R_3N*), which have two and three substituents on nitrogen, commonly are named as *N*-substituted amines. As for substituted amides, *N* is included to indicate that the substituent is on the nitrogen atom unless there is no ambiguity as to where the substituent is located. Systematic nomenclature of secondary and tertiary amines is related to the systematic ether nomenclature.

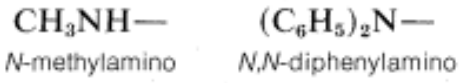
N-ethyl-1-propanamine





Alphabetical order puts chloro- ahead of chloroethyl-.

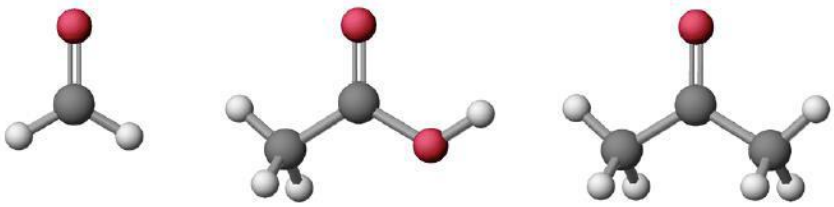
As a substituent, the $-NH_2$ group is called *amino*. N-Substituted amino groups are named accordingly:



Compounds with a Carbonyl group, C=O

Another class of organic molecules contains a carbon atom connected to an oxygen atom by a double bond, commonly called a carbonyl group. The trigonal planar carbon in the carbonyl group can attach to two other substituents leading to several subfamilies:

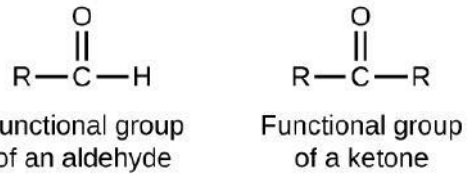
- Aldehydes
- Ketones
- Carboxylic Acids
- Esters

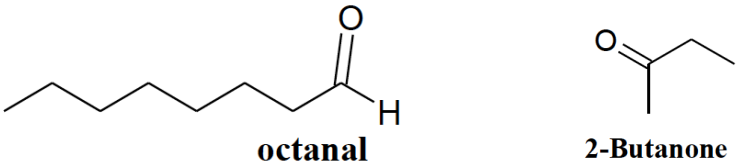


Formaldehyde CH_2O | Acetic acid CH_3CO_2H | Acetone CH_3COCH_3

Aldehydes and Ketones

Both aldehydes and ketones contain a carbonyl group, a functional group with a carbon-oxygen double bond. The names for aldehyde and ketone compounds are derived using similar nomenclature rules as for alkanes and alcohols, and include the class-identifying suffixes *-al* and *-one*, respectively.

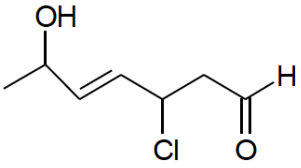




octanal **2-Butanone**

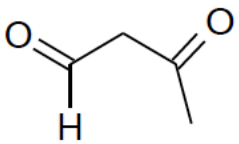
In an aldehyde, the carbonyl group is bonded to at least one hydrogen atom. In a ketone, the carbonyl group is bonded to two carbon atoms. As text, an aldehyde group is represented as –CHO; a ketone is represented as –C(O)– or –CO–.

When it comes to naming priorities, aldehydes get a higher priority over ketones. Aldehyde have a higher naming priority over all-but-four functional groups (acids, esters, amides, and nitriles). In the case of compounds involving halides and alcohols, they are identified as substituents in their naming.

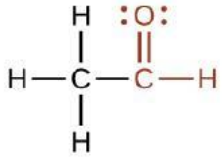


3-chloro-6-hydroxy-4-heptenal

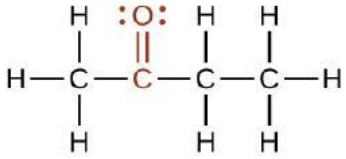
When a carbonyl group is substituent, the term *oxo* is used.



3-oxobutanal



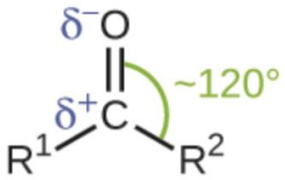
CH_3CHO
An aldehyde
ethanal (acetaldehyde)



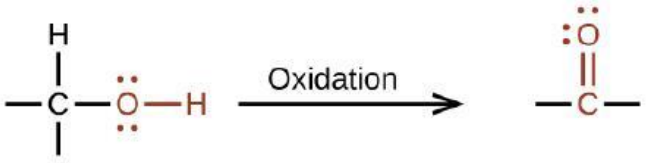
$CH_3COCH_2CH_3$
A ketone
butanone

Though this will be better understood in Topic 4, it is worth having this information here:
In both aldehydes and ketones, the geometry around the carbon atom in the carbonyl group is trigonal planar; the carbon atom exhibits *sp*2 hybridization. Two of the *sp*2 orbitals on the carbon atom in the carbonyl group are used to form σ bonds to the other carbon or hydrogen atoms in a molecule. The remaining *sp*2 hybrid orbital forms a σ bond to the oxygen atom. The *unhybridized p* orbital on the carbon atom in the carbonyl group overlaps a *p* orbital on the oxygen atom to form the π bond in the double bond.

Like the C=O bond in carbon dioxide, the C=O bond of a carbonyl group is polar (recall that oxygen is significantly more electronegative than carbon, and the shared electrons are pulled toward the oxygen atom and away from the carbon atom). Many of the reactions of aldehydes and ketones start with the reaction between a Lewis base and the carbon atom at the positive end of the polar C=O bond to yield an unstable intermediate that subsequently undergoes one or more structural rearrangements to form the final product.



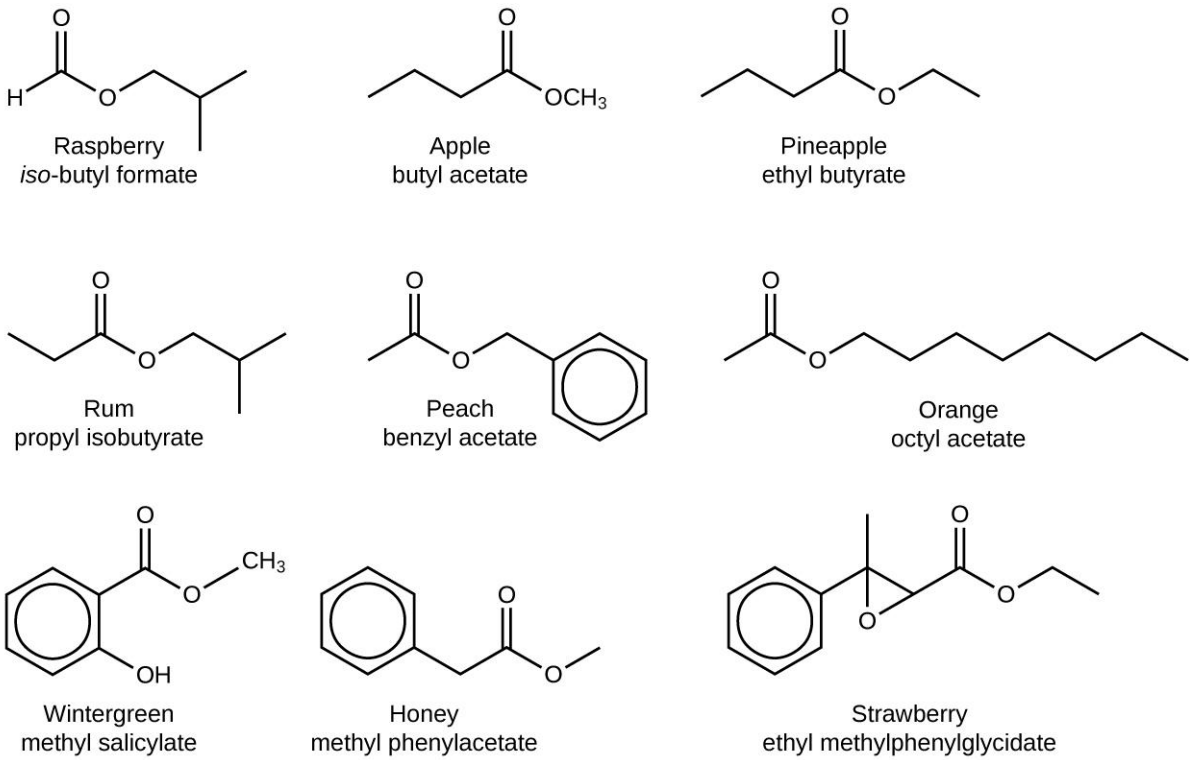
The importance of molecular structure in the reactivity of organic compounds is illustrated by the reactions that produce aldehydes and ketones. We can prepare a carbonyl group by oxidation of an alcohol—for organic molecules, oxidation of a carbon atom is said to occur when a carbon-hydrogen bond is replaced by a carbon-oxygen bond. The reverse reaction—replacing a carbon-oxygen bond by a carbon-hydrogen bond—is a reduction of that carbon atom. Recall that oxygen is generally assigned a –2 oxidation number (unless it is elemental or attached to a fluorine). Hydrogen is generally assigned an oxidation number of +1 unless it is attached to a metal. Since carbon does not have a specific rule, its oxidation number is determined algebraically by factoring the atoms it is attached to and the overall charge of the molecule or ion. In general, a carbon atom attached to an oxygen atom will have a more positive oxidation number and a carbon atom attached to a hydrogen atom will have a more negative oxidation number. This should fit nicely with your understanding of the polarity of C–O and C–H bonds. The other reagents and possible products of these reactions are beyond the scope of this chapter, so we will focus only on the changes to the carbon atoms:



alcohol carbonyl group

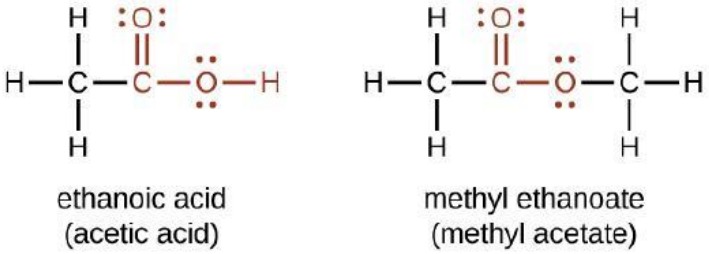
Carboxylic Acids & Esters

The odor of vinegar is caused by the presence of acetic acid, a carboxylic acid, in the vinegar. The odor of ripe bananas and many other fruits is due to the presence of esters, compounds that can be prepared by the reaction of a carboxylic acid with an alcohol. Because esters do not have hydrogen bonds between molecules, they have lower vapor pressures than the alcohols and carboxylic acids from which they are derived.

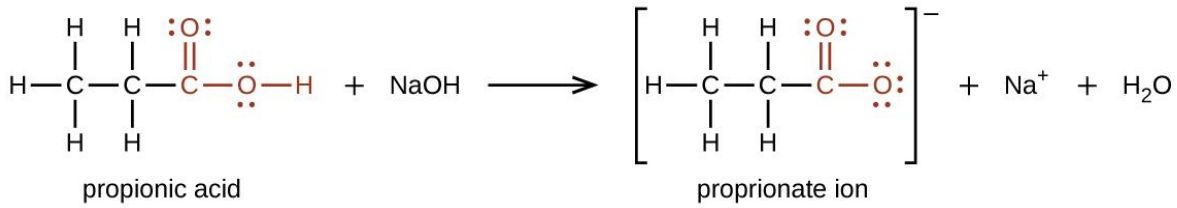


Esters are responsible for the odors associated with various plants and their fruits.

Both carboxylic acids and esters contain a carbonyl group with a second oxygen atom bonded to the carbon atom in the carbonyl group by a single bond. In a carboxylic acid, the second oxygen atom also bonds to a hydrogen atom. In an ester, the second oxygen atom bonds to another carbon atom. The names for carboxylic acids and esters include prefixes that denote the lengths of the carbon chains in the molecules and are derived following nomenclature rules similar to those for inorganic acids and salts (see these examples):

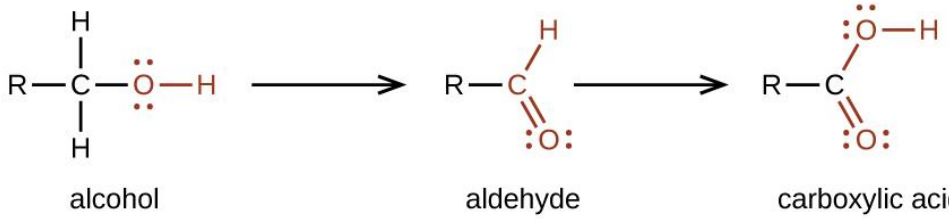


The functional groups for an acid and for an ester are shown in red in these formulas.
The hydrogen atom in the functional group of a carboxylic acid will react with a base to form an ionic salt:

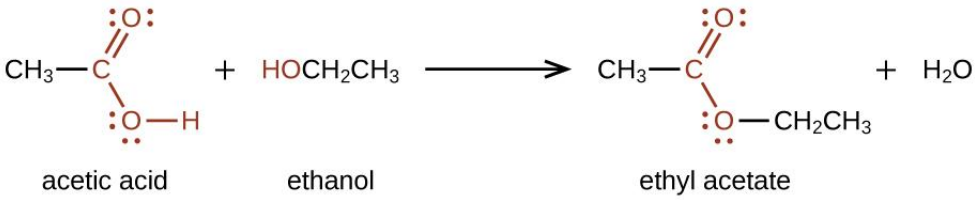


Carboxylic acids are weak acids, meaning they are not 100% ionized in water. Generally, only about 1% of the molecules of a carboxylic acid dissolved in water are ionized at any given time. The remaining molecules are undissociated in solution.

We prepare carboxylic acids by the oxidation of aldehydes or alcohols whose –OH functional group is located on the carbon atom at the end of the chain of carbon atoms in the alcohol:



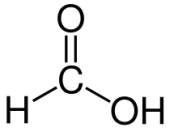
Esters are produced by the reaction of acids with alcohols. For example, the ester ethyl acetate, $CH_3CO_2CH_2CH_3$, is formed when acetic acid reacts with ethanol:



When an acid reacts with a base, a carboxylate salt is formed.

Naming Carboxylic Acids

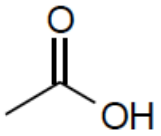
The simplest carboxylic acid is formic acid, HCO_2H, known since 1670. Its name comes from the Latin word *formicus*, which means "ant"; it was first isolated by the distillation of red ants. It is partially responsible for the pain and irritation of ant and wasp stings, and is responsible for a characteristic odor of ants that can be sometimes detected in their nests.



Formic acid is, however, a common name. The standardized IUPAC method for naming is to drop the *–e* of the alkane name and replace it with *–oic acid*. Thus, formic acid is, by IUPAC standards, methanoic acid.

Acetic acid, CH_3CO_2H, constitutes 3–6% vinegar. Cider vinegar is produced by allowing apple juice to ferment without oxygen present. Yeast cells present in the juice carry out the fermentation reactions. The fermentation reactions change the sugar present in the juice to ethanol, then to acetic acid. Pure acetic acid

has a penetrating odor and produces painful burns. It is an excellent solvent for many organic and some inorganic compounds, and it is essential in the production of cellulose acetate, a component of many synthetic fibers such as rayon.



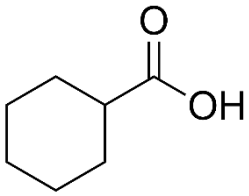
acetic acid

Here again, acetic acid is the common. Using IUPAC process, the systematic name is ethanoic acid.

The distinctive and attractive odors and flavors of many flowers, perfumes, and ripe fruits are due to the presence of one or more. Among the most important of the natural esters are fats (such as lard, tallow, and butter) and oils (such as linseed, cottonseed, and olive oils), which are esters of the trihydroxyl alcohol glycerine, $C_3H_5(OH)_3$, with large carboxylic acids, such as palmitic acid, $CH_3(CH_2)14CO_2H$, stearic acid, $CH_3(CH_2)16CO_2H$, and oleic acid, $CH_3(CH_2)_7CH = CH(CH_2)_7CO_2H$. Oleic acid is an unsaturated acid; it contains a C=C double bond. Palmitic and stearic acids are saturated acids that contain no double or triple bonds.

Naming Carboxylic Acids with Rings

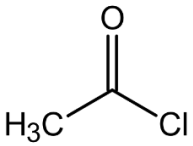
Rather than replacing or substituting letters, the general rule is that adding "*carboxylic acid*" at the end of the compound is what is done for all acid rings.

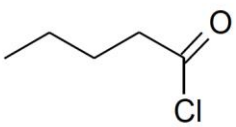


Cyclohexanecarboxylic Acid

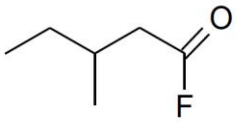
Naming Carboxylic Acid with Halides

An exception to the naming rules of carboxylic acids are when a halide is in place of the –OH that would normally be in a carboxylic acid. When that occurs, instead of using the *–oic acid* suffix, we use *–oyl halide* is the suffix. For example: acetyl chloride.





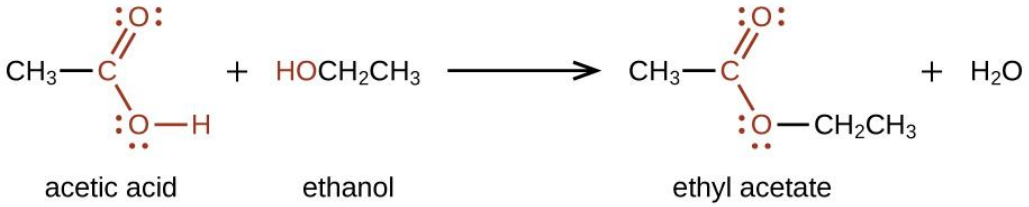
pentanoyl chloride



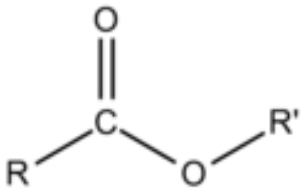
3-methylpentanoyl fluoride

Esters

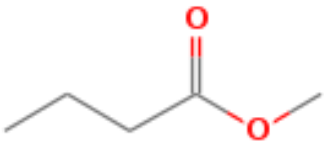
Cellulose acetate is a complicated example of another group of organic compounds, **esters**, which can be made by combining alcohols with acids. A simpler case is the reaction of ethanol with acetic acid to give ethyl acetate:



The general formula for an ester can be written/seen as:



In the case of ethyl acetate, R is CH_3CH_2 and R′ is CH_3. When this notation is used, esters are named based on the number of carbon atoms present in the alcohol and carboxylic acid groups that helped to form it. The term from the alcohol is given the "-yl" suffix, and is followed by the acid term with the suffix "-ate". As an example, the ester formed by the condensation reaction between methanol and butanoic acid would be called "methyl butanoate".

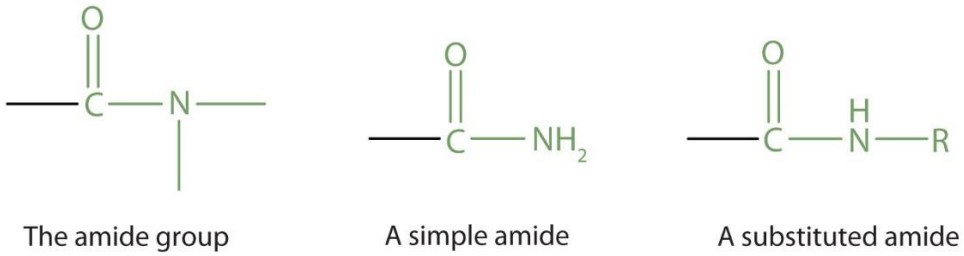


Formation of an ester is an example of an important class of reactions called condensations. In a condensation reaction, a pair of molecules join together, giving off a small, very stable molecule like H_2O or HCl. A condensation can often be undone if large numbers of the small molecules are added to the product. In the case of an ester, addition of large quantities of H_2O causes **hydrolysis,** which literally means the "splitting by means of water."

Although the ester functional group has a polar carbonyl, it contains no hydrogen atoms suitable for hydrogen bonding. Therefore, esters have low boiling points relative to most molecules of similar size. In many cases, even though its molecules are almost twice as large as those of the constituent alcohol and acid, an ester is found to have a lower boiling point than either. Ethyl acetate, for example, boils at 77.1°C, lower than ethanol (78.5°C) or acetic acid (117.9°C). By contrast to acids and alcohols which have unpleasant and rather weak odors, respectively, esters usually smell good. The odors of many fruits and flowers are due to esters. Ethyl acetate, for example, is the most important factor in the flavor of pineapples.

Amides

The amide functional group has a nitrogen atom attached to a carbonyl carbon atom. If the two remaining bonds on the nitrogen atom are attached to hydrogen atoms, the compound is a **simple amide**. If one or both of the two remaining bonds on the atom are attached to alkyl or aryl groups, the compound is a **substituted amide.**



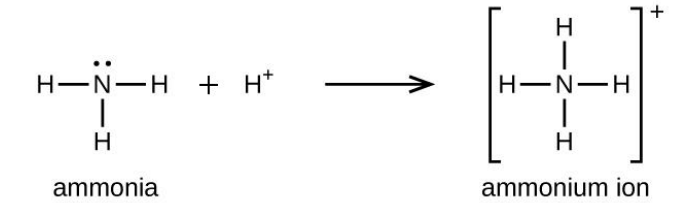
The amide group | A simple amide | A substituted amide

The carbonyl carbon-to-nitrogen bond is called an **amide linkage**. This bond is quite stable and is found in the repeating units of protein molecules, where it is called a *peptide linkage*.

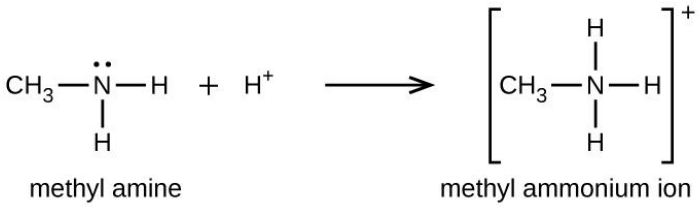
Simple amides are named as derivatives of carboxylic acids. The *-ic* ending of the common name or the *-oic* ending of the IUPAC name of the carboxylic acid is replaced with the suffix *-amide*.

Formic acid (methanoic acid) | Formamide (methanamide)

Like ammonia, amines are weak bases due to the lone pair of electrons on their nitrogen atoms:



ammonia | ammonium ion



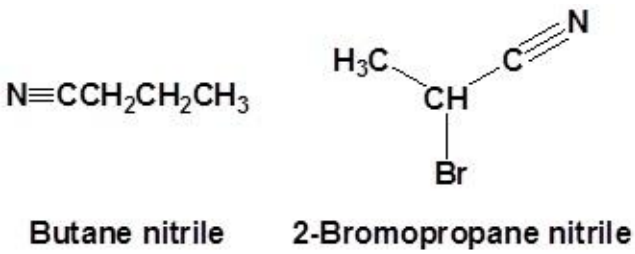
methyl amine | methyl ammonium ion

The basicity of an amine's nitrogen atom plays an important role in much of the compound's chemistry. Amine functional groups are found in a wide variety of compounds, including natural and synthetic dyes, polymers, vitamins, and medications such as penicillin and codeine. They are also found in many molecules essential to life, such as amino acids, hormones, neurotransmitters, and DNA.

Nitriles

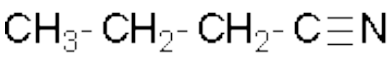
A **nitrile** is any organic compound with a −C≡N functional group. The prefix cyano- is used interchangeably with the term nitrile in literature. Nitriles used to be known as cyanides; the smallest organic nitrile is ethanenitrile, CH_3CN, (old name: methyl cyanide or acetonitrile - and sometimes now called ethanonitrile).

Name the parent alkane (include the carbon atom of the nitrile as part of the parent) followed with the word -nitrile. The carbon in the nitrile is given the #1 location position. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.



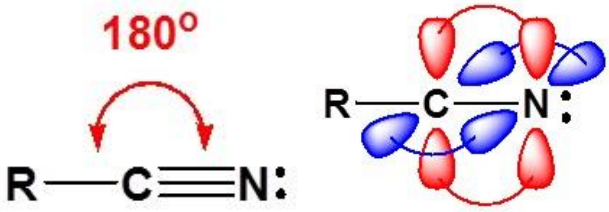
Butane nitrile **2-Bromopropane nitrile**

Cycloalkanes are followed by the word -carbonitrile. The substituent name is cyano.

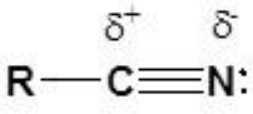


1-butanenitrile or 1-cyanopropane

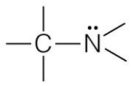
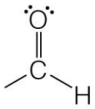
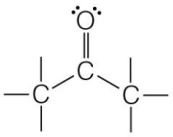
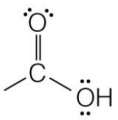
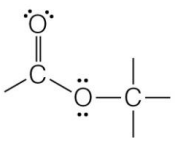
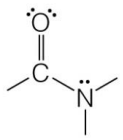
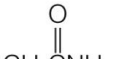
The electronic structure of nitriles is very similar to that of an alkyne with the main difference being the presence of a set of lone pair electrons on the nitrogen. Both the carbon and the nitrogen are *sp* hydridized which leaves them both with two p orbitals which overlap to form the two π bond in the triple bond. The R-C-N bond angle in and nitrile is 180° which give a nitrile functional group a linear shape.



The lone pair electrons on the nitrogen are contained in a *sp* hybrid orbital which makes them much less basic and an amine. The presence of an electronegative nitrogen causes nitriles to be very polar molecules. Consequently, nitriles tend to have higher boiling points than molecules with a similar size.



Summary of Important Families of Organic Compounds

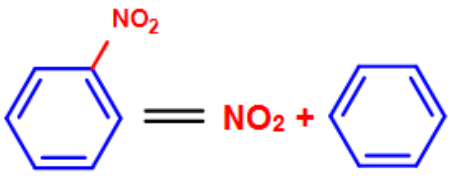
Family						
Amine	**Aldehyde**	**Ketone**	**Carboxylic Acid**	**Ester**	**Amide**	**Nitrile**
						
RNH_2 R_2NH R_3N					  	RCN
CH_3NH_2						
Methanamine	Ethanal	Propanone	Ethanoic acid	Methyl ethanoate	Ethanamide	Ethanenitrile
Methylamine	Acetaldehyde	Acetone	Acetic acid	Methyl acetate	Acetamide	Acetonitrile

Benzenes & Derivatives

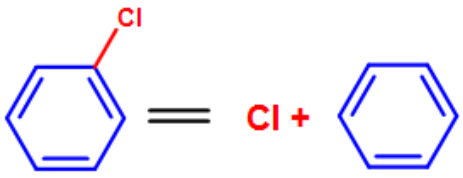
Benzene

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.

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.)

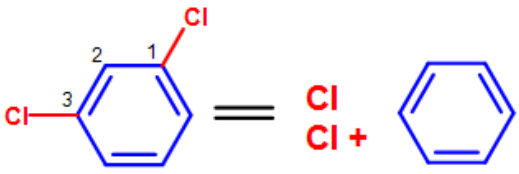


Nitrobenzene = Nitro + Benzene

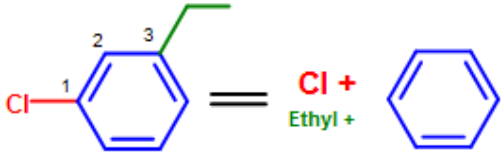


Chlorobenzene = Chloro + Benzene

Adding multiple substituents is the same idea as if the benzene ring were a main chain.

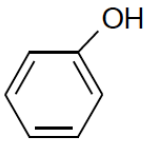


1,3-dichlorobenzene = 2 Chloro + Benzene

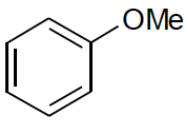


1-chloro-3-ethylbenzene = Chloro (1) + Benzene
Ethyl (3)

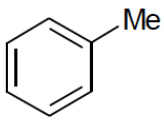
Common Names for Bezene Derivatives



phenol



anisole



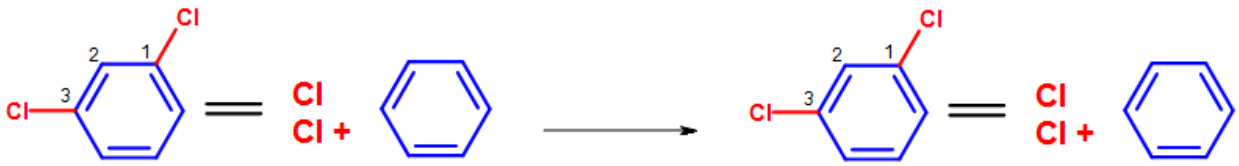
toluene

Ortho-, Meta-, Para- (OMP) Nomenclature for Disubstituted Benzenes

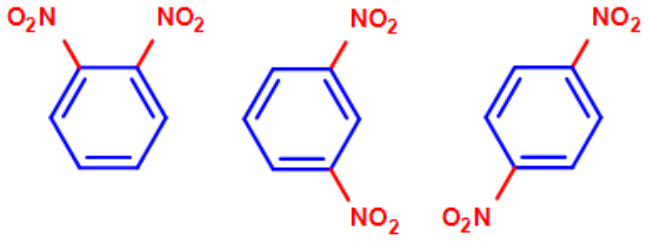
Instead of using numbers to indicate substituents on a benzene ring, *ortho- (o-), meta- (m-), or para (p-)* can be used in place of positional markers when there are **two** substituents on the benzene ring (disubstituted benzenes). They are defined as the following:

- *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)

Using the same example from earlier (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.

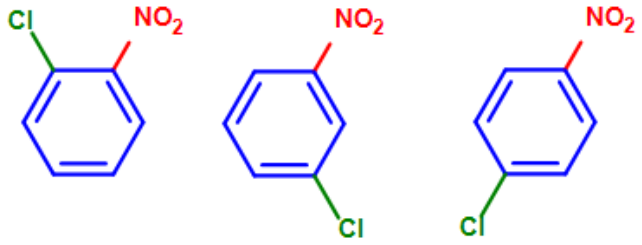


Here are some other examples of ortho-, meta-, para- nomenclature used in context:



1) o-dinitrobenzene
2) m-dinitrobenzene
3) p-dinitrobenzene

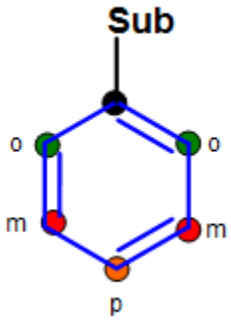
However, the substituents used in ortho-, meta-, para- nomenclature do not have to be the same. For example, we can use chlorine and a nitro group as substituents in the benzene ring.



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:

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.



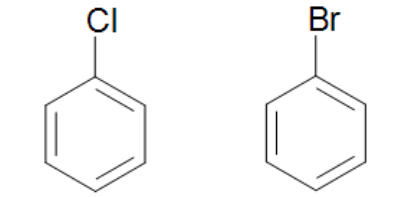
OMP nomenclature is considered an older naming format, because of its limitation where it cannot be used if there are more than two groups on a benzene ring.

Base Name Nomenclature

In addition to simple benzene naming and OMP nomenclature, benzene derived compounds are also sometimes used as **bases**. The concept of a base is similar to the nomenclature of aliphatic and cyclic compounds, where the parent for the organic compound is used as a base (a name for its chemical name. For example, the following compounds have the base names *hexane* and *cyclohexane*, respectively.

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**.



Phenyl Chloride **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.

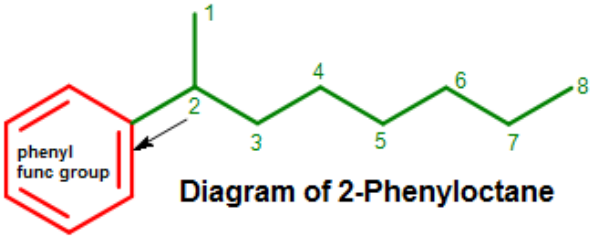
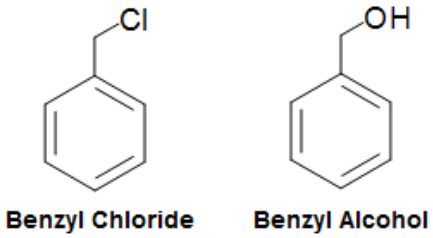


Diagram of 2-Phenyloctane

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 CH2 group to where the hydrogen was removed. Its molecular fragment can be written as C6H5CH2-R, PhCH2-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.



Additionally, other substituents can attach on the benzene ring in the presence of the benzyl group. An example of this can be seen in 2,4-difluorobenzyl chloride.

Similar to the base name nomenclatures 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.**

TOPIC 4: BASIC BONDING THEORIES

Valence Bond Theory
The formation of σ (sigma) bonds
The formation of π (pi) bonds

What is Valence Bond Theory?

Carrying over from Chemistry 1110, there are key terms to recall and be introduced to:

Overlap: coexistence of orbitals from two different atoms sharing the same region of space, leading to formation of a covalent bond.
lp: lone pair of electrons (non-bonding, no overlap)
bp: bonding pair of electrons (result of orbital overlap)
central atom: the atom of concern in a molecule
***σ*-bond**: sigma bond (overlap) of orbitals along the bond axis
***π*-bond**: pi bond (overlap) of orbitals above and below the bond axis
single bond: one σ bond
double bond: one σ bond and one π bond
triple bond: one σ bond and two π bonds

This chapter is written as half a review, where we expand beyond what we already know.

As we know, a scientific theory is a strongly supported explanation for observed natural laws or large bodies of experimental data. For a theory to be accepted, it must explain experimental data and be able to predict behavior. For example, VSEPR theory has gained widespread acceptance because it predicts three-dimensional molecular shapes that are consistent with experimental data collected for thousands of different molecules. However, VSEPR theory does not provide an explanation of chemical bonding.

There are successful theories that describe the electronic structure of atoms. We can use quantum mechanics to predict the specific regions around an atom where electrons are likely to be located: A spherical shape for an *s* orbital, a dumbbell shape for a *p* orbital, and so forth. However, these predictions only describe the orbitals around free atoms. When atoms bond to form molecules, atomic orbitals are not sufficient to describe the regions where electrons will be located in the molecule. A more complete understanding of electron distributions requires a model that can account for the electronic structure of molecules. One popular theory holds that a covalent bond is formed when a pair of electrons is shared by two atoms and is simultaneously attracted by the nuclei of both atoms. In the following sections, we will discuss how such bonds are described by valence bond theory and hybridization.

Ionic bonding

Ions are atoms or molecules which are electrically charged. **Cations** are positively charged and **anions** carry a negative charge. Ions form when atoms gain or lose electrons. Since electrons are negatively charged, an atom that loses one or more electrons will become positively charged; an atom that gains one or more electrons becomes negatively charged.

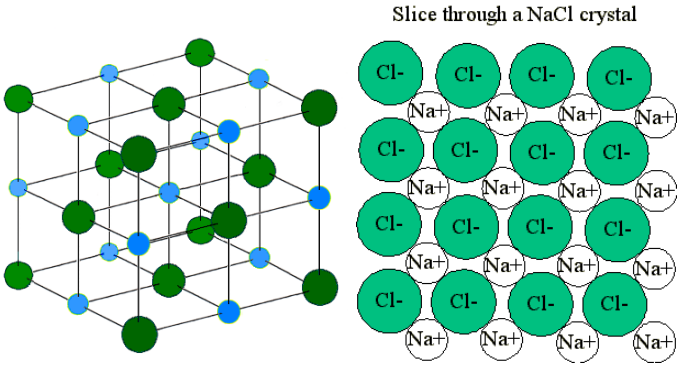
Ionic bonding is the attraction between positively- and negatively-charged **ions**. These oppositely charged ions attract each other to form ionic networks (or lattices). Electrostatics explains why this happens: opposite charges attract and like charges repel. When many ions attract each other, they form large, ordered, crystal lattices in which each ion is surrounded by ions of the opposite charge. Generally, when metals react with

non-metals, electrons are transferred from the metals to the non-metals. The metals form positively-charged ions and the non-metals form negatively-charged ions.

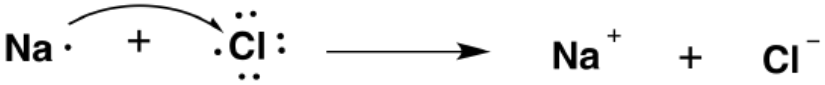
Ionic bonds form when metals and non-metals chemically react. By definition, a metal is relatively stable if it loses electrons to form a complete valence shell and becomes positively charged. Likewise, a non-metal becomes more stable by gaining electrons to complete its valence shell and become negatively charged. When metals and non-metals react, the metals lose electrons by transferring them to the non-metals, which gain them. Consequently, ions are formed, which instantly attract each other—ionic bonding.

Example: Sodium Chloride
For example, in the reaction of Na (sodium) and Cl (chlorine), each Cl atom takes one electron from a Na atom. Therefore, each Na becomes a Na+ cation and each Cl atom becomes a Cl- anion. Due to their opposite charges, the ions of sodium and chloride attract each other to form an ionic lattice. The formula (ratio of positive to negative ions) in the lattice is **NaCl**.

These ions are arranged in solid NaCl in a regular three-dimensional arrangement (or lattice):



The chlorine has a high affinity for electrons, and the sodium has a low ionization potential. Thus, the chlorine gains an electron from the sodium atom. This can be represented using *electron-dot symbols* (here we will consider one chlorine atom, rather than Cl2):



The arrow indicates the transfer of the electron from sodium to chlorine to form the Na+ metal ion and the Cl- chloride ion. Each ion now has an **octet** of electrons in its valence shell:

Na+: $2s^2\ 2p^6$
Cl-: $3s^2\ 3p^6$

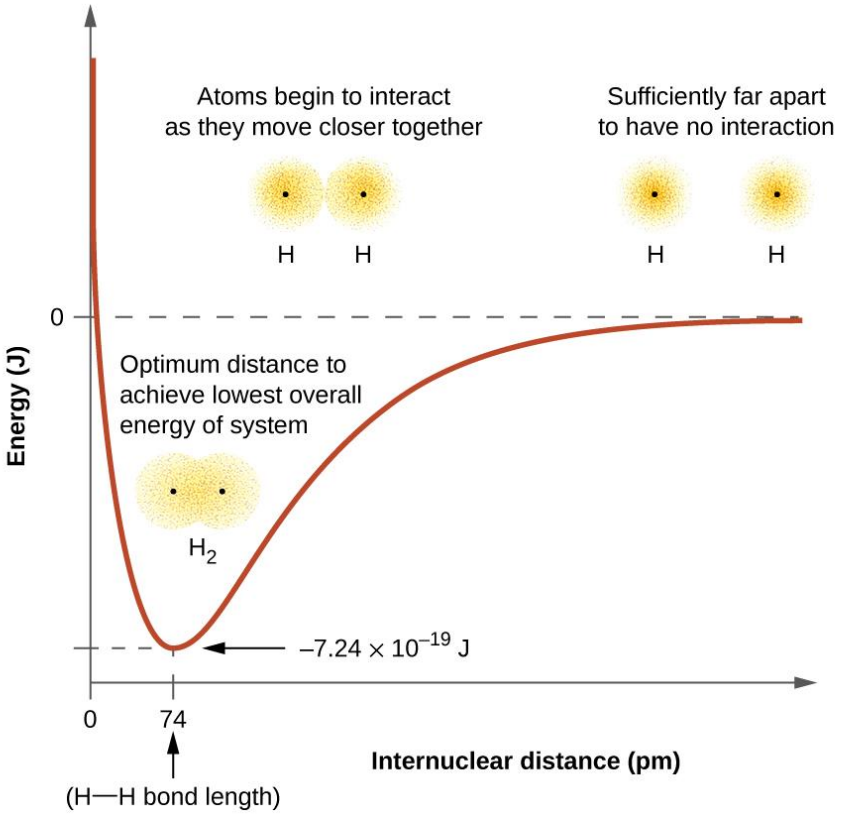
Chemical Bonds

Chemical bonds are the attractive forces that hold atoms together in the form of compounds. They are formed when electrons are shared between two atoms. There are 3 types of bonds: covalent bonds, polar covalent bonds and ionic bonds. The simplest example of bonding can be demonstrated by the H_2 molecule. We can see from the periodic table that each hydrogen atom has a single electron. If 2 hydrogen atoms come together to form a bond, then each hydrogen atom effectively has a share in both electrons and thus each resembles a

noble gas and is more stable. The 2 electrons that are shared can be represented either by 2 dots or a single dash between the atoms.

Valence bond theory describes a chemical bond as the overlap of atomic orbitals. In the case of the hydrogen molecule, the 1s orbital of one hydrogen atom overlaps with the 1s orbital of the second hydrogen atom to form a molecular orbital called a **sigma bond**. Attraction increases as the distance between the atoms gets closer but nuclear-nuclear repulsion becomes important if the atoms approach too close.

The energy of the system depends on how much the orbitals overlap. The figure below illustrates how the sum of the energies of two hydrogen atoms (the colored curve) changes as they approach each other. When the atoms are far apart there is no overlap, and by convention we set the sum of the energies at zero. As the atoms move together, their orbitals begin to overlap. Each electron begins to feel the attraction of the nucleus in the other atom. In addition, the electrons begin to repel each other, as do the nuclei. While the atoms are still widely separated, the attractions are slightly stronger than the repulsions, and the energy of the system decreases. (A bond begins to form.) As the atoms move closer together, the overlap increases, so the attraction of the nuclei for the electrons continues to increase (as do the repulsions among electrons and between the nuclei). At some specific distance between the atoms, which varies depending on the atoms involved, the energy reaches its lowest (most stable) value. This optimum distance between the two bonded nuclei is the bond distance between the two atoms. The bond is stable because at this point, the attractive and repulsive forces combine to create the lowest possible energy configuration. If the distance between the nuclei were to decrease further, the repulsions between nuclei and the repulsions as electrons are confined in closer proximity to each other would become stronger than the attractive forces. The energy of the system would then rise (making the system destabilized), as shown at the far left.



Valence bond theory describes a covalent bond as the overlap of half-filled atomic orbitals (each containing a single electron) that yield a pair of electrons shared between the two bonded atoms. We say that orbitals on two different atoms overlap when a portion of one orbital and a portion of a second orbital occupy the same region of space. According to valence bond theory, a covalent bond is formed when two conditions are met:

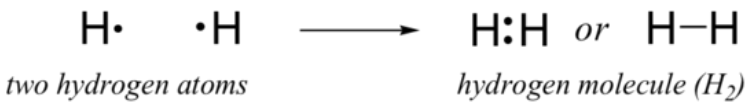
1. an orbital on one atom overlaps an orbital on a second atom and
2. the single electrons in each orbital combine to form an electron pair.

There are 3 methods of showing the formulas of molecules. Molecular formulas show only the types and numbers of atoms in the molecule. Structural formulas show the atoms in their correct placement in the molecule and allow for distinguishing isomers. Electron-dot formulas are similar to structural formulas but also include all of the non-bonding outer electrons. Knowledge of electron placement allows us to understand not only the shape of molecules but their chemical character. If we understand the chemical character of a molecule, we can predict how it will react with other molecules without having to blindly memorize reactions.

Covalent bonds and Lewis structures

Lewis structures, also known as Lewis-dot diagrams, show the bonding relationship between atoms of a molecule and the lone pairs of electrons in the molecule. Lewis structures can also be useful in predicting molecular geometry in conjunction with hybrid orbitals. A compound may have multiple resonance forms that are also all correct Lewis structures. This section will discuss the rules for correctly writing Lewis structures.

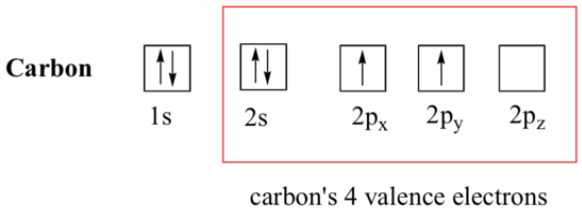
Before we begin, there are a few things to know. An electron is represented as a dot. A bond, which is made up of 2 shared electrons, is represented by two dots between the bonded atoms or a line. Double bonds and triple bonds are represented as two and three lines (pairs of electrons), respectively. Lone pairs on the outer rims of an atom are represented as two dots. The electrons represented in a Lewis structure are the outer-shell electrons, which are called valence electrons. This is because they are the ones involved in chemical reactions.
While alkali metals (such as sodium and potassium), alkaline earth metals (such as magnesium and calcium), and halogens (such as fluorine and chlorine) often form ions in order to achieve a full octet, the principle elements of organic chemistry - carbon, hydrogen, nitrogen, and oxygen - instead tend to fill their second shell orbitals by *sharing* electrons with other atoms, forming what we call covalent bonds. Consider the simplest case of hydrogen gas. An isolated hydrogen atom has only one electron, located in the 1*s* orbital. If two hydrogen atoms come close enough so that their respective 1*s* orbitals overlap, the two electrons can be shared between the two nuclei, and a covalently bonded H_2 molecule is formed. In the 'Lewis method', each pair of electrons that is shared between two atoms is drawn as a single line, designating a single covalent bond.



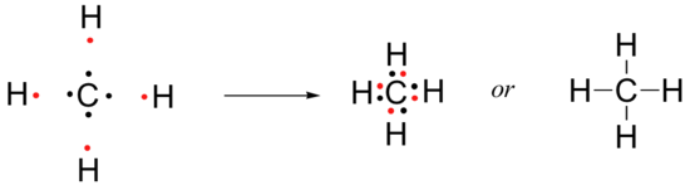
Hydrogen represents is a special case, of course – a hydrogen atom cannot fulfill the octet rule; it needs only two electrons to have a full shell (you could think of this as the 'doublet rule' for hydrogen).

One of the simplest organic molecules is methane with the molecular formula CH_4. Methane is the 'natural gas' burned in home furnaces and hot water heaters, as well as in electrical power generating plants. To illustrate the covalent bonding in methane using the Lewis method, we first must recognize that, although a carbon atom has a total of six electrons, the two electrons in the inner 1*s* orbital do not participate in bonding interactions. It is the other four- those in the 2*s* and 2*p* orbitals - that form covalent bonds with other atoms.

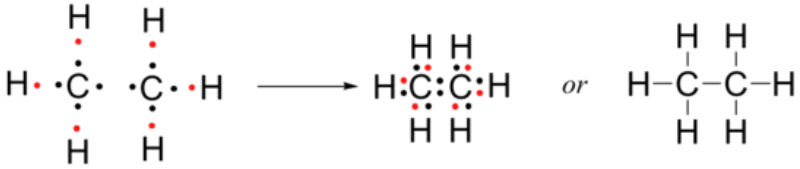
Only the partially occupied, highest energy shell of orbitals - in this case the 2*s* and 2*p* orbitals - can overlap with orbitals on other atoms to form covalent bonds. Electrons in these orbitals are termed 'valence electrons'.



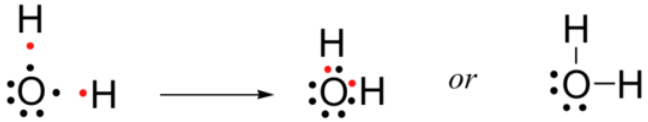
A carbon atom, then, has four valence electrons with which to form covalent bonds. In order to fulfill the octet rule and increase the occupancy of its second shell to eight electrons, it must participate in four electron-sharing interactions - in other words, it must form four covalent bonds. In a methane molecule, the central carbon atom shares its four valence electrons with four hydrogen atoms, thus forming four bonds and fulfilling the octet rule (for the carbon) and the 'doublet rule' (for each of the hydrogens).



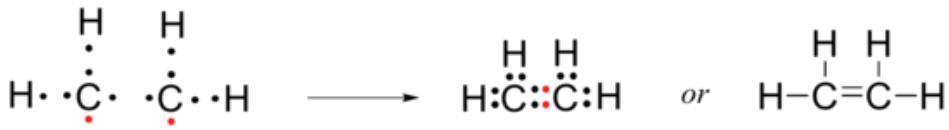
The next relatively simple organic molecule to consider is ethane, which has the molecular formula C_2H_6. If we draw each atom with its valence electron(s) separately, we can see that the octet/doublet rule can be fulfilled for all of them by forming one carbon-carbon bond and six carbon-hydrogen bonds.



The same approach can be used for molecules in which there is no carbon atom. In a water molecule, two of the six valence electrons on the oxygen atom are used to form bonds to hydrogen atoms, while the remaining four are non-bonding 'lone pairs'.

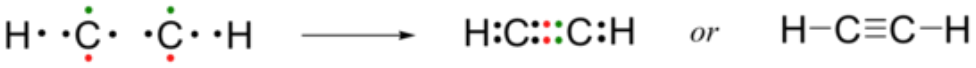


What about multiple bonds? The molecular formula for ethene (also known as ethylene, a compound found in fruits, such as apples, that signals them to ripen) is C_2H_4. Arranging the atoms and surrounding them with their valence electrons, you can see that the octet/doublet rule can be fulfilled for all atoms only if the two carbons share *two* pairs of electrons between them - in other words, only if a double bond is formed.

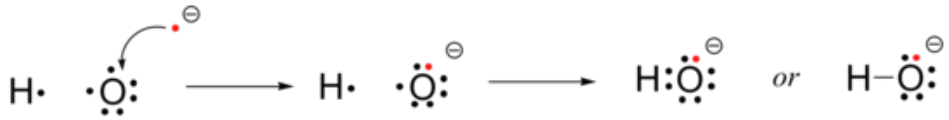


Because a hydrogen atom has only a 1*s* orbital to work with, it cannot form more than one single bond, otherwise it would exceed its doublet rule.

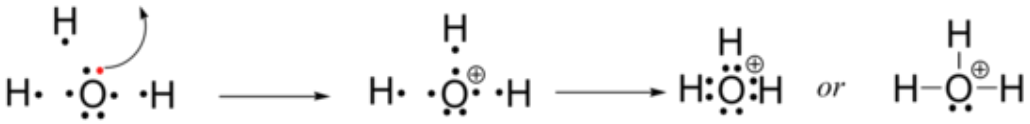
Following this pattern, the triple bond in ethyne molecular formula C_2H_2, (also known as acetylene, the fuel used in welding torches), is formed when the two carbon atoms share *three* pairs of electrons between them.



What about ions? The hydroxide ion, OH-, is drawn simply by showing the oxygen atom with its six valence electrons, then adding one more electron to account for the negative charge. Now the oxygen has three non-bonding lone pairs, and can only form one bond to a hydrogen. (Keep in mind that this is merely a description of the *thought process* going into drawing a Lewis structure, and is not meant to describe any actual chemical process).

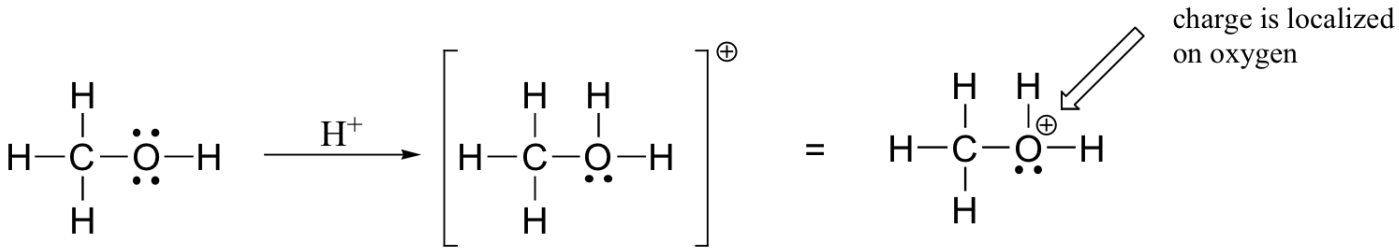


To draw a Lewis structure of the hydronium ion, H_3O^+, you again start with the oxygen atom with its six valence electrons, then take one away to account for the positive charge (there is now one more proton than there are electrons). The oxygen now can form bonds to three hydrogen atoms.



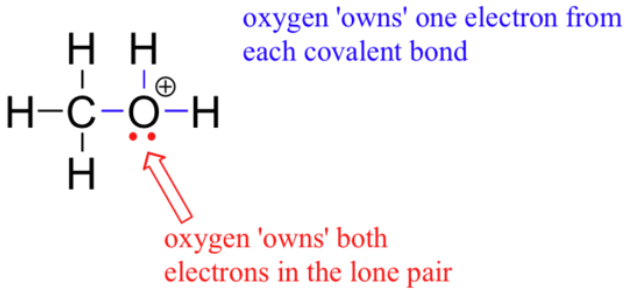
Formal charges

Consider the Lewis structure of methanol, CH_3OH. Just like in a water molecule, the oxygen atom in a methanol molecule has two non-bonding lone pairs of electrons. And just like a water molecule can be protonated to form the H_3O^+ cation, a methanol molecule can be protonated to form the $CH_3OH_2^+$ cation.



This polyatomic cation, as you can see, has an overall charge of +1. But we can be more specific than that. We can also state that the positive charge is located specifically on the oxygen atom, rather than on the carbon or any of the hydrogens. When a charge can be located on a particular atom in a polyatomic ion, this atom is said to have a 'formal charge'. Figuring out the formal charge on different atoms of a polyatomic ion is a straightforward process - it's simply a matter of adding up valence electrons. Remember that an oxygen atom needs six valence electrons (in addition to the two electrons in the non-valence 1*s* orbital) to completely

balance the charge of the eight protons in its nucleus. Let's figure out how many electrons the oxygen atom in our CH_3OH_2+ ion 'owns'.



First, we see that there is one lone pair of electrons that the oxygen is not sharing with any other atom - thus it 'owns' both of these electrons. In addition, the oxygen atom is sharing one *pair* of electrons each with three other atoms - since these electrons are shared, we decide that oxygen 'owns' one electron from each pair, meaning that it owns three bonding electrons. In total then, the oxygen owns five valence electrons: two non-bonding and three bonding. This is one short of the six valence electrons needed to achieve neutrality - thus the oxygen atom has a formal charge of +1.

What is the formal charge, if any, on the other atoms? The carbon needs to 'own' four valence electrons (once again, in addition to the two electrons in its 1*s* orbital) in order to balance the six protons in its nucleus. Because the carbon atom has four single bonds in this structure, and no lone pairs, it does indeed own four electrons (remember that it owns one of each pair of electrons that it shares in a covalent bond). So, the carbon has a formal charge of zero.

Each hydrogen needs to own only one electron to balance the charge of its single proton. Indeed, in the CH_3OH_2+ structure, each hydrogen atom has one single bond, meaning that each one owns one electron. Thus, all of the hydrogen atoms have formal charges of zero. Notice that, as you would expect, the sum of the formal charges of all the atoms in the ion equals the total charge on the ion - this will always be true for every example you encounter, and is a good way to check to make sure you are figuring individual formal charges correctly.

An abbreviated formula for determining formal charges can be expressed as follows:

formal charge = (# valence electrons) - (# non-bonding electrons) - (½ # bonding electrons)

When drawing structures, it is very important to show all non-zero formal charges, being clear about where the charges are located. When all non-zero formal charges are shown in the structure, the overall charge on an ion does not need to be indicated - that information is obvious from the sum of the formal charges.

At this point, thinking back to what you learned in general chemistry, you are probably asking "What about dipoles? Doesn't an oxygen atom in an O-H bond 'own' more of the electron density than the hydrogen, because of its greater electronegativity?" You are absolutely correct, and we will be reviewing the concept of dipoles later on. For the purpose of calculating formal charges, however, dipoles don't matter - we always consider the two electrons in a bond to be shared equally, even if that is not an accurate reflection of chemical reality. Formal charges are just that - a formality, a method of electron book-keeping that is tied into the Lewis system for drawing the structures of organic compounds and ions. Later, however, we will see how the concept can help us to visualize how organic molecules react.

Hybridization of Atomic Orbitals and the Shape of Molecules

If the four hydrogen atoms in a methane molecule, CH_4, were bound to the three 2p orbitals and the 2s orbital of the carbon atom, the H-C-H bond angles would be 90º for 3 of the hydrogen atoms and the 4th hydrogen atom would be at 135º from the others. Experimental evidence has shown that the bond angles in methane are not arranged that way but are 109.5º giving the overall shape of a tetrahedron. The tetrahedral structure makes much more sense in that hydrogen atoms would naturally repel each other due to their negative electron clouds and form this shape. If you think electron-electron repulsion isn't significant, try walking through a wall! There is plenty of space for your nuclei to pass through the nuclei of the wall material but ouch, it just doesn't work that way.

Experimental evidence has also shown that the H-N-H bond angles in ammonia (NH_3) are 107º and the H-O-H bond angles in water are 105º. It is clear from these bond angles that the non-bonding pairs of electrons occupy a reasonable amount of space and are pushing the hydrogen atoms closer together compared to the angles found in methane.

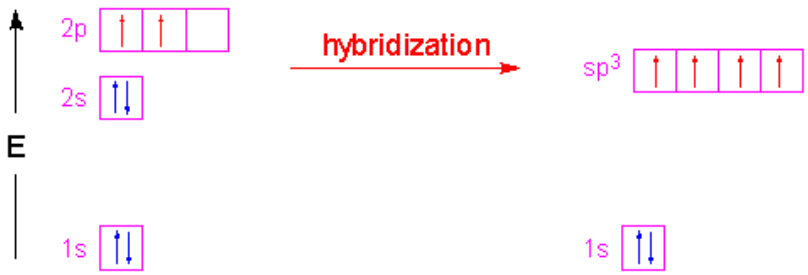
The valence shell electron-pair repulsion model (VSEPR) was devised to account for these molecular shapes. In this model, atoms and pairs of electrons will be arranged to minimize the repulsion of these atoms and pairs of electrons. Since the non-bonded electron pairs are held somewhat closer to the nucleus than the attached hydrogen atoms, they tend to crowd the hydrogen atoms. Thus, ammonia exists as a distorted tetrahedron (trigonal pyramidal) rather than a trigonal plane and water also exists as a distorted tetrahedron (bent) rather than a linear molecule with the hydrogen atoms at a 180º bond angle.

This concept proposes that since the attached groups are not at the angles of the p orbitals and their atomic orbitals would not have maximum overlap (to form strong bonds) the s and p orbitals will be hybridized to match the bond angles of the attached groups.

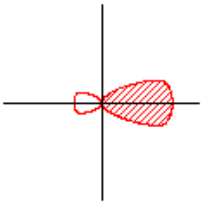
The number of these new hybrid orbitals must be equal to the numbers of atoms and non-bonded electron pairs surrounding the central atom!

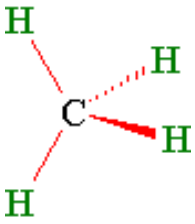
Example: Methane

In the case of methane, the three 2p orbitals of the carbon atom are combined with its 2s orbital to form four new orbitals called *sp3* hybrid orbitals. The name is simply a tally of all the orbitals that were blended together to form these new hybrid orbitals. Four hybrid orbitals were required since there are four atoms attached to the central carbon atom. These new orbitals will have an energy slightly above the 2s orbital and below the 2p orbitals as shown in the following illustration. Notice that no change occurred with the 1s orbital.



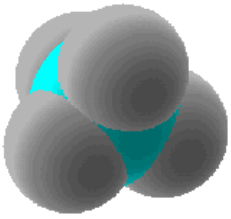
These hybrid orbitals have 75% p-character and 25% s-character which gives them a shape that is shorter and fatter than a p-orbital. The new shape looks a little like...





A stick and wedge drawing of methane shows the tetrahedral angles. The wedge is coming out of the paper and the dashed line is going behind the paper. The solid lines are in the plane of the paper.

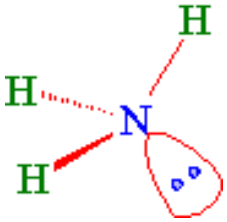
A space-filling model of methane would look like...



Example: Ammonia

In the case of ammonia, the three 2p orbitals of the nitrogen atom are combined with the 2s orbital to form four sp3 hybrid orbitals. We need a hybrid orbital for each atom and the pair of non-bonding electrons. Ammonia has three hydrogen atoms and one non-bonded pair of electrons when we draw the electron-dot formula. In order to determine the hybridization of an atom, you must first draw the electron-dot formula.

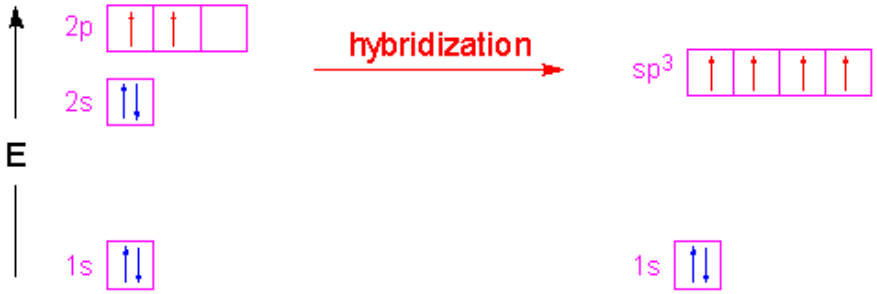
A stick and wedge drawing of ammonia showing the non-bonding electrons in a probability area for the hybrid orbital...

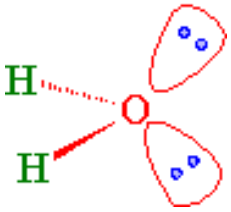


A space-filling model of ammonia would look like... (Note the non-bonded electron pair is not shown in this model.)

Example: Water

In the case of water, the three 2p orbitals of the oxygen atom are combined with the 2s orbital to form four *sp3* hybrid orbitals. The two non-bonded electron pairs will occupy hybrid orbitals. Again, we need a hybrid orbital for each atom and each pair of non-bonding electrons. Water has two hydrogen atoms and two non-bonded pairs of electrons when we draw the electron-dot formula.



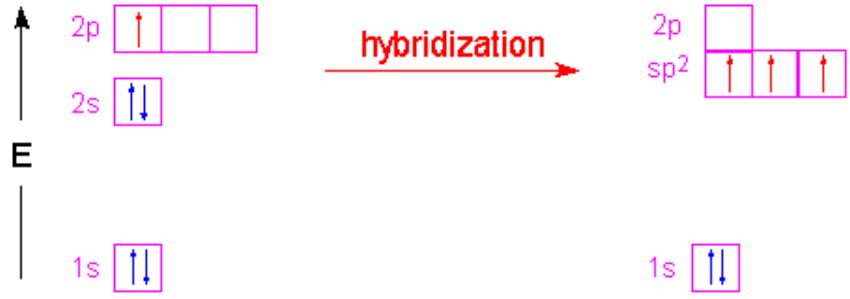


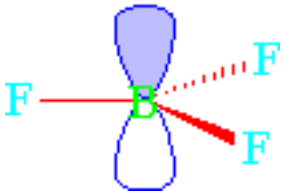
A stick and wedge drawing of water showing the non-bonding electron pairs in probability areas for the hybrid orbital...

A space-filling model of water would look like... (Note the non-bonded electron pairs are not shown in this model.)

Example: Boron Trifluoride

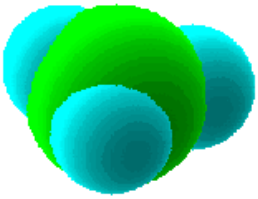
Now let's look at something a bit different. In the boron trifluoride molecule, only three groups are arranged around the central boron atom. In this case, the 2s orbital is combined with only two of the 2p orbitals (since we only need three hybrid orbitals for the three groups...thinking of groups as atoms and non-bonding pairs) forming three hybrid orbitals called *sp2* hybrid orbitals. The other p-orbital remains non-hybridized and is at right angles to the trigonal planar arrangement of the hybrid orbitals. The trigonal planar arrangement has bond angles of 120º.





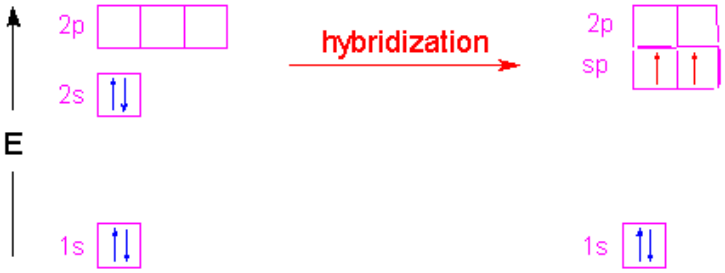
In the following stick model, the empty p orbital is shown as the probability area...one end shaded blue and the other is white...there are no electrons in this orbital!

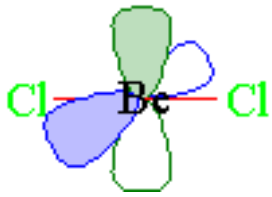
A space-filling model of boron trifluoride would look like...



Example: Beryllium Dichloride

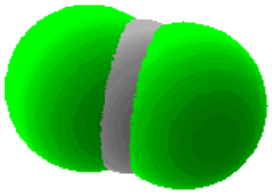
Finally let's look at beryllium dichloride. Since only two groups are attached to beryllium, we only will have two hybrid orbitals. In this case, the 2s orbital is combined with only one of the 2p orbitals to yield two *sp* hybrid orbitals. The two hybrid orbitals will be arranged as far apart as possible from each other with the result being a linear arrangement. The two non-hybridized p-orbitals stay in their respective positions (at right angles to each other) and perpendicular to the linear molecule.





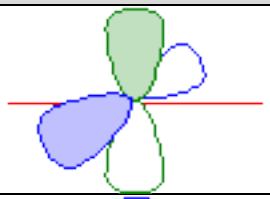
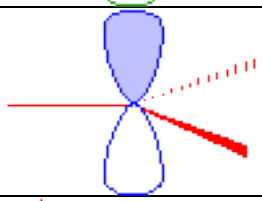
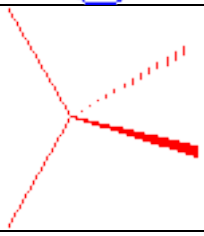
In the following stick model, the empty p orbitals are shown as the probability areas...one green and one blue.

A space-filling model of beryllium dichloride would look like...



Summary of Hybridization

In the following summary, groups are considered to be atoms and/or pairs of electrons and hybrid orbitals are the red lines and wedges. When the octet of an element is exceeded, then hybridization will involve d-orbitals. Non-hybridized p-orbitals are shown as probability areas in blue and green for *sp* hybridization and blue for *sp2* hybridization. A single electron as found in a radical would occupy a non-hybridized p-orbital.

Number of Groups Attached to a Central Atom	Description	3-Dimensional Shape
Two – sp	**180° bond angle** **linear electron-pair geometry**	
Three – sp2	**120° bond angle** **trigonal planar electron-pair geometry**	
Four – sp3	**109.5° bond angle** **tetrahedral electron-pair geometry**	

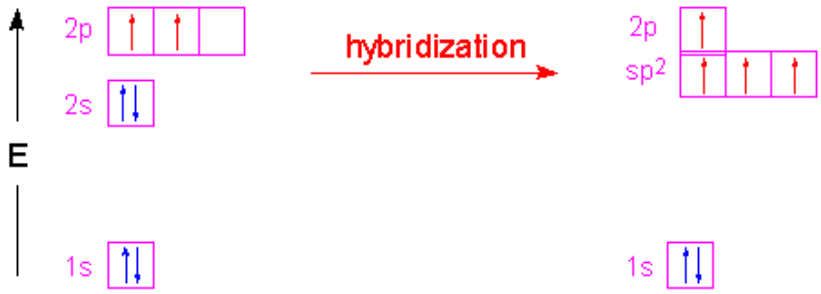
Hybridization Involving Multiple Bonds

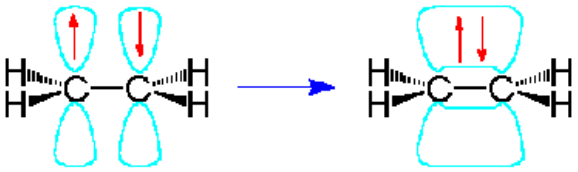
Only a maximum of two electrons can occupy any orbital whether it is an atomic orbital or a molecular orbital due to electron-electron repulsion. When we draw a double or a triple-bond between two atoms, we imply that either four or six electrons are directly between these two atoms. Since this is impossible, we must have these extra electrons off to the side in what we refer to as **pi bonds**. Therefore, all multiple bonds are composed of two different kinds of molecular bonds called pi bonds and sigma bonds.

- The sigma (σ) bond is defined as the linear overlap of atomic orbitals in which two electrons are directly between the two bonded nuclei.
- Pi (π) bonds are defined as the parallel overlap of p-orbitals. A double bond has one sigma bond and one pi bond. A triple bond thus consists of a sigma bond and two pi bonds with the pi bonds in different planes.

Example: Ethene

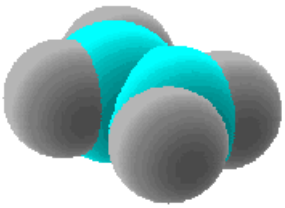
In the ethene molecule, C_2H_4, both carbon atoms will be sp2 hybridized and have one unpaired electron in a non-hybridized p-orbital.





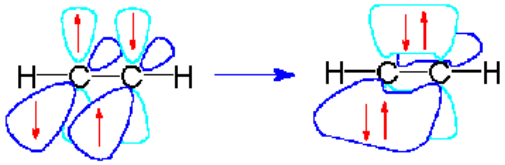
These p-orbitals will undergo parallel overlap and form one pi bond with bean-shaped probability areas above and below the plane of the six atoms. This pair of bean-shaped probability areas constitutes one pi bond and the pair of electrons in this bond can be found in either bean-shaped area.

The 3-dimensional model of ethene is planar with H-C-H and H-C-C bond angles of 120º... the pi bond is not shown in this picture.



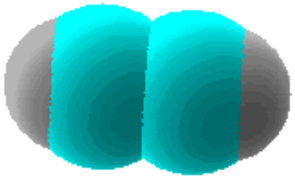
Example: Acetylene

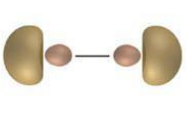
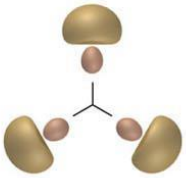
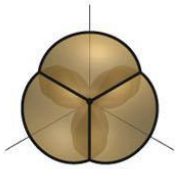
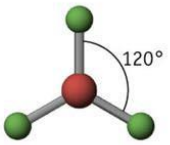
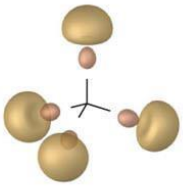
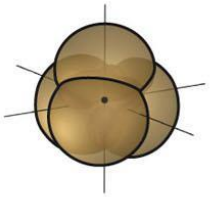
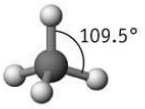
Now let's look at acetylene, C_2H_2. Both carbon atoms will be *sp* hybridized and have one electron in each of two non-hybridized p-orbitals.



These p orbitals will undergo parallel overlap to form two pi bonds at right angles to each other.

The 3-dimensional model of acetylene is therefore linear...the pi bonds are not shown in this picture.

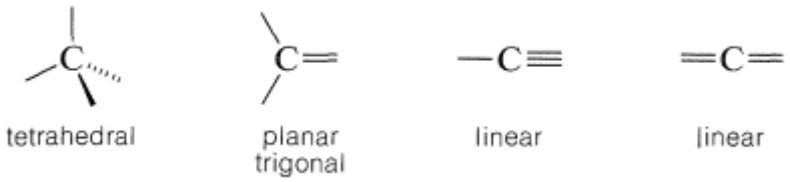


Hybrid Orbitals	Arrangement of Hybrid Orbitals	Geometry	Example
Two electron pairs *sp*	 	 Linear	 $BeCl_2$
Three electron pairs sp^2	 	 Trigonal-planar	 BF_3
Four electron pairs sp^3	 	 Tetrahedral	 CH_4

TOPIC 5: ISOMERISM I

By now you should be familiar with **constitutional isomers** (or *position isomers)* wherein compounds of the same molecular formula differ because substituents, chain branches, and so on, are not at the same positions in the molecules. 1-chloropropane and 2-chloropropane are straightforward examples of position isomers. A much subtler form of isomerism is present when two *different* compounds have the *same* molecular formulas, the *same* substituent and chain-branching positions, and, indeed, even have the *same* names by all of the nomenclature rules we have given you so far. *Such isomers are different because their molecules have different arrangements of the atoms in space*. These are **stereoisomers** and this type of isomerism, called **stereoisomerism**, is of enormous importance to all areas of organic chemistry and biochemistry.

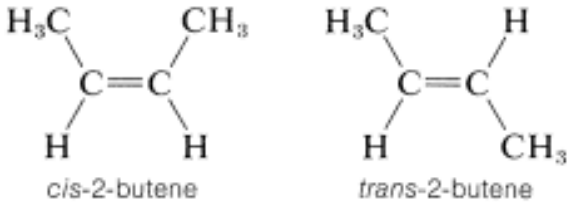
To understand stereoisomerism of carbon compounds, we must understand the ways in which the bonds to carbon atoms are arranged in space; this depends on whether the carbon atoms form single, double, or triple bonds to another atom. Thus, four single bonds to a carbon form a tetrahedral arrangement; two single bonds and one double bond to a carbon give a planar array with bond angles near 120°, while one single bond and one triple bond (or two double bonds) to a carbon are arranged linearly:



Stereoisomers (Configurational Isomers)

We have defined isomers in a very general way as non-identical molecules that possess the same number and kind of atoms. However, there are several ways in which isomers can be non-identical. Among the alkenes, 1- and 2-butene are position isomers, because in these compounds the double bond has a different position in the carbon chain:

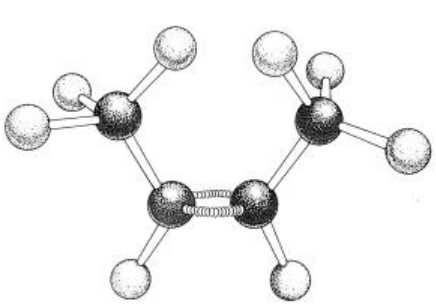
Most, but not all alkenes, have stereoisomers that are not identical because of different *spatial* arrangements of the component atoms. Thus, there are two stereoisomers of 2-butene that differ in the geometric arrangement of the groups attached to the double bond. In one isomer, both methyl groups are on the *same* side of the double bond (*cis*-2-butene) and in the other, the methyl groups are on *opposite* sides of the double bond (*trans*-2-butene):

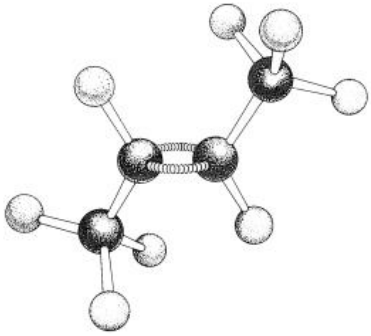


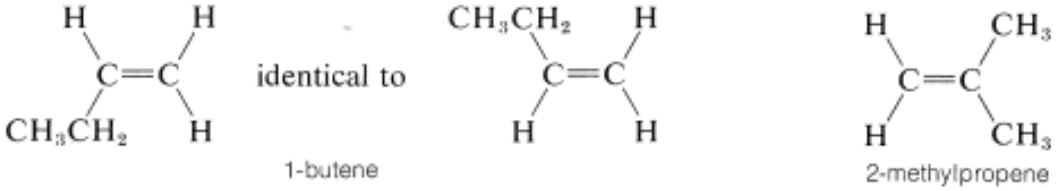
The two isomers clearly have the same structural framework but they differ in the arrangement of this framework in space - hence the designation *stereoisomers*. They owe their separate existence to the fact that the double bond is rigid and the parts of the molecule are not free to rotate with respect to each other about this bond. Therefore, the isomers do not interconvert without breaking the double bond, and they exist as different compounds, each with its own chemical and physical properties. Ball-and-stick models of *cis*- and *trans*-2-butene are shown below, and the rigidity of the double bond is simulated in the model by a pair of stiff springs or bent sticks connecting the two carbons of the double bond.

It should be clear to you that there will be no cis-trans isomers of alkenes in which one end of the double bond carries identical groups. Thus, we do not expect there to be cis-trans isomers of 1-butene or 2-methylpropene, and indeed none are known:

Cis **Trans**

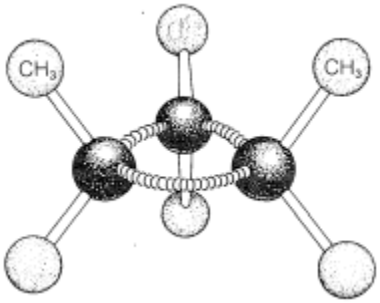


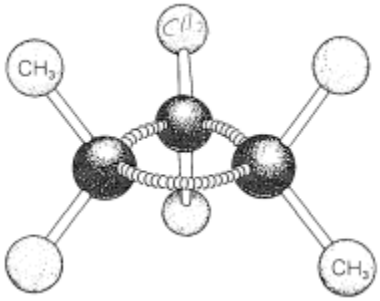




Ring formation also confers rigidity on molecular structure such that rotation about the ring bonds is prevented. As a result, stereoisomerism of the cis-trans type is possible. For example, 1,2-dimethylcyclopropane exists in two forms that differ in the arrangement of the two methyl groups with respect to the ring. In the cis isomer, the methyl groups both are situated above (or below) the plane of the ring and in the trans isomer they are situated one above and one below, as shown below. Interconversion of these isomers does not occur without breaking one or more chemical bonds.

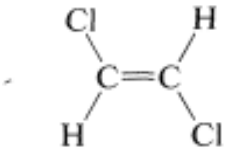
Cis **Trans**



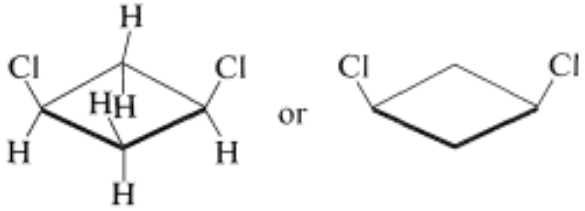


Stereoisomers that do not interconvert rapidly under normal conditions, and therefore are stable enough to be separated, specifically are called **configurational isomers**. Thus *cis*- and *trans*-2-butene are configurational

isomers, as are *cis*- and *trans*-1,2-dimethylcyclopropane. The terms *cis-trans isomerism* or *geometric isomerism* commonly are used to describe **configurational isomerism** in compounds with double bonds and rings. When referring to the *configuration* of a particular isomer, we mean to specify its geometry. For instance, the isomer of 1,2-dichloroethene shown below has the trans configuration; the isomer of 1,3-dichlorocyclobutane has the cis configuration:



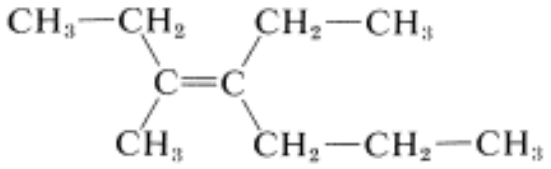
trans-1,2-dichloroethene



cis-1,3-dichlorocyclobutane

(These structures are drawn in perspective; the ring carbons are shown to be in a horizontal plane and the attached atoms are above or below this plane. If not all of the attached hydrogens are explicitly shown, as in the structure at right, their presence is understood.)

Cis-trans isomerism is encountered very frequently. By one convention, *the configuration of a complex alkene is taken to correspond to the configuration of the longest continuous chain as it passes through the double bond*. Thus, the following compound is *trans*-4-ethyl-3-methyl-3-heptene, despite the fact that two identical groups are cis with respect to each other, because the longest continuous chain is trans as it passes through the double bond:

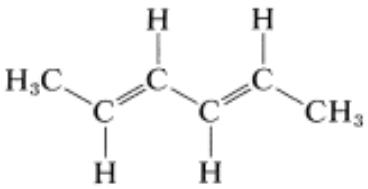


trans-4-ethyl-3-methyl-3-heptene

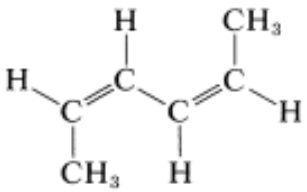
Notice that cis-trans isomerism is not possible at a carbon-carbon triple bond, as for 2-butyne, because the bonding arrangement at the triply bonded carbons is linear:

2-butyne
(linear arrangement of bonds)

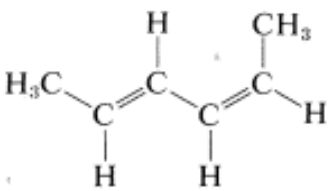
Many compounds have more than one double bond and each may have the potential for the cis or trans arrangement. For example, 2,4-hexadiene has *three* different configurations, which are designated as trans-trans, cis-cis, and trans-cis. Because the two ends of this molecule are identically substituted, the trans-cis becomes identical with cis-trans:



trans-trans-2,4-hexadiene



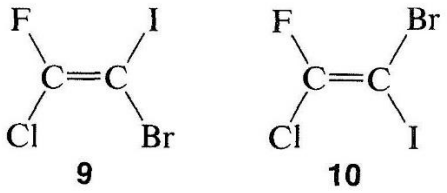
cis-cis-2,4-hexadiene



trans-cis- or *cis-trans*-
2,4-hexadiene

E,Z Notation

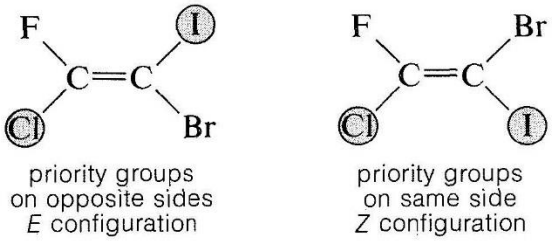
The configuration about double bonds is undoubtedly best specified by the cis-trans notation when there is no ambiguity involved. Unfortunately, many compounds cannot be described adequately by the cis-trans system. Consider, for example, configurational isomers of 1-fluoro-1-chloro-2-bromo-2-iodo-ethene, 9 and 10 below. There is no obvious way in which the cis-trans system can be used:



The **Cahn-Ingold Rules** for assigning priorities to substituents:

1. First, examine at the atoms directly attached to the stereocenter of the compound. A substituent with a higher atomic number takes precedence over a substituent with a lower atomic number. Hydrogen is the lowest possible priority substituent, because it has the lowest atomic number.
   - at carbon atom 1, Cl>F
   - at carbon atom 2, I>Br

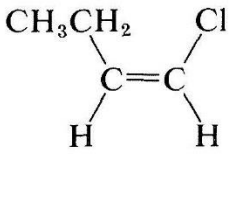
2. If there are two substituents with equal rank, proceed along the two substituent chains until there is a **point of difference**. First, determine which of the chains has the first connection to an atom with the highest priority (the highest atomic number). That chain has the higher priority. If the chains are similar, proceed down the chain, until a point of difference.



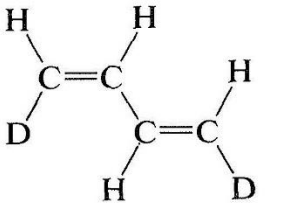
3. If a chain is connected to the same kind of atom twice or three times, check to see if the atom it is connected to has a greater atomic number than any of the atoms that the competing chain is connected to.
4.

- If none of the atoms connected to the competing chain(s) at the same point has a greater atomic number: the chain bonded to the same atom multiple times has the greater priority
- If, however, one of the atoms connected to the competing chain has a higher atomic number: that chain has the higher priority.

The *Z* isomer is designated as the isomer in which the top priority groups are on the *same* side (*Z* is taken from the German word *zusammen* - together). The *E* isomer has these groups on o*pposite* sides (*E*, German for *entgegen* - across). Two further examples show how the nomenclature is used:

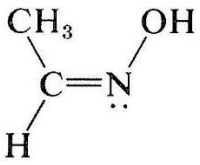


(*Z*)-1-chloro-1-butene



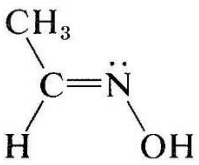
(1*Z*,3*E*)-1,3-butadiene-1,4-d_2

This system is especially useful for oximes, which have the structural feature −C=N−OH. The two possible configurations at the double bond in the oxime of ethanal are 11 and 12:



11

Z (syn)



12

E (anti)

The cis-trans notation does not work well here, and structure 11 has the *Z* configuration and 12 the *E* configuration. In the older chemical literature, these stereoisomers were designated as *syn* and *anti*-forms, but these names are really no better than *cis* and *trans*.

TOPIC 6: MOLECULAR ORBITAL THEORY

In Valence Bond theory, atomic orbitals (*hybridized or not)* overlap to form localized bonds. Each central atom has an EPG predicted by *VSEPR* theory. VB theory works well in this aspect. However, it does not explain the delocalization of electrons observed in certain molecules.

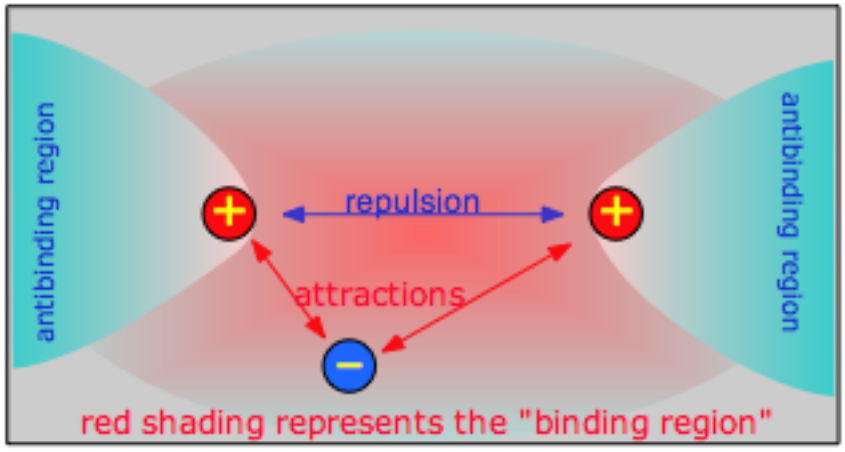
In **Molecular Orbital** (MO) **Theory**, the atomic orbitals are combined altogether to form new Molecular Orbitals. In this approach, the electrons are distributed over the entire molecule and are naturally *delocalized.* This is the advantage of MO theory.

The molecular orbital model is by far the most productive of the various models of chemical bonding, and serves as the basis for most quantitative calculations, including those that lead to many of the computer-generated images that you have seen elsewhere in these units. In its full development, molecular orbital theory involves a lot of complicated mathematics, but the fundamental ideas behind it are quite easily understood, and this is all we will try to accomplish in this lesson.

This is a big departure from the simple *Lewis* and *VSEPR* models that were based on the one-center orbitals of individual atoms. The more sophisticated *hybridization* model recognized that these orbitals will be modified by their interaction with other atoms. But all of these *valence-bond* models, as they are generally called, are very limited in their applicability and predictive power, because they fail to recognize that distribution of the pooled valence electrons is governed by the totality of positive centers.

Molecular Orbitals

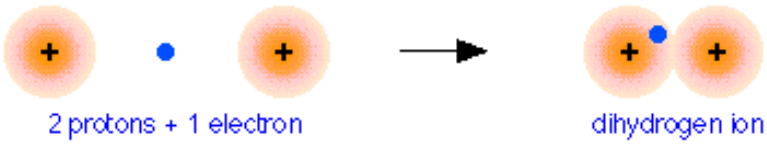
Chemical bonding occurs when the net attractive forces between an electron and two nuclei exceeds the electrostatic repulsion between the two nuclei. For this to happen, the electron must be in a region of space which we call the *binding region*. Conversely, if the electron is off to one side, in an *anti-binding region*, it actually adds to the repulsion between the two nuclei and helps push them away.



The easiest way of visualizing a molecular orbital is to start by picturing two isolated atoms and the electron orbitals that each would have separately. These are just the orbitals of the separate atoms, by themselves, which we already understand. We will then try to predict the manner in which these atomic orbitals interact as we gradually move the two atoms closer together. Finally, we will reach some point where the internuclear distance corresponds to that of the molecule we are studying. The corresponding orbitals will then be the *molecular orbitals* of our new molecule.

The Hydrogen Molecule Ion: The Simplest Molecule

To see how this works, we will consider the simplest possible molecule, H_2^+. This is the hydrogen molecule ion, which consists of two nuclei of charge +1, and a single electron shared between them.

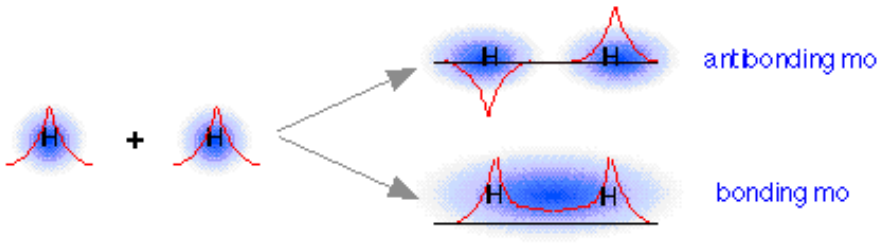


As two H nuclei move toward each other, the 1*s* atomic orbitals of the isolated atoms gradually merge into a new molecular orbital in which the greatest electron density falls between the two nuclei. Since this is just the location in which electrons can exert the most attractive force on the two nuclei simultaneously, this arrangement constitutes a *bonding molecular orbital*. Regarding it as a three-dimensional region of space, we see that it is symmetrical about the line of centers between the nuclei; in accord with our usual nomenclature, we refer to this as a *σ (sigma) orbital*.

Bonding and Antibonding Molecular Orbitals

There is one minor difficulty: we started with two orbitals (the 1*s* atomic orbitals), and ended up with only one orbital. Now, according to the rules of quantum mechanics, orbitals cannot simply appear and disappear at our convenience. For one thing, this would raise the question of at just what inter-nuclear distance do we suddenly change from having two orbitals, to having only one? It turns out that when orbitals interact, they are free to change their forms, but there must always be the same number. This is just another way of saying that there must always be the same number of possible allowed sets of electron quantum numbers.

How can we find the missing orbital? To answer this question, we must go back to the wave-like character of orbitals that we developed in our earlier treatment of the hydrogen atom. You are probably aware that wave phenomena such as sound waves, light waves, or even ocean waves can combine or interact with one another in two ways: they can either reinforce each other, resulting in a stronger wave (known as constructive interference), or they can interfere with and partially destroy each other (known as destructive interference). A roughly similar thing occurs when the "matter waves" corresponding to two separate hydrogen 1*s* orbitals are interacting; both in-phase and out-of-phase combinations are possible, and both occur. The in-phase, reinforcing interaction yields the *bonding orbital* that we just considered. The other, corresponding to out-of-phase combination of the two orbitals, gives rise to a molecular orbital that has its greatest electron probability in what is clearly the antibonding region of space. This second orbital is therefore called an *antibonding* orbital.



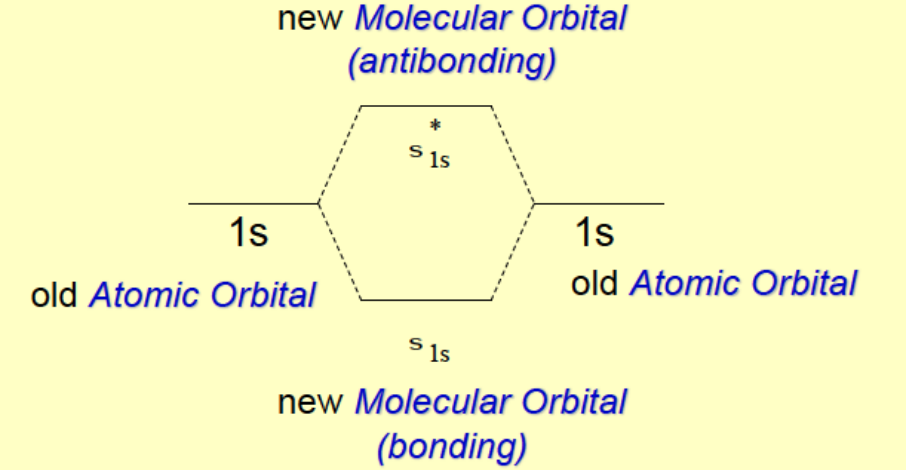
When the two 1*s* wave functions combine out-of-phase, the regions of high electron probability do not merge. In fact, the orbitals act as if they actually repel each other. Notice particularly that there is a region of space exactly equidistant between the nuclei at which the probability of finding the electron is zero. This

region is called a *nodal surface*, and is characteristic of antibonding orbitals. It should be clear that any electrons that find themselves in an antibonding orbital cannot possibly contribute to bond formation; in fact, they will actively oppose it.

We see, then, that whenever two orbitals, originally on separate atoms, begin to interact as we push the two nuclei toward each other, these two atomic orbitals will gradually merge into a pair of molecular orbitals, one of which will have bonding character, while the other will be antibonding. In a more advanced treatment, it would be fairly easy to show that this result follows quite naturally from the wave-like nature of the combining orbitals.

What is the difference between these two kinds of orbitals, as far as their potential energies are concerned? More precisely, which kind of orbital would enable an electron to be at a lower potential energy? Clearly, the potential energy decreases as the electron moves into a region that enables it to "see" the maximum amount of positive charge. In a simple diatomic molecule, this will be in the inter-nuclear region— where the electron can be simultaneously close to two nuclei. The bonding orbital will therefore have the lower potential energy.

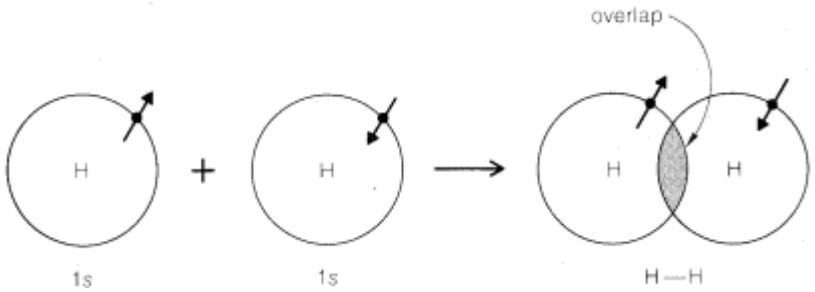
Molecular Orbital Diagram



Bond Formation Using Atomic Orbitals

In writing the conventional Lewis structures for molecules, we assume that a covalent chemical bond between two atoms involves sharing a pair of elections, one from each atom. Figure 6-5 shows how atomic orbitals can be considered to be used in bond formation. Here, we postulate that a *single* bond is formed by the pulling together of two atomic nuclei by attractive forces exerted by the nuclei for the two paired electrons in overlapping atomic orbitals.

Because *two* atomic orbitals can hold a maximum of *four* electrons, it is reasonable to ask why it is that two rather than one, three, or four electrons normally are involved in a bond. The answer is that two overlapping atomic orbitals can be considered to combine to give one low-energy **bonding molecular orbital** and one high-energy **antibonding molecular orbital**.



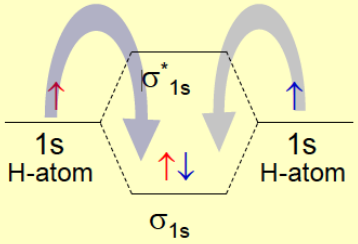
Representation of the formation of an H–H bond by sharing of electrons in overlapping orbitals

Orbitals that overlap as shown in Figure 6-6(a) are said to overlap in the sigma manner, and the bonding orbital is called a **sigma orbital** (*σ)*); the antibonding orbital is called a ***σ* orbital*** (read "sigma star"). Two paired electrons suffice to fill the *σ* orbital. Any additional electrons must go into the high-energy *σ** orbital and contribute not to bonding but to repulsion between the atoms.

The **Aufbau principle** states that an electron occupies orbitals in order from lowest energy to highest. The Aufbau (German: "building up, construction") principle is sometimes referred to as the "building up" principle. It is worth noting that in reality atoms are not built by adding protons and electrons one at a time and that this method is merely an aid for us to understand the end result.

The **Pauli exclusion principle** which states that no two electrons in an atom can have the same set of four quantum numbers. The energy of the electron is specified by the principal, angular momentum, and magnetic quantum numbers. If those three numbers are identical for two electrons, the spin numbers must be different in order for the two electrons to be differentiated from one another. The two values of the spin quantum number allow each orbital to hold two electrons.

Distributing Electrons in Molecular Orbits

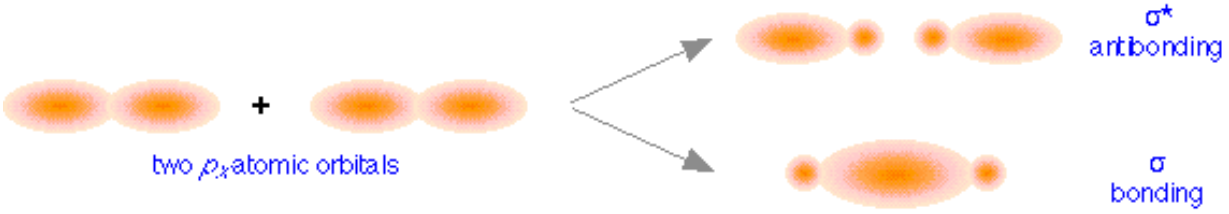


Similar to filling in electron configurations of atoms, the electrons fill the lowest energy MO first (***Aufbau principle***). Each MO can only hold two electrons of opposite spin (***Pauli principle***)

Sigma (σ) and Pi (π) Orbitals

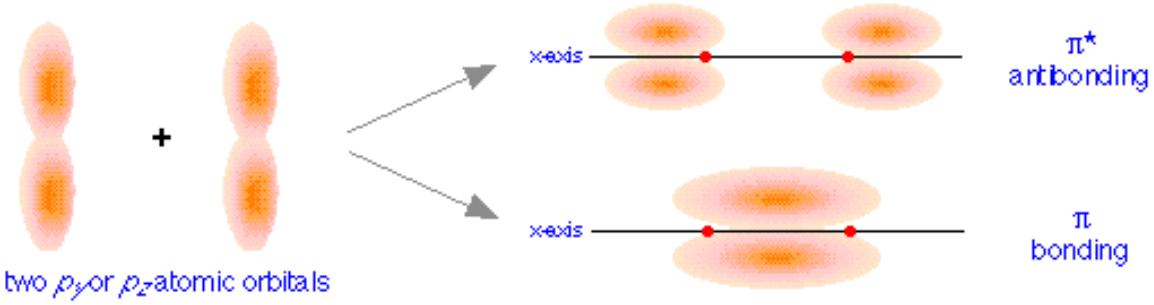
The molecules we have considered thus far are composed of atoms that have no more than four electrons each; our molecular orbitals have therefore been derived from *s*-type atomic orbitals only. If we wish to apply our model to molecules involving larger atoms, we must take a close look at the way in which *p*-type orbitals interact as well. Although two atomic *p* orbitals will be expected to split into bonding and antibonding orbitals just as before, it turns out that the extent of this splitting, and thus the relative energies of the resulting molecular orbitals, depend very much on the nature of the particular *p* orbital that is involved.

You will recall that there are three possible *p* orbitals for any value of the principal quantum number. You should also recall that *p* orbitals are not spherical like *s* orbitals, but are elongated, and thus possess definite directional properties. The three *p* orbitals correspond to the three directions of Cartesian space, and are frequently designated p_x, p_y, and p_z, to indicate the axis along which the orbital is aligned. Of course, in the free atom, where no coordinate system is defined, all directions are equivalent, and so are the *p* orbitals. But when the atom is near another atom, the electric field due to that other atom acts as a point of reference that defines a set of directions. The line of centers between the two nuclei is conventionally taken as the *x* axis. If this direction is represented horizontally on a sheet of paper, then the *y* axis is in the vertical direction and the *z* axis would be normal to the page.



These directional differences lead to the formation of two different classes of molecular orbitals. The above figure shows how two p_x atomic orbitals interact. In many ways, the resulting molecular orbitals are similar to what we got when *s* atomic orbitals combined; the bonding orbital has a large electron density in the region between the two nuclei, and thus corresponds to the lower potential energy. In the out-of-phase combination, most of the electron density is away from the internuclear region, and as before, there is a surface exactly halfway between the nuclei that corresponds to zero electron density. This is clearly an *antibonding orbital*— again, in general shape, very much like the kind we saw in hydrogen and similar molecules. Like the ones derived from *s*-atomic orbitals, these molecular orbitals are σ (*sigma*) orbitals.

Sigma orbitals are cylindrically symmetric with respect to the line of centers of the nuclei; this means that if you could look down this line of centers, the electron density would be the same in all directions.

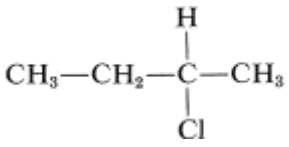


When we examine the results of the in- and out-of-phase combination of p_y and p_z orbitals, we get the bonding and antibonding pairs that we would expect, but the resulting molecular orbitals have a different symmetry: rather than being rotationally symmetric about the line of centers, these orbitals extend in both perpendicular directions from this line of centers. Orbitals having this more complicated symmetry are called π (*pi*) orbitals. There are two of them, π*y* and π*z* differing only in orientation, but otherwise completely equivalent.

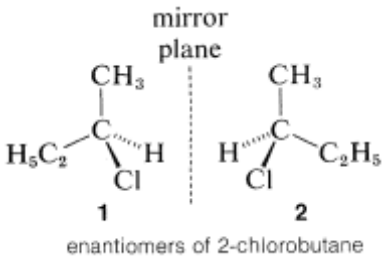
The different geometric properties of the π and σ orbitals causes the latter orbitals to split more than the π orbitals, so that the σ* antibonding orbital always has the highest energy. The σ bonding orbital can be either higher or lower than the π bonding orbitals, depending on the particular atom.

TOPIC 7: ISOMERISM II

The most important type of stereoisomerism is that which arises when molecules possess two structures that are not identical and also are mirror images of one another. This is not a difficult or unfamiliar concept. Many things around us, such as our hands, and pairs of shoes, are not identical and also are mirror images of one another. In the same way, non-identical molecules exist in which the only distinction between them is that one is the mirror image of the other.



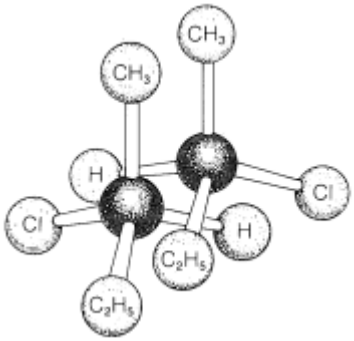
A common statement is that such isomers are mirror images of one another, but these images are *not* "superimposable." A simple example of this type of stereoisomerism is 2-chlorobutane, which can exist in two spatial configurations, 1 and 2, that correspond to reflections of each other. These isomers are specifically called **enantiomers**.



enantiomers of 2-chlorobutane

To be convinced that there really are two non-identical forms of this molecule, you should construct molecular models of both configurations and try to superimpose them.

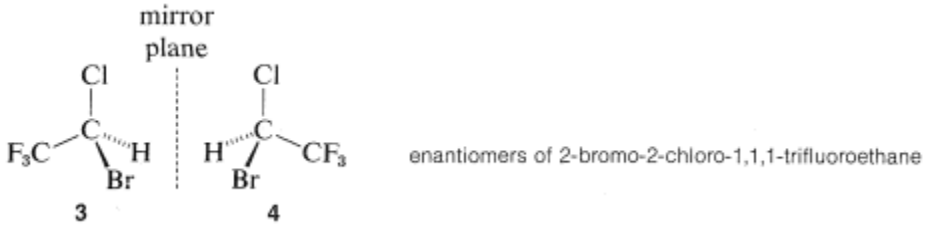
If you put *CH*$_3$ and *CH*$_3$ together, and *C*$_2$*H*$_5$ and *C*$_2$*H*$_5$ together, you find that *Cl* and *Cl* are on opposite sides, and *H* and *H* are on opposite sides. No matter how you turn the models around, they cannot be superimposed unless you break bonds at the number 2 carbon and interchange the positions of any two atoms or groups.



Chiral Molecules

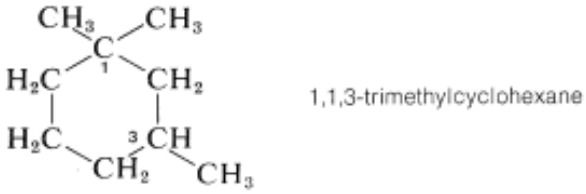
Compounds that lack **reflection symmetry** - meaning that they are *not* identical with their mirror images - are said to be **chiral** (pronounced "ki-rall", rhymes with spiral). This term is derived from the Greek word *χειρ*= hand; and "handedness" or **chirality** is a property of **dissymmetric** molecules such that *two* configurational isomers are possible that are non-identical mirror images. Compounds that possess reflection symmetry - meaning that they are identical with their mirror images - are said to be **achiral**. Enantiomers are not possible for achiral compounds. An **enantiomeric pair** is a pair of substances whose molecules are *non-identical* mirror images.

The pressing question at this point is how can we tell whether the substances will be chiral or achiral. The most common origin of chirality in molecules is the presence of one or more atoms, usually carbon atoms, each of which forms coplanar bonds to *four different atoms or groups*. This is the case for 2-chlorobutane, because the second tetrahedral carbon along the chain is bonded to four different groups: hydrogen, chlorine, methyl, and ethyl. Therefore, there is a pair of enantiomers, 1 and 2. Another example is 2-bromo-2-chloro-1,1,1-trifluoroethane, which is a widely used inhalation anesthetic. The four different groups in this case are hydrogen, chlorine, bromine, and trifluoromethyl; the pair of enantiomers is shown in Structures 3 and 4:

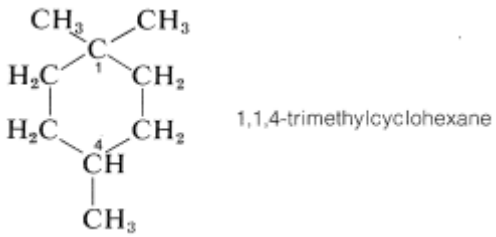


The atom that carries the four different substituents in 1 and 2, or 3 and 4, is called a **chiral atoms** or **chiral center**. The latter is the more general term because dissymmetry in molecules need not be centered at an atom. A chiral center is sometimes marked with an asterisk.

In evaluating a chemical structure for chirality, you should look for carbons carrying four *different* attached groups. There may be more than one chiral carbon, and you should be alert to the fact that structural differences in the attached groups do not necessarily show up at the first, or even the second, position along a chain. As an example, consider the chirality of 1,1,3-trimethylcyclohexane, carbons *C*2, *C*4, *C*5, and *C*6 are clearly achiral because each is connected to two identical groups, which for these atoms are hydrogens.



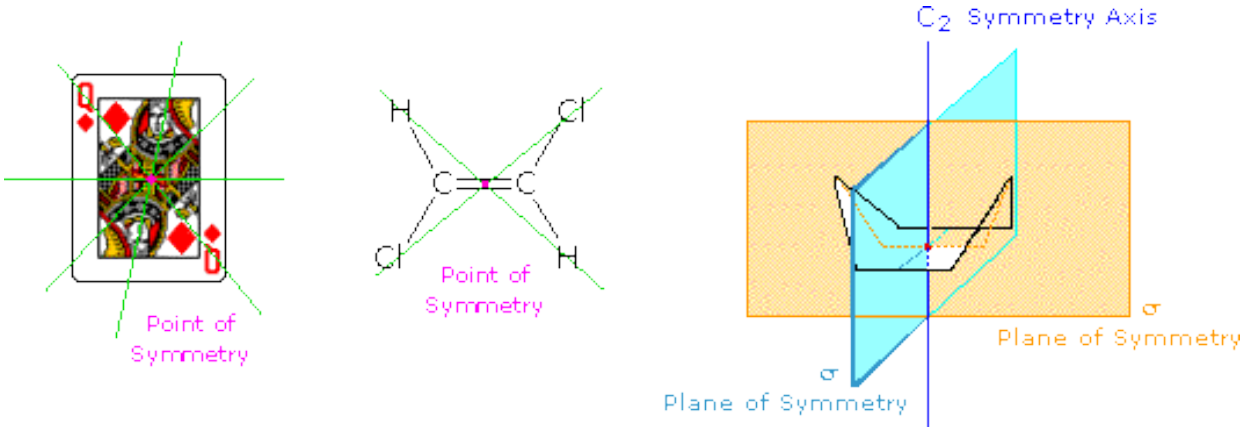
The same is true for *C*1 because it is connected to two CH_3 groups. You might conclude that *C*3 also is an achiral position because it is connected to two CH_2 groups. But this would be wrong. If you look farther, you will see that the groups attached to *C*3 actually are different and are *H*, CH_3, $-CH_2CH_2CH_2-$, and $-CH_2C(CH_3)_2$. Therefore 1,1,3-trimethylcyclohexane has a chiral center at *C*3. In contrast, the 1,1,4-isomer has no chiral centers because the groups attached to the ring at *C*4 are identical:



Several other terms that we shall use frequently in addition to chirality are **racemic mixture**, **resolution**, and **racemization**. A mixture of *equal* amounts of both enantiomers is a **racemic mixture**; separation of a racemic mixture into its component enantiomers is a **resolution**, and the conversion of either enantiomer into equal parts of both is called **racemization**.

Symmetry

All objects may be classified with respect to a property we call **chirality** (from the Greek *cheir* meaning hand). A **chiral object** is not identical in all respects (i.e. superimposable) with its mirror image. An **achiral object** is identical with (superimposable on) its mirror image. Chiral objects have a "handedness", for example, golf clubs, scissors, shoes and a corkscrew. Thus, one can buy right or left-handed golf clubs and scissors. Likewise, gloves and shoes come in pairs, a right and a left. Achiral objects do not have a handedness, for example, a baseball bat (no writing or logos on it), a plain round ball, a pencil, a T-shirt and a nail. The chirality of an object is related to its symmetry, and to this end it is useful to recognize certain **symmetry elements** that may be associated with a given object. A symmetry element is a plane, a line or a point in or through an object, about which a rotation or reflection leaves the object in an orientation indistinguishable from the original. Some examples of symmetry elements are shown below.



The face playing card provides an example of a center or point of symmetry. Starting from such a point, a line drawn in any direction encounters the same structural features as the opposite (180º) line. Four random lines of this kind are shown in green. An example of a molecular configuration having a point of symmetry is (E)-1,2-dichloroethene. Another way of describing a point of symmetry is to note that any point in the object is reproduced by reflection through the center onto the other side. In these two cases the point of symmetry is colored magenta.

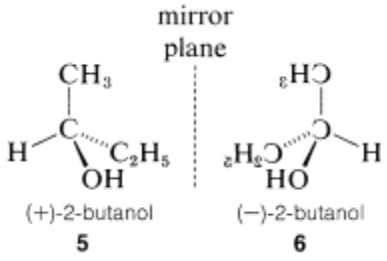
The existence of a reflective symmetry element (a point or plane of symmetry) is sufficient to assure that the object having that element is **achiral**. Chiral objects, therefore, do not have any reflective symmetry elements, but may have rotational symmetry axes, since these elements do not require reflection to operate. In addition to the chiral vs achiral distinction, there are two other terms often used to refer to the symmetry of an object.

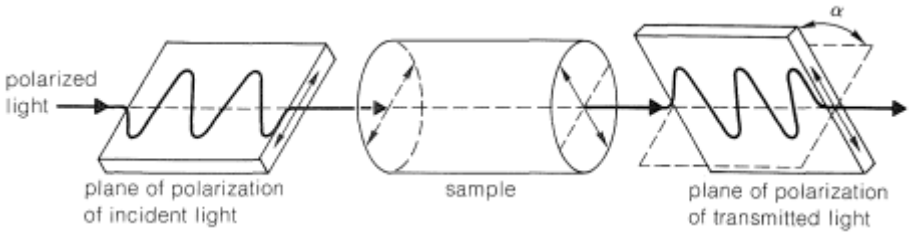
Enantiomers: Optical Activity

Until recently, the phenomenon of chirality has been better known as **optical isomerism**, and configurational isomers that are enantiomers were referred to as **optical antipodes**. The reasons for this are mainly historical. It was discovered early in the nineteenth century that many compounds, whether solid, liquid, or gas, have the property of rotating the plane of polarization of polarized light and can be said to be "**optically active**."

Optical activity is an experimentally useful property and usually is measured as the angle of rotation (α) of the plane of polarization of polarized light passing through solutions of the substances under investigation. Where measurable optical activity is present, it is found that one enantiomer rotates the plane of polarization in one direction, whereas the other causes the plane to rotate *equally* but in the opposite direction. With

reference to the plane of incident light, the enantiomer that rotates the plane to the right is called *dextrorotatory* and is symbolized by either *d* or (+); the enantiomer that rotates the plane to the left is *levorotatory*, symbolized by *l* or (−). A racemic mixture then can be designated as *dl* or (±), and will have no net optical rotation. It is very important to know that *d*, *l*, (+), or (−) do not designate configurations. Thus, although (+)-2-butanol actually has configuration 5 and (−)-2-butanol has configuration 6, there is no simple way to predict that a particular sign of rotation will be associated with a particular configuration. Methods used in assigning the true configurations to enantiomers will be discussed later.





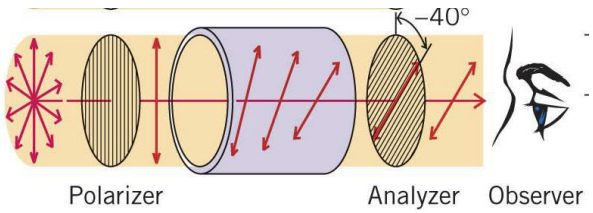
Above is a schematic representation of the rotation of the plane of polarization of polarized light by an optically active compound. Plane-polarized light is different from ordinary light in that its electrical component vibrates in a plane rather than in all directions. The angle α is the angle between the plane of polarization of light entering the sample and the plane of polarization of the emerging light.

A very important point to keep in mind about any pair of enantiomers is that they will have identical chemical and physical properties, except for the signs of their optical rotations, with one important proviso: All of the properties to be compared must be determined using achiral reagents in a solvent made up of achiral molecules or, in short, in an *achiral environment*. Thus, the melting and boiling points (but not the optical rotations) of 5 and 6 will be identical in an achiral environment.

Specific Rotation Formula

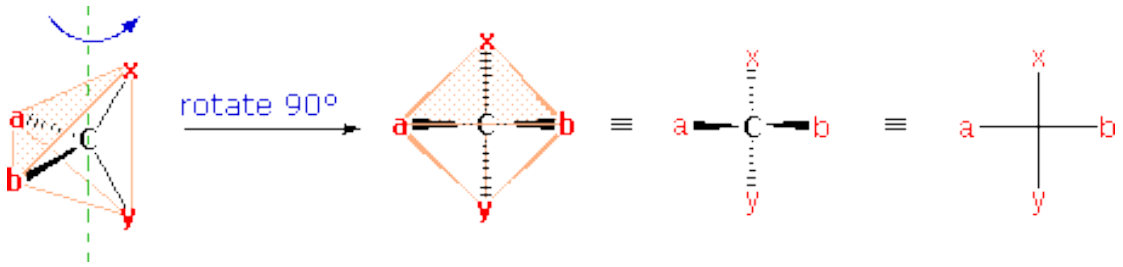
$$[\alpha] = \frac{\alpha}{c \cdot l}$$

$[\alpha]$ = the specific rotation
α = the observed rotation
c = the concentration of the solution in grams per millimeter of solution
l = the length of the tube in decimeters (1 dm = 10 cm)



Fischer Projection Formulas

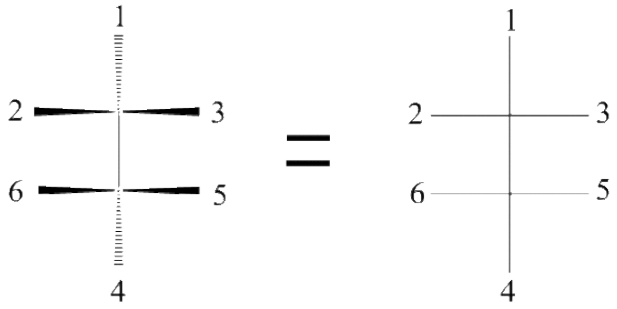
The problem of drawing three-dimensional configurations on a two-dimensional surface, such as a piece of paper, has been a long-standing concern of chemists. The wedge and hatched line notations we have been using are effective, but can be troublesome when applied to compounds having many chiral centers. 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. In a Fischer projection drawing, 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). Since this is not the usual way in which we have viewed such structures, the following diagram shows how a stereogenic carbon positioned in the common two-bonds-in-a-plane orientation (x–C–y defines the reference plane) is rotated into the Fischer projection orientation (the far-right formula). When writing Fischer projection formulas, it is important to remember these conventions. Since the vertical bonds extend away from the viewer and the horizontal bonds toward the viewer, a Fischer structure may only be turned by 180º within the plane, thus maintaining this relationship. **The structure must not be flipped over or rotated by 90º**.

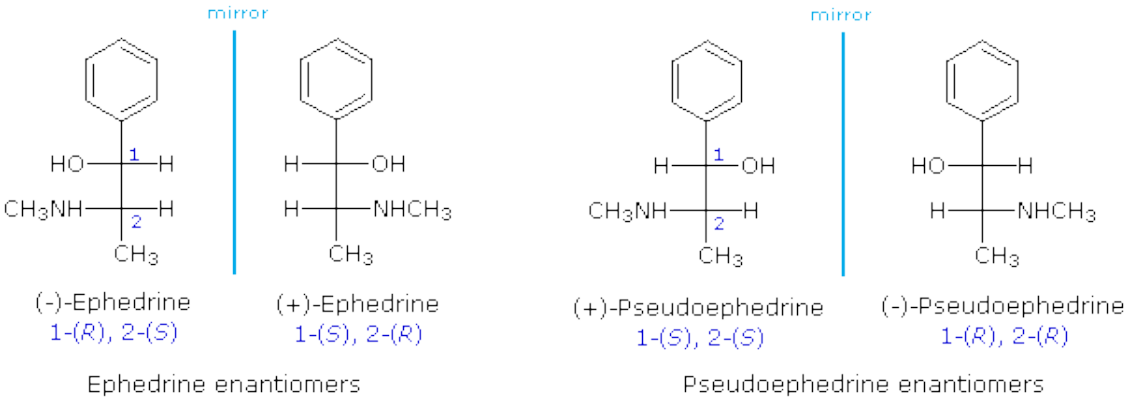


If x = CO2H, y = CH3, a = H & b = OH, the resulting formula describes (R)-(–)-lactic acid. The mirror-image formula, where x = CO2H, y = CH3, a = OH & b = H, would, of course, represent (S)-(+)-lactic acid.

The Fischer Projection consists of both horizontal and vertical lines, where the horizontal lines represent the atoms that are pointed toward the viewer while the vertical line represents atoms that are pointed away from the viewer. The point of intersection between the horizontal and vertical lines represents the central carbon.

Using the Fischer projection notation, the stereoisomers of 2-methylamino-1-phenylpropanol are drawn in the following manner. Note that it is customary to set the longest carbon chain as the vertical bond assembly.



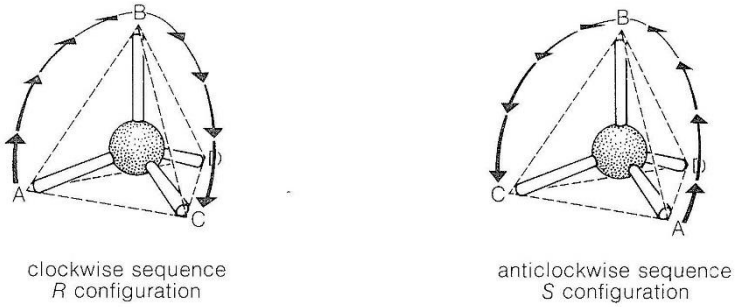


Nomenclature of Enantiomers: The R,S System

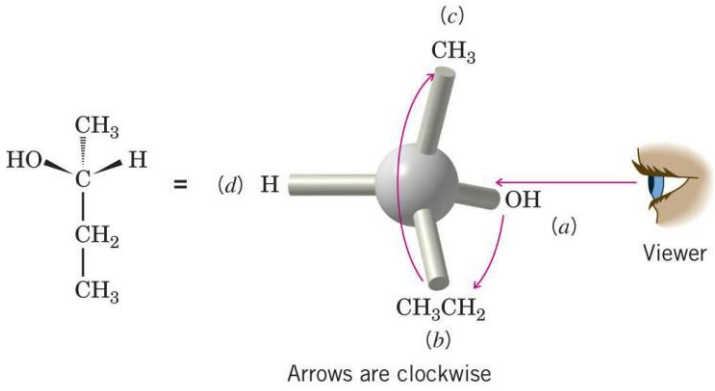
The R,S system is used to denote the configuration of a chiral center by the *R,S* convention, the groups at the center are assigned an order of precedence according to a specific set of rules based on atomic numbers. Suppose a carbon atom is bonded to four different substituents, which we will designate *A*, *B*, *C*, and *D* and to which we assign the following priority sequences:

A before *B* before *C* before *D*. If we now view the arrangement of *A*, *B*, and *C* from the site remote from the substituent of *lowest* priority, *D*, as shown in Figure 19-6, and the sequence turns out to be *A*→*B*→*C* in the *clockwise* direction, then the configuration is said to be *R*. If the sequence *A*→*B*→*C* occurs in the counterclockwise direction, the configuration is *S*. The symbols

R and *S* are taken from the Latin words *rectus* and *sinister*, meaning right and left, respectively.

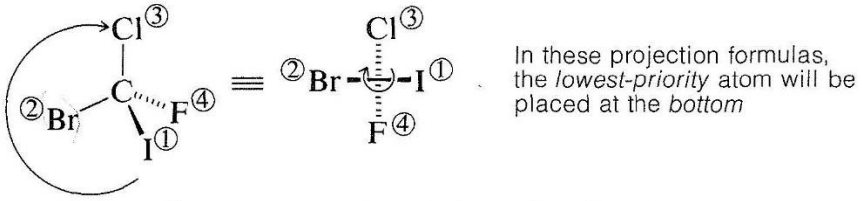


The order of substituent priority in the R,S system with an asymmetric center, decreases in the order A, B, C, D, or 1, 2, 3, 4.



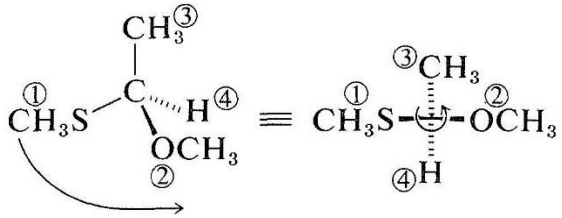
The understanding of *R* and *S* is simple; the problems are in assigning the priority sequences for actual substituents. The rules follow the Cahn-Ingold Prelog system, used with the E,Z system:

1. *Priority is given to the substituent atoms that have the highest atomic number*. This means that four different atoms arranged tetrahedrally about the chiral center have a priority sequence that decreases with decreasing atomic number. For example, the sequence among the halogens is I>Br>Cl>F, and Structure 5 (shown here in perspective and in projection) therefore has the *R* configuration:



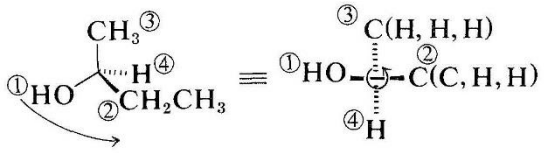
5 1 ⟶ 2 ⟶ 3 clockwise = *R* configuration

For more complex substituents, *priority is determined by the atomic number of the first bonded atom*. The sequence $CH_3S>CH_3O>NH_2>CH_3>H$ thus reflects the fact that atomic number decreases in the order S>O>N>C>H. Structure 6, accordingly has the *S* configuration:



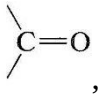
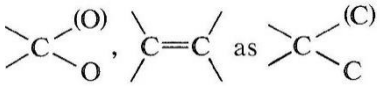
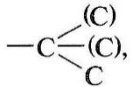
6 1 ⟶ 2 ⟶ 3 counterclockwise = *S* configuration

2. The first atoms in two or more substituents often are identical, in which case it is necessary to explore further and compare the atomic numbers of the second attached atoms. *Precedence is given to the substituent with a second atom of higher atomic number*. For example, in 2-butanol, $CH_3CH(OH)CH_2CH_3$, two of the groups at the chiral atom have carbon as the first atom. We therefore must compare the other atoms bonded to these two carbons. It is convenient to represent the arrangement at the chiral atom as shown in 7, where the first atoms are shown attached to the chiral center and the second atoms are listed in their priority order; thus, (C, H, H) for ethyl and (H, H, H) for methyl:

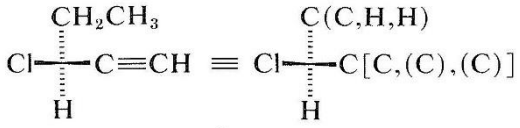


7 1 ⟶ 2 ⟶ 3 anticlockwise = *S* configuration

When we compare (H, H,H) with (C,H,H) in 7, we give ethyl precedence over methyl because carbon has a higher atomic number than hydrogen. The configuration 7 therefore must be *S*.

3. Double and triple bonds are treated as if they had duplicate or triplicate single bonds. Thus, a carbonyl group,  , is treated as if it were  and C≡C as  where the symbols in parentheses represent the duplicate atoms.

Let us see how this works for 3-chloro-1-pentyne, 8:

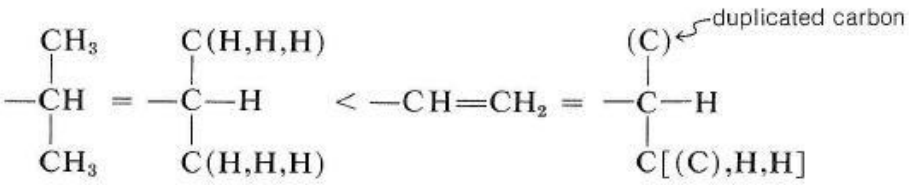


8

The first-atom priority sequence is Cl>C and C>H. We now need to order $-CH_2CH_3$ and $-C{\equiv}CH$ and, in doing this, we compare the three atoms attached to the first carbon of the ethyl group (C, H, H) with the three attached to the first carbon of the ethynyl group [C, (C), (C)]. On this basis, ethynyl comes ahead of ethyl, and the overall sequence is $Cl>C{\equiv}CH>CH_2CH_3>H$, so 8 will have the *S* configuration.

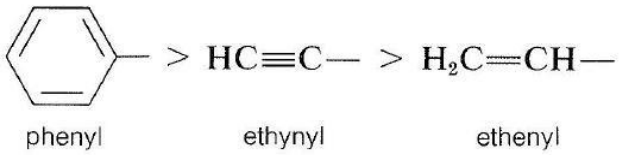
The sequence rules described thus far can be used without ambiguity in most of the examples we are likely to meet. The important thing to remember is to look at the kind of atoms attached as far out as necessary. Suppose we have to compare the aldehyde group, $-CH{=}O$, with the dimethoxymethyl group, $CH(OCH_3)_2$. The first atoms are the same (C), the second atoms are the same [O, (O), H], and the difference arrives at the third-atom level where we are comparing lone pairs (priority zero) with carbons. Thus $-CH(OCH_3)_2$, outranks $-CH{=}O$.

Comparison of groups such as isopropyl and ethenyl is more difficult and requires knowing what the convention is when we have to go to the far end of a double bond. A useful way of writing these groups is as follows:

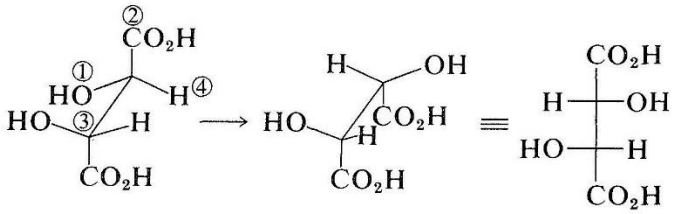


We put ethenyl ahead of isopropyl because [(C), H, H] takes priority over (H, H, H). It is important to understand that the nonduplicated carbon is considered to be connected to the duplicated carbon as well as the two hydrogens in arriving at the connection pattern ((C), H, H).

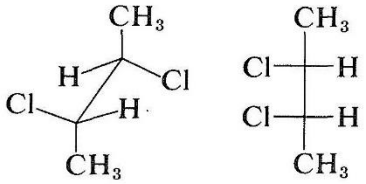
The same kind of logic leads to the following sequence:



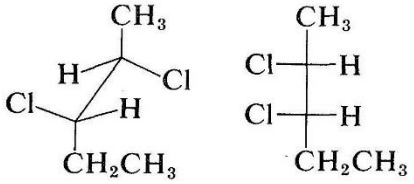
If more than one chiral center is present, the configuration at each is specified by the symbol *R* or *S* together with the number of the chiral atom. Thus the configuration of (+)-tartaric acid is known to be that designated in the name (2*R*,3*R*)-(+)-tartaric acid:



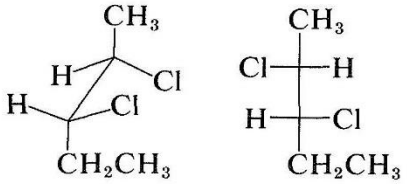
(2*R*,3*R*)-(+)-tartaric acid
or
D$_s$-(+)-tartaric acid
or
L$_g$-(+)-tartaric acid



(2*R*,3*S*)- or (2*S*,3*R*)-2,3-dichlorobutane
(*meso*-2,3-dichlorobutane)



(2*R*,3*S*)-2,3-dichloropentane
(L$_g$-*erythro*-2,3-dichloropentane)

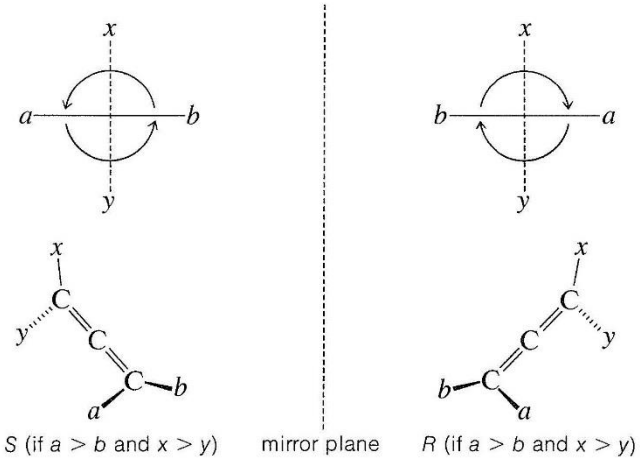


(2*R*,3*R*)-2,3-dichloropentane
(D$_g$-*threo*-2,3-dichloropentane)

The *R*,*S* system is quite general and has many advantages (and a few disadvantages) compared with the *D*, *L* notation for simple molecules. For diastereomers, it provides much clearer notations than *meso*, *erythro*, and *threo* that have been used for many years to designate the configurations of achiral and chiral diastereomers having two chiral carbon atoms:

The *R*,*S* system can be used to designate the configuration of a molecule with no chiral carbons but with a chiral center as, for example, a chiral 1,2-diene. To do this for a 1,2-diene, the molecule is best drawn in projection, looking along the C=C=C bond with the *highest-ranking* group in *front*. The bonds in the rear will then project at 90° to the bonds of the groups in front.

For a 1,2-diene, *ab*C=C=C*xy*, where is the highest-ranking group, the possible enantomeric projections are:

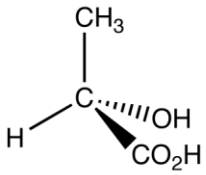


We now determine the priority of the groups and then assign the configurations *R* and *S* as shown, provided that the highest-ranking group is in front and $a > b$ and $x > y$. In proceeding this way, it is important to recognize that no matter what the priority is of the group *b* based on atomic number, *b always outranks a rear group* so that the priority sequence is $a \rightarrow b \rightarrow x$ with *R* clockwise and *S* counterclockwise.

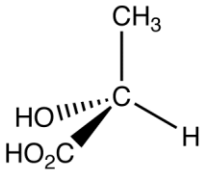
Racemic Mixture

A racemic mixture or racemate (±) is a mixture of enantiomers at 1:1 molar ratio.

Example: Lactic acid exists as a pair of enantiomers, (*R*)-lactic acid and (*S*)-lactic acid. A 1:1 ratio has an optical rotation of zero.



(*R*)–lactic acid

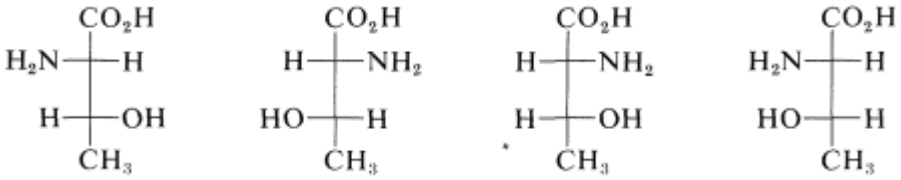


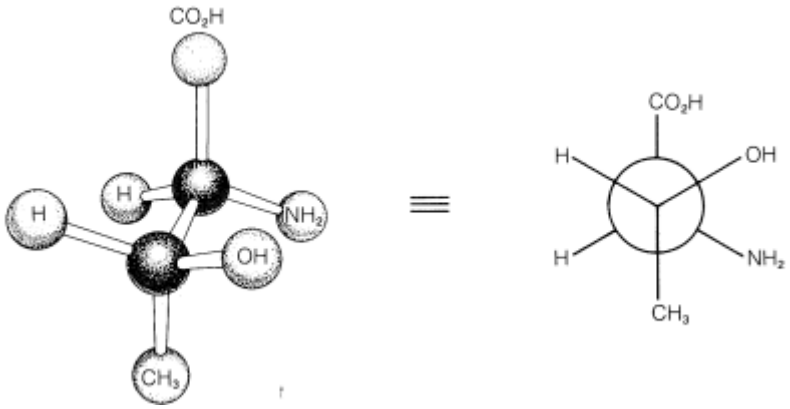
(*S*)–lactic acid

A mixture of (*R*)-lactic acid and (*S*)-lactic acid at 1:1 molar ratio is a racemic mixture of lactic acid (± – lactic acid).

Molecules with More than One Stereocenters

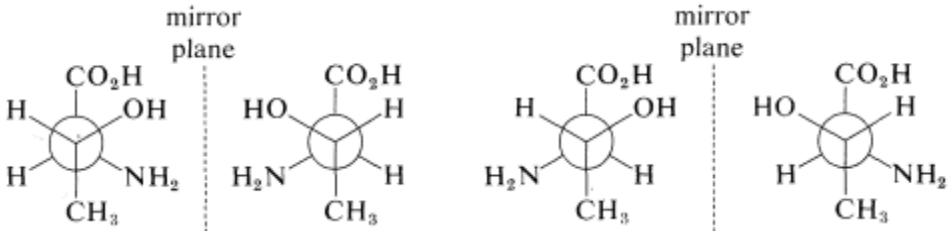
We have seen examples of molecules with one chiral center that exist in two mirror-image configurations, which we call enantiomers. What happens when there is more than one chiral center? How many stereoisomers should we expect? Consider the stereoisomers of the important amino acid, threonine, (2-amino-3-hydroxybutanoic acid). For this substance, if we write all of the possible configurations of its *two* chiral carbons, we have *four* different projection formulas corresponding to four different stereoisomers:





Because each chiral center added to a chain doubles the number of possible configurations, we expect eight different stereoisomers with three chiral carbons, sixteen with four, and so on, the simple rule the is 2^n possible different stereoisomers for *n* chiral centers. As we shall see later, this rule has to be modified in some special cases.

What is the relationship between the above stereoisomers? This will be clearer if we translate each of the projection formulas into a three-dimensional representation. Drawn as Newman projections, respectively:



It should be clear (and, if it isn't, ball-and-stick models will be invaluable) that two left stereoisomers are mirror images of one another and that the two right stereoisomers are similarly mirror images.

What about other combinations such as the two left or the two right? If you look at the pairs closely you will find that they are not mirror images and are not identical. Such substances, related to each other in this way and which can be converted one into the other only by changing the configurations at one or more chiral centers, are called **diastereomers**.

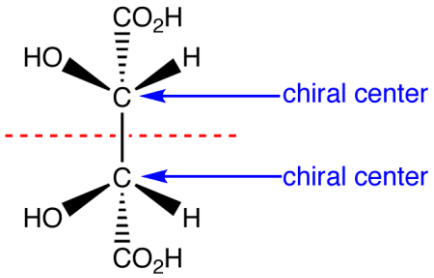
The difference between enantiomers and diastereomers is more than just geometry. Diastereomers have substantially different chemical and physical properties, whereas enantiomers have identical physical properties (apart from their optical rotations). The reason for the difference in physical properties between diastereomers can be seen very simply for a substance with two chiral centers by noting that a right shoe on a right foot (*D*,*D*) is a mirror image, or has the same physical properties, as a left shoe on a left foot (*L*,*L*), but is not a mirror image, nor does it have the same physical properties, as a left show on a right foot (*L*,*D*), or a right shoe on a left foot (*D*,*L*).

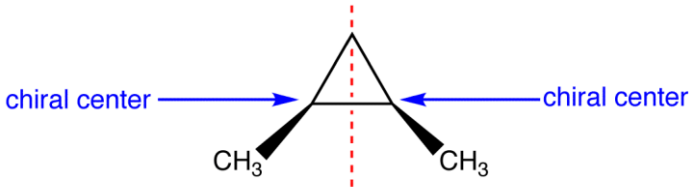
Meso Compounds

A meso compound contains two or more identical substituted stereocenters with an internal symmetry plane that divides the compound in half. These two halves reflect each other by the internal mirror. The stereochemistry of stereocenters should "cancel out". What it means here is that when we have an internal plane that splits the compound into two symmetrical sides, the stereochemistry of both left and right side

should be opposite to each other, and therefore, result in **optically inactive**. Cyclic compounds may also be meso.

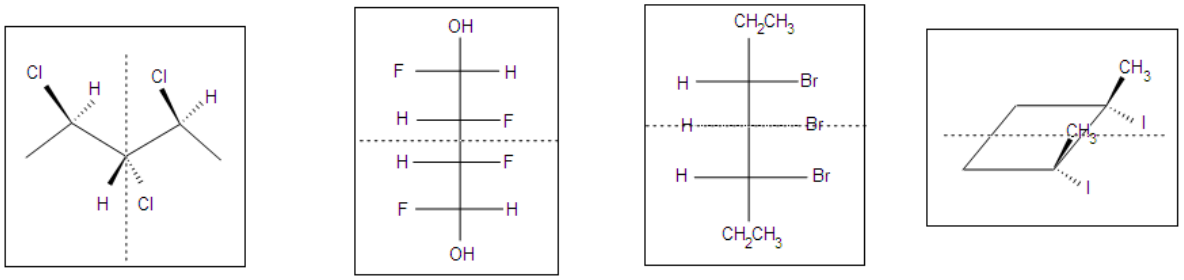
This molecule has a plane of symmetry (the horizontal plane going through the red broken line) and, therefore, is achiral; it has chiral centers. Thus, it is a meso compound.

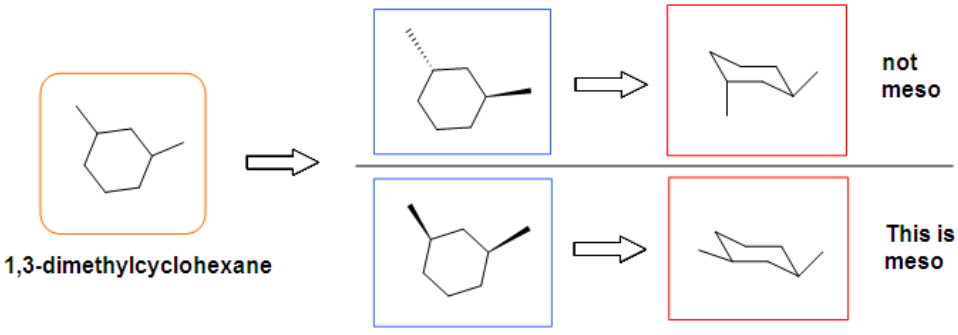




This molecule has a plane of symmetry (the vertical plane going through the red broken line perpendicular to the plane of the ring) and, therefore, is achiral, but has two chiral centers. Thus, it is a meso compound.

Meso compounds can exist in many different forms such as pentane, butane, heptane, and even cyclobutane. They do not necessarily have to be two stereocenters, but can have more.



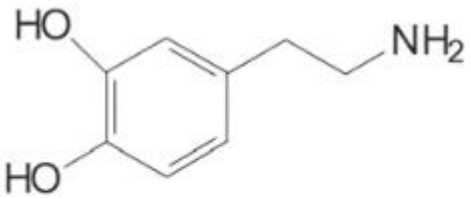


TOPIC 8: BUILDING BLOCKS OF LIFE

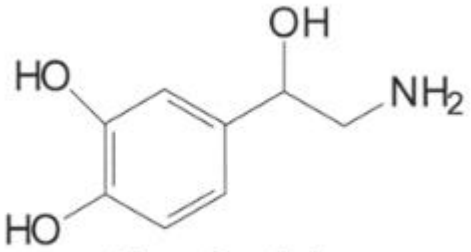
Amines and Nitrogen Heterocycles

Dopamine

Dopamine (DA), 4,5-dihydroxyphenethylamine or 4-(2-aminoethyl)1,2-benzenediol, is a known neurotransmitter that is involved in the chemical transmission of nerve impulses in the mammalian brain. It is a member of the catecholamine family and a precursor to epinephrine (adrenaline) and norepinephrine (noradrenaline) in the biosynthetic pathways.



Dopamine



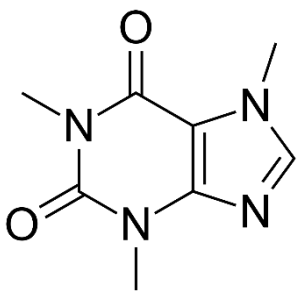
Norepinephrine

DA has a molecular formula of C8H11NO2 and a formula weight of 153.18. It is a water-soluble hormone released by the hypothalamus. Imbalance in dopamine activity can cause brain dysfunction related to two major disorders, Parkinson's disease and schizophrenia. Researchers are also looking at dopamine neurotransmission in drug abuse ranging from stimulants, such as amphetamines and cocaine, to depressants, such as morphine and other opioids, and alcohol.

Several amine neurotransmitters such as DA, noradrenaline (norepinephrine), adrenaline and serotonin are electroactive so that they can be monitored electrochemically. Most undergo a chemical reaction following the initial electron transfer step, an electrochemical (EC) reaction mechanism, as evaluated by cyclic voltammetry (CV) in this experiment. In biological fluids, prior separation with high -performance liquid chromatography (HLPC) is recommended in conjunction with an electrochemical detector (HPLC-ECD).

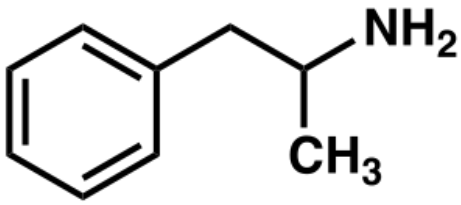
Central Nervous System Stimulants

Stimulants are drugs that exert their action through excitation of the central nervous system. Psychic stimulants include caffeine, cocaine, and various amphetamines. These drugs are used to enhance mental alertness and reduce drowsiness and fatigue. However, increasing the dosage of caffeine above 200 mg (about 2 cups of coffee) does not increase mental performance but may increase nervousness, irritability, tremors, and headache. Heavy coffee drinkers become psychically dependent upon caffeine. If caffeine is withheld, a person may experience mild withdrawal symptoms characterized by irritability, nervousness, and headache.



Caffeine and the chemically related xanthines, theophylline and theobromine, decrease in the order given in their stimulatory action. They may be included in some over-the-counter drugs. The action of caffeine is to block adenosine receptors as an antagonist. As caffeine has a similar structure to the adenosine group. This means that caffeine will fit adenosine receptors as well as adenosine itself. It inhibits the release of neurotransmitters from presynaptic sites but works in concert with norepinephrine or angiotensin to augment their actions. Antagonism of adenosine receptors by caffeine would appear to promote neurotransmitter release, thus explaining the stimulatory effects of caffeine.

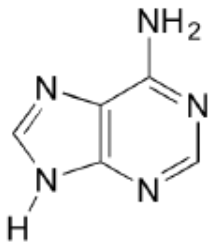
The stimulation caused by **amphetamines** is caused by excessive release of norepinephrine from storage sites in the peripheral nervous system. It is not known whether the same action occurs in the central nervous system. Two other theories for their action are that they are degraded slower than norepinephrine or that they could act on serotonin receptor sites. Therapeutic doses of amphetamine elevate mood, reduce feelings of fatigue and hunger, facilitate powers of concentration, and increase the desire and capacity to carry out work. They induce exhilarating feelings of power, strength, energy, self-assertion, focus and enhanced motivation. The need to sleep or eat is diminished.



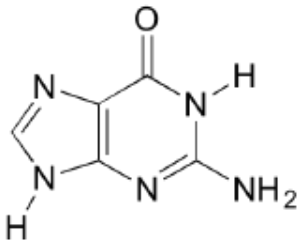
DNA and RNA

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are polymers composed of monomers called **nucleotides**. An RNA nucleotide consists of a five-carbon sugar phosphate linked to one of four nucleic acid **bases**: guanine (G), cytosine (C), adenine (A) and uracil (U).

purine bases

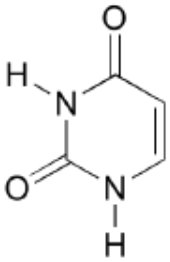


adenine (A)

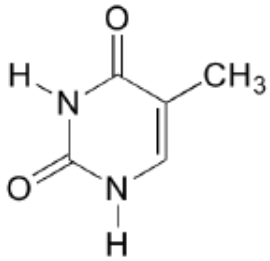


guanine (G)

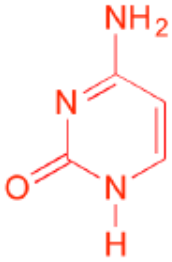
pyrimidine bases



uracil (U)
(RNA)



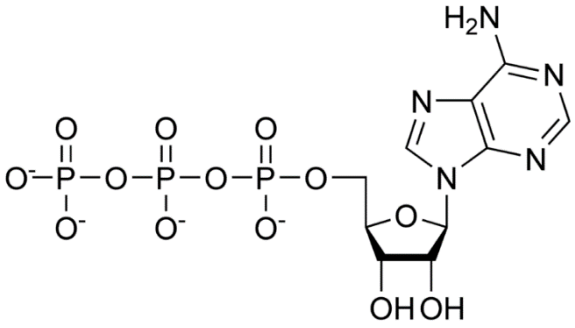
thymine (T)
(DNA)



cytosine (C)

ATP (Adenosine Triphosphate)

ATP is the primary energy transporter for most energy-requiring reactions that occur in the cell. The continual synthesis of ATP and the immediate usage of it results in ATP having a very fast turnover rate. This means that ADP is synthesized into ATP very quickly and vice versa. For example, it takes only a few seconds for half of the ATP molecules in a cell to be converted into ADP to be used in driving endergonic (non-spontaneous) reactions and then converted back into ATP using exergonic (spontaneous) reactions.



ATP is useful in many cell processes such as glycolysis, photosynthesis, beta oxidation, anaerobic respiration, active transport across cell membranes (as in the electron transport chain), and synthesis of macromolecules such as DNA.

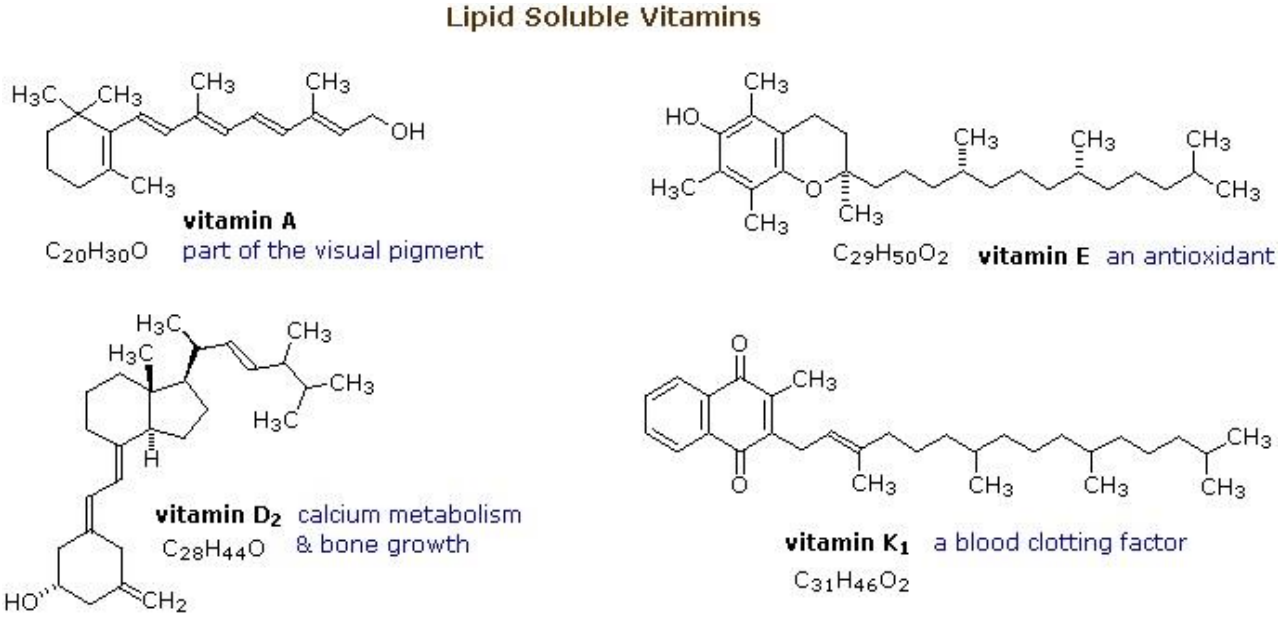
Adenosine-5'-triphosphate (ATP) is comprised of an adenine ring, a ribose sugar, and three phosphate groups. ATP is often used for energy transfer in the cell. ATP synthase produces ATP from ADP or AMP + P_i. ATP has many uses. It is used as a coenzyme, in glycolysis, for example. ATP is also found in nucleic acids in the processes of DNA replication and transcription. In a neutral solution, ATP has negatively charged groups that allow it to chelate metals. Usually, Mg^{2+} stabilizes it.

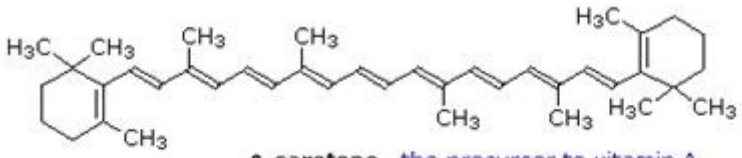
Vitamins

The essential dietary substances called **vitamins** are commonly classified as "water soluble" or "fat soluble". Water soluble vitamins, such as vitamin C, are rapidly eliminated from the body and their dietary levels need to be relatively high. The recommended daily allotment (RDA) of vitamin C is 100 mg, and amounts as large as 2 to 3 g are taken by many people without adverse effects. The lipid soluble vitamins, shown in the diagram below, are not as easily eliminated and may accumulate to toxic levels if consumed in large quantity. The RDA for these vitamins are:

- Vitamin A 800 µg (upper limit ca. 3000 µg)
- Vitamin D 5 to 10 µg (upper limit ca. 2000 µg)
- Vitamin E 15 mg (upper limit ca. 1 g)
- Vitamin K 110 µg (upper limit not specified)

From this data, it is clear that vitamins A and D, while essential to good health in proper amounts, can be very toxic. Vitamin D, for example, is used as a rat poison, and in equal weight is more than 100 times as poisonous as sodium cyanide.



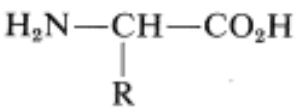


β-carotene the precursor to vitamin A

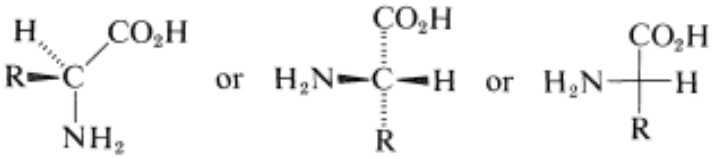
ergosterol the precursor to vitamin D_2

Protein Amino Acids

The amino acids that occur naturally as constituents of proteins have an amino group (NH_2) and a carboxylic acid group (CO_2H) attached to the *same* carbon. They are called ***α*-amino acids** and have the general formula.



They differ only in the nature of the R group on the α carbon and, with few exceptions, they are chiral molecules with the *L* configuration at the chiral α carbon:



L-amino acid
(*S*-amino acid)

The nature of the substituent RR varies considerably. In some amino acids, RR is a hydrocarbon group, whereas in others it possesses functional groups such as OHOH, SHSH, SCH_3SCH_3, CO_2HCO_2H, or NH_2NH_2. Amino acids that have amine or other basic functions in the RR group are called **basic amino acids** (lysine and arginine), whereas those with acidic groups are called **acidic amino acids** (aspartic and glutamic acids).

TOPIC 9: RADICAL REACTIONS

In chemistry, a **radical** (more precisely, a **free radical**) is an atom, molecule, or ion that has unpaired valence electrons or an open electron shell, and therefore may be seen as having one or more "dangling" covalent bonds.

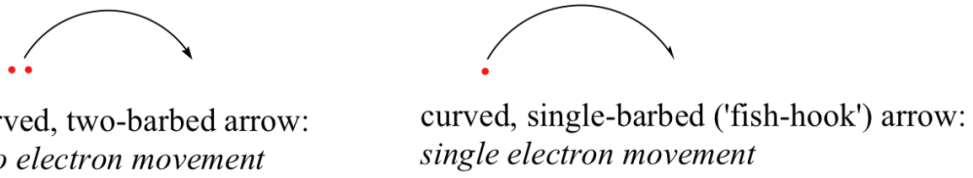
With some exceptions, these "dangling" bonds make free radicals highly chemically reactive towards other substances, or even towards themselves: their molecules will often spontaneously dimerize or polymerize if they come in contact with each other. Most radicals are reasonably stable only at very low concentrations in inert media or in a vacuum.

Free radicals may be created in a number of ways, including synthesis with very dilute or rarefied reagents, reactions at very low temperatures, or breakup of larger molecules. The latter can be affected by any process that puts enough energy into the parent molecule, such as ionizing radiation, heat, electrical discharges, electrolysis, and chemical reactions. Indeed, radicals are intermediate stages in many chemical reactions.

The first organic free radical identified was triphenylmethyl radical. This species was discovered by Moses Gomberg in 1900 at the University of Michigan USA. Historically, the term *radical* in radical theory was also used for bound parts of the molecule, especially when they remain unchanged in reactions. These are now called functional groups. For example, methyl alcohol was described as consisting of a methyl "radical" and a hydroxyl "radical". Neither are radicals in the modern chemical sense, as they are permanently bound to each other, and have no unpaired, reactive electrons; however, they can be observed as radicals in mass spectrometry when broken apart by irradiation with energetic electrons.

Depiction in chemical reactions

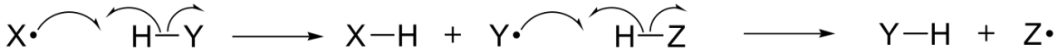
In this chapter, we will learn about some reactions in which the key steps involve the movement of *single* electrons. Single electron movement is depicted by a single-barbed **'fish-hook'** arrow (as opposed to the familiar double-barbed arrows that we have been using throughout the book to show two-electron movement).



Single-electron mechanisms involve the formation and subsequent reaction of free radical species, highly unstable intermediates that contain an unpaired electron. We will learn in this chapter how free radicals are often formed from **homolytic cleavage**, an event where the two electrons in a breaking covalent bond move in opposite directions.

When both electrons move in the same direction, this is called **heterolytic cleavage**).

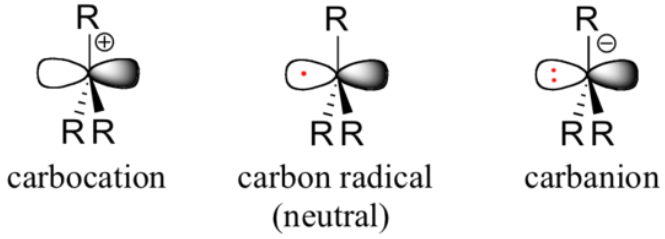
We will also learn that many single-electron mechanisms take the form of a radical chain reaction, in which one radical causes the formation of a second radical, which in turn causes the formation of a third radical, and so on.



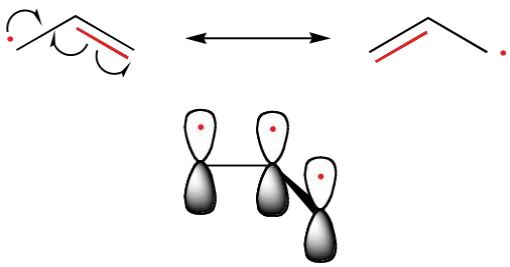
The high reactivity of free radical species and their ability to initiate chain reactions is often beneficial - we will learn in this chapter about radical polymerization reactions that form useful materials such as plexiglass and polypropylene fabric. We will also learn about radical reactions that are harmful, such as the degradation of atmospheric ozone by Freon, and the oxidative damage done to lipids and DNA in our bodies by free radicals species. Finally, we will see how some enzymes use bound metals to catalyze high e

The geometry and relative stability of carbon radicals

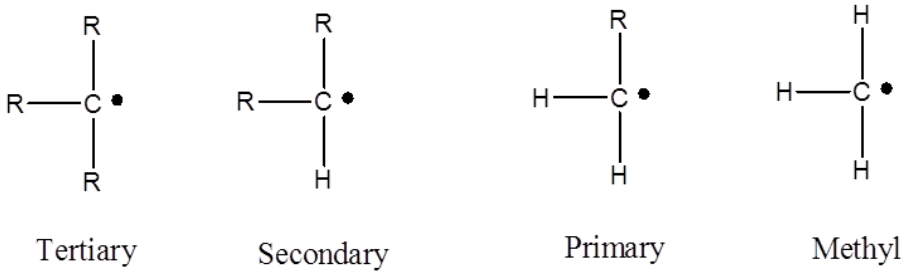
As organic chemists, we are particularly interested in radical intermediates in which the unpaired electron resides on a carbon atom. Experimental evidence indicates that the three bonds in a carbon radical have trigonal planar geometry, and therefore the carbon is considered to be sp2-hybridized with the unpaired electron occupying the perpendicular, unhybridized $2p_z$ orbital. Contrast this picture with carbocation and carbanion intermediates, which are both also trigonal planar but whose $2p_z$ orbitals contain zero or two electrons, respectively.



The trend in the stability of carbon radicals parallels that of carbocations: tertiary radicals, for example, are more stable than secondary radicals, followed by primary and methyl radicals. This should make intuitive sense, because radicals, like carbocations, can be considered to be electron deficient, and thus are stabilized by the electron-donating effects of nearby alkyl groups. Benzylic and allylic radicals are more stable than alkyl radicals due to resonance effects - an unpaired electron can be delocalized over a system of conjugated pi bonds. An allylic radical, for example, can be pictured as a system of three parallel $2p_z$ orbitals sharing three electrons.



Trends in radical stability



Allyic & Benzlic > 3o > 2o > 1o > Methyl

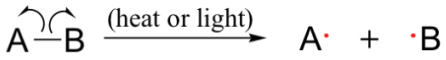
AS STABILITY DECREASES, REACTIVITY INCREASES.

General Features of Radical Reactions

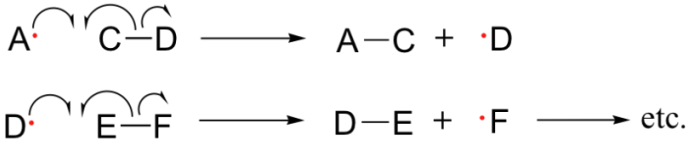
The three phases of radical chain reactions

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.

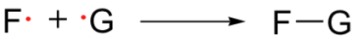
initiation



propagation

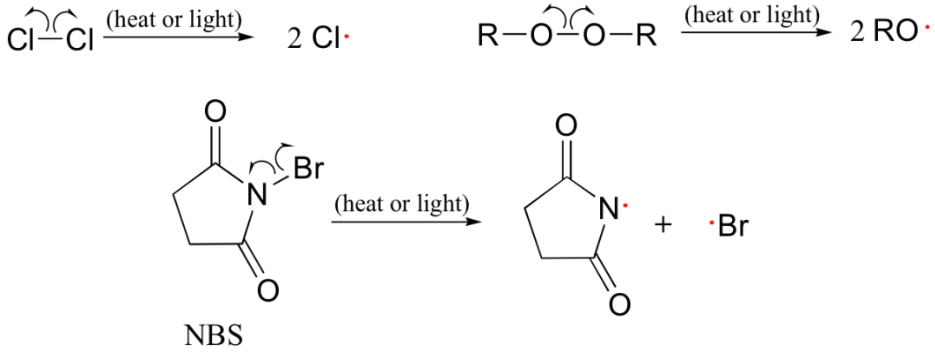


termination

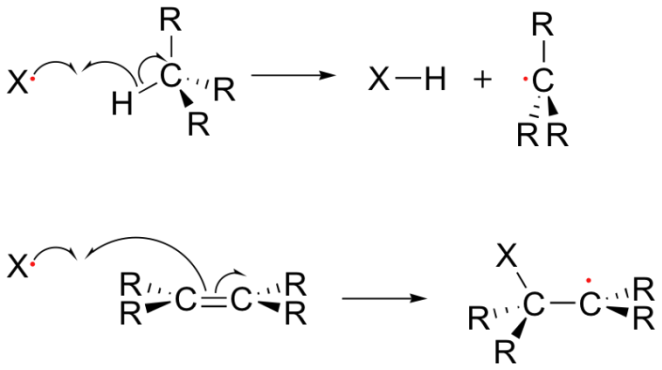


The **initiation phase** describes the step that initially creates a radical species. In most cases, this is a homolytic cleavage event, and takes place very rarely due to the high energy barriers involved. Often the influence of heat, UV radiation, or a metal-containing catalyst is necessary to overcome the energy barrier.

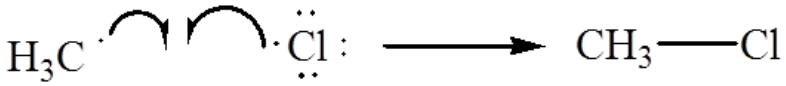
Molecular chlorine and bromine will both undergo homolytic cleavage to form radicals when subjected to heat or light. Other functional groups which also tend to form radicals when exposed to heat or light are chlorofluorocarbons, peroxides, and the halogenated amide N-bromosuccinimide (NBS).



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.



Halogenation of Alkanes

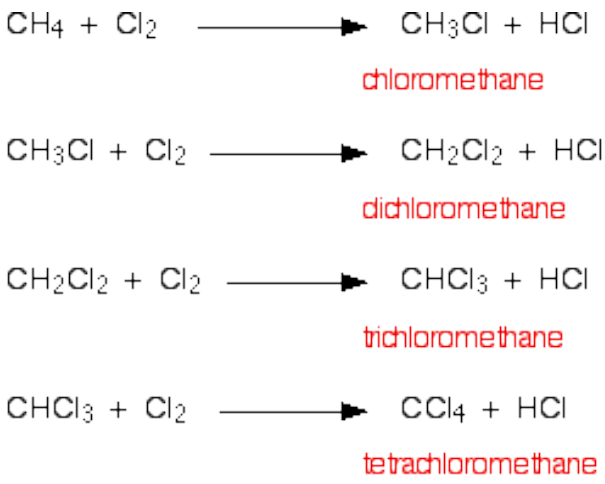
Methane and Chlorine

If a mixture of methane and chlorine is exposed to a flame, it explodes - producing carbon and hydrogen chloride. This is not a very useful reaction! The reaction we are going to explore is a gentler one between methane and chlorine in the presence of ultraviolet light - typically sunlight. This is a good example of a photochemical reaction - a reaction brought about by light.

$$CH_4 + Cl_2 + \text{energy} \rightarrow CH_3Cl + HC$$

The organic product is chloromethane. One of the hydrogen atoms in the methane has been replaced by a chlorine atom, so this is a substitution reaction. However, the reaction doesn't stop there, and all the hydrogens in the methane can in turn be replaced by chlorine atoms. Multiple substitution is dealt with on a separate page, and you will find a link to that at the bottom of this page.

Substitution reactions happen in which hydrogen atoms in the methane are replaced one at a time by chlorine atoms. You end up with a mixture of chloromethane, dichloromethane, trichloromethane and tetrachloromethane.



The original mixture of a colorless and a green gas would produce steamy fumes of hydrogen chloride and a mist of organic liquids. All of the organic products are liquid at room temperature with the exception of the chloromethane which is a gas.

If you were using bromine, you could either mix methane with bromine vapor, or bubble the methane through liquid bromine - in either case, exposed to UV light. The original mixture of gases would, of course, be red-brown rather than green.

You wouldn't choose to use these reactions as a means of preparing these organic compounds in the lab because the mixture of products would be too tedious to separate. The mechanisms for the reactions are explained on separate pages.

The Mechanism of Halogenation

Alkanes (the most basic of all organic compounds) undergo very few reactions. One of these reactions is halogenation, or the substitution of a single hydrogen on the alkane for a single halogen to form a haloalkane. This reaction is very important in organic chemistry because it opens a gateway to further chemical reactions.

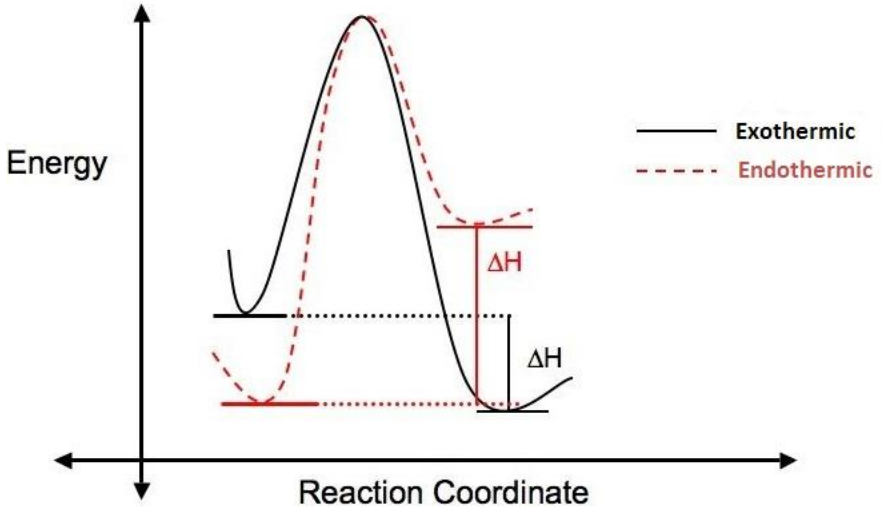
While the reactions possible with alkanes are few, there are many reactions that involve haloalkanes. In order to better understand the mechanism (a detailed look at the step by step process through which a reaction occurs), we will closely examine the chlorination of methane. When methane (CH_4) and chlorine (Cl_2) are mixed together in the absence of light at room temperature nothing happens. However, if the conditions are changed, so that either the reaction is taking place at high temperatures (denoted by Δ) or there is ultra violet irradiation, a product is formed, chloromethane (CH_3Cl).

Energetics

Why does this reaction occur? Is the reaction favorable? A way to answer these questions is to look at the change in enthalpy (ΔH) that occurs when the reaction takes place.

$$\Delta H = (\text{Energy put into reaction}) - (\text{Energy given off from reaction})$$

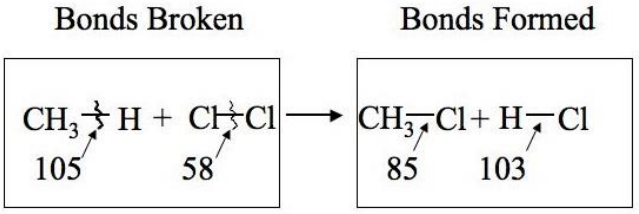
If more energy is put into a reaction than is given off, the ΔH is positive, the reaction is endothermic and not energetically favorable. If more energy is given off in the reaction than was put in, the ΔH is negative, the reaction is said to be exothermic and is considered favorable. The figure below illustrates the difference between endothermic and exothermic reactions.



ΔH can also be calculated using bond dissociation energies (ΔH°):

$$\Delta H = \sum \Delta H^\circ \text{ of bonds broken} - \sum \Delta H^\circ \text{ of bonds formed}$$

Let's look at our specific example of the chlorination of methane to determine if it is endothermic or exothermic:



Change in enthalpy = (105 + 58) - (85 + 103)
= -25kcal/mol

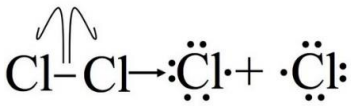
Since, the ΔH for the chlorination of methane is negative, the reaction is exothermic. Energetically, this reaction is favorable. In order to better understand this reaction, we need to look at the mechanism (a detailed step by step look at the reaction showing how it occurs) by which the reaction occurs.

Radical Chain Mechanism

The reaction proceeds through the radical chain mechanism. The radical chain mechanism is characterized by three steps: **initiation**, **propagation** and **termination**. Initiation requires an input of energy but after that the reaction is self-sustaining. The first propagation step uses up one of the products from initiation, and the second propagation step makes another one, thus the cycle can continue until indefinitely.

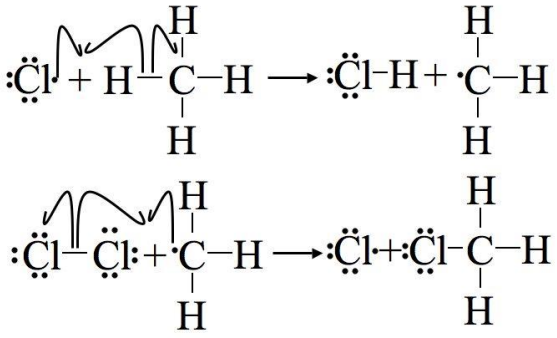
Step 1: Initiation

Initiation breaks the bond between the chlorine molecule (Cl_2). For this step to occur energy must be put in, this step is not energetically favorable. After this step, the reaction can occur continuously (as long as reactants provide) without input of more energy. It is important to note that this part of the mechanism cannot occur without some external energy input, through light or heat.

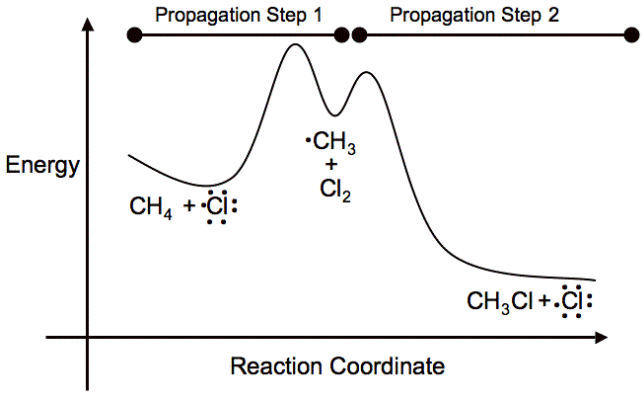


Step 2: Propagation

The next two steps in the mechanism are called propagation steps. In the first propagation step, a chlorine radical combines with a hydrogen on the methane. This gives hydrochloric acid (HCl, the inorganic product of this reaction) and the methyl radical. In the second propagation step, more of the chlorine starting material (Cl_2) is used, one of the chlorine atoms becomes a radical and the other combines with the methyl radical.

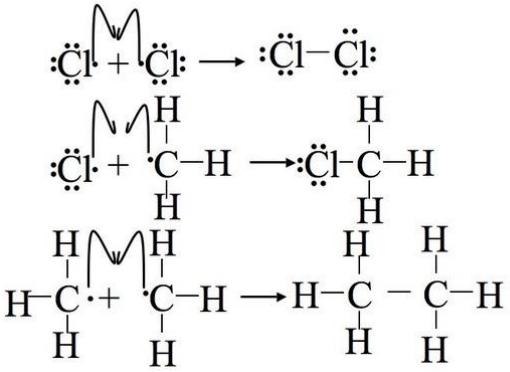


The first propagation step is endothermic, meaning it takes in heat (requires 2 kcal/mol) and is not energetically favorable. In contrast, the second propagation step is exothermic, releasing 27 kcal/mol. Since the second propagation step is so exothermic, it occurs very quickly. The second propagation step uses up a product from the first propagation step (the methyl radical) and following Le Chatelier's principle, when the product of the first step is removed the equilibrium is shifted towards its products. This principle is what governs the unfavorable first propagation step's occurrence.



Step 3: Termination

In the termination steps, all the remaining radicals combine (in all possible manners) to form more product (CH_3Cl), more reactant (Cl_2) and even combinations of the two methyl radicals to form a side product of ethane (CH_3CH_3).



Problems with the Chlorination of Methane

The chlorination of methane does not necessarily stop after one chlorination. It may actually be very hard to get a monosubstituted chloromethane. Instead di-, tri- and even tetra-chloromethanes are formed. One way to avoid this problem is to use a much higher concentration of methane in comparison to chloride. This reduces the chance of a chlorine radical running into a chloromethane and starting the mechanism over again to form a dichloromethane. Through this method of controlling product ratios one is able to have a relative amount of control over the product.

Chlorination of Other Alkanes

When alkanes larger than ethane are halogenated, isomeric products are formed. Thus, chlorination of propane gives both 1-chloropropane and 2-chloropropane as mono-chlorinated products. Four constitutionally isomeric dichlorinated products are possible, and **five constitutional isomers** exist for the trichlorinated propanes. Can you write structural formulas for the four dichlorinated isomers?

$CH_3CH_2CH_3 + 2Cl_2 \rightarrow$ Four **$C_3H_6Cl_2$** isomers **+ $2HCl$** **$CH_3CH_2CH_3 + 2Cl_2 \rightarrow$** Four **$C_3H_6Cl_2$** isomers **+ $2HCl$**

The halogenation of propane discloses an interesting feature of these reactions. **All the hydrogens in a complex alkane do not exhibit equal reactivity**. For example, propane has eight hydrogens, six of them being structurally equivalent **primary**, and the other two being **secondary**. If all these hydrogen atoms were equally reactive, halogenation should give a 3:1 ratio of 1-halopropane to 2-halopropane mono-halogenated products, reflecting the primary/secondary numbers. This is not what we observe. Light-induced gas phase chlorination at 25 ºC gives 45% 1-chloropropane and 55% 2-chloropropane.

CH_3-CH_2-CH_3 + Cl_2 → 45% CH_3-CH_2-CH_2Cl + 55% CH_3-$CHCl$-CH_3

The results of bromination (light-induced at 25 ºC) are even more surprising, with 2-bromopropane accounting for 97% of the mono-bromo product.

CH_3-CH_2-CH_3 + Br_2 → 3% CH_3-CH_2-CH_2Br + 97% CH_3-$CHBr$-CH_3

These results suggest strongly that 2º-hydrogens are inherently more reactive than 1º-hydrogens, by a factor of about 3:1. Further experiments showed that 3º-hydrogens are even more reactive toward halogen atoms. Thus, light-induced chlorination of 2-methylpropane gave predominantly (65%) 2-chloro-2-methylpropane, the substitution product of the sole 3º-hydrogen, despite the presence of nine 1º-hydrogens in the molecule.

$(CH_3)_3CH$ + Cl_2 → 65% $(CH_3)_3CCl$ + 35% $(CH_3)_2CHCH_2Cl$

It should be clear from a review of the two steps that make up the free radical chain reaction for halogenation that the first step (hydrogen abstraction) is the **product determining step**. Once a carbon radical is formed, subsequent bonding to a halogen atom (in the second step) can only occur at the radical site. Consequently, an understanding of the preference for substitution at 2º and 3º-carbon atoms must come from an analysis of this first step.

First Step: **$R_3CH + X\cdot \rightarrow R_3C\cdot + H\text{-}X$**

Second Step: **$R_3C\cdot + X_2 \rightarrow R_3CX + X\cdot$**

Since the H-X product is common to all possible reactions, differences in reactivity can only be attributed to differences in C-H bond dissociation energies. In our previous discussion of bond energy, we assumed average values for all bonds of a given kind, but now we see that this is not strictly true. In the case of

carbon-hydrogen bonds, there are significant differences, and the specific dissociation energies (energy required to break a bond homolytically) for various kinds of C-H bonds have been measured.

The difference in C-H bond dissociation energy reported for primary (1º), secondary (2º) and tertiary (3º) sites agrees with the halogenation observations, in that we would expect weaker bonds to be broken more easily than are strong bonds. By this reasoning we would expect benzylic and allylic sites to be exceptionally reactive in free radical halogenation, as experiments have shown. The methyl group of toluene, $C_6H_5CH_3$, is readily chlorinated or brominated in the presence of free radical initiators (usually peroxides), and ethylbenzene is similarly chlorinated at the benzylic location exclusively. The hydrogens bonded to the aromatic ring (referred to as phenyl hydrogens above) have relatively high bond dissociation energies and are not substituted.

$$\mathbf{C_6H_5CH_2CH_3 + Cl_2 \rightarrow C_6H_5CHClCH_3 \quad + \quad HCl}$$

Chlorination versus Bromination

A Free Radical Substitution Reaction

This page gives you the facts and a simple, uncluttered mechanism for the free radical substitution reaction between methane and bromine. This reaction between methane and bromine happens in the presence of ultraviolet light - typically sunlight. This is a good example of a photochemical reaction - a reaction brought about by light.

$$\mathbf{CH_4 + Br_2 \rightarrow CH_3Br + HBr}$$

The organic product is bromomethane. One of the hydrogen atoms in the methane has been replaced by a bromine atom, so this is a substitution reaction. However, the reaction doesn't stop there, and all the hydrogens in the methane can in turn be replaced by bromine atoms.

The mechanism

The mechanism involves a chain reaction. During a chain reaction, for every reactive species you start off with, a new one is generated at the end - and this keeps the process going. The over-all process is known as free radical substitution, or as a free radical chain reaction.

- **Chain initiation:** The chain is initiated (started) by UV light breaking a bromine molecule into free radicals.
-

$$Br_2 \longrightarrow 2Br^{\bullet}$$

- **Chain propagation reactions:** These are the reactions which keep the chain going.
-

$$\mathbf{CH_4 + Br^{\bullet} \longrightarrow CH_3^{\bullet} + HBr}$$

$$\mathbf{CH_3^{\bullet} + Br2 \longrightarrow CH_3Br + Br^{\bullet}}$$

- **Chain termination reactions:** These are reactions which remove free radicals from the system without replacing them by new ones.
-

$$\mathbf{2Br^{\bullet} \longrightarrow Br_2}$$

$$CH_3^{\bullet} + Br^{\bullet} \longrightarrow CH_3Br$$

$$CH_3^{\bullet} + CH_3^{\bullet} \longrightarrow CH_3CH_3$$

Selectivity

When alkanes larger than ethane are halogenated, isomeric products are formed. Thus, chlorination of propane gives both 1-chloropropane and 2-chloropropane as mono-chlorinated products. Four constitutionally isomeric dichlorinated products are possible, and **five constitutional isomers** exist for the trichlorinated propanes. Can you write structural formulas for the four dichlorinated isomers?

$$CH_3CH_2CH_3 + 2Cl_2 \rightarrow \text{Four } C_3H_6Cl_2 \text{ isomers} + 2HCl$$

The halogenation of propane discloses an interesting feature of these reactions. **All the hydrogens in a complex alkane do not exhibit equal reactivity**. For example, propane has eight hydrogens, six of them being structurally equivalent **primary**, and the other two being **secondary**. If all these hydrogen atoms were equally reactive, halogenation should give a 3:1 ratio of 1-halopropane to 2-halopropane mono-halogenated products, reflecting the primary/secondary numbers. This is not what we observe. Light-induced gas phase chlorination at 25 ºC gives 45% 1-chloropropane and 55% 2-chloropropane.

$$CH_3\text{-}CH_2\text{-}CH_3 + Cl_2 \rightarrow 45\%\ CH_3\text{-}CH_2\text{-}CH_2Cl + 55\%\ CH_3\text{-}CHCl\text{-}CH_3$$

The results of bromination (light-induced at 25 ºC) are even more surprising, with 2-bromopropane accounting for 97% of the mono-bromo product.

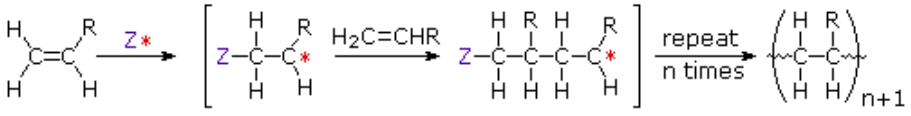
$$CH_3\text{-}CH_2\text{-}CH_3 + Br_2 \rightarrow 3\%\ CH_3\text{-}CH_2\text{-}CH_2Br + 97\%\ CH_3\text{-}CHBr\text{-}CH_3$$

These results suggest strongly that 2º-hydrogens are inherently more reactive than 1º-hydrogens, by a factor of about 3:1. Further experiments showed that 3º-hydrogens are even more reactive toward halogen atoms. Thus, light-induced chlorination of 2-methylpropane gave predominantly (65%) 2-chloro-2-methylpropane, the substitution product of the sole 3º-hydrogen, despite the presence of nine 1º-hydrogens in the molecule.

$$(CH_3)_3CH + Cl_2 \rightarrow 65\%\ (CH_3)_3CCl + 35\%\ (CH_3)_2CHCH_2Cl$$

Free Radical Polymerization

All the monomers from which addition polymers are made are alkenes or functionally substituted alkenes. 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.



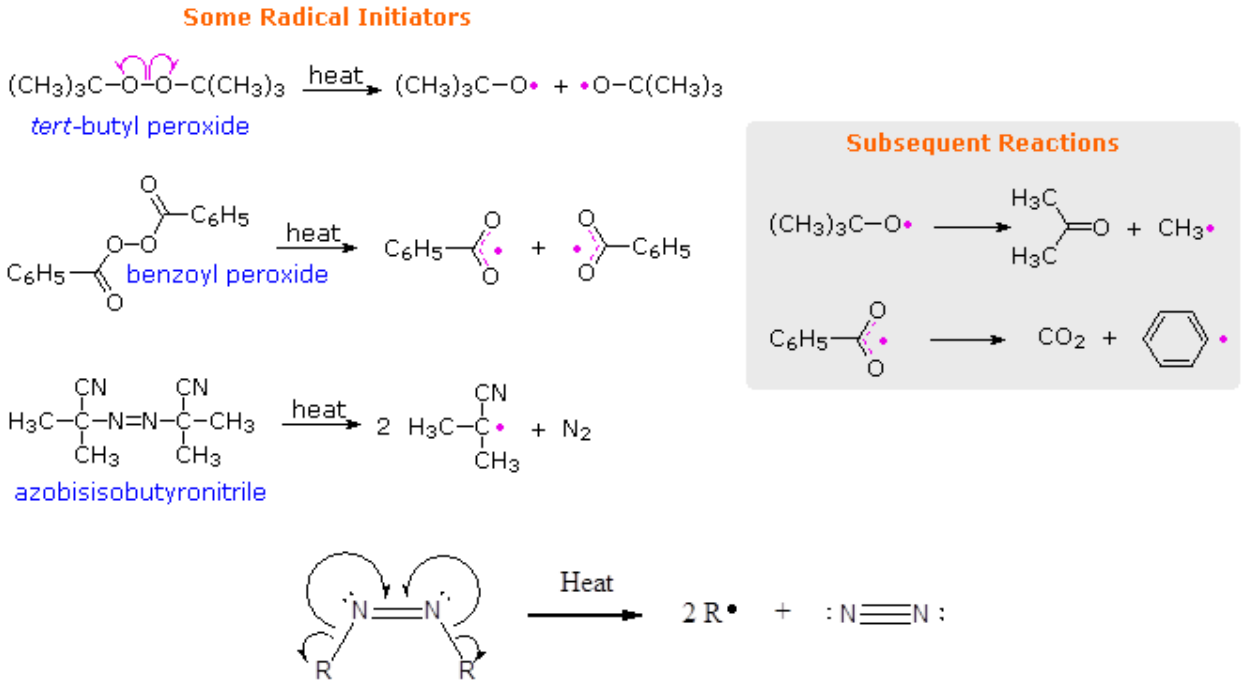
Z* is an initiating species * may be a radical, a cation or an anion

It is useful to distinguish four polymerization procedures fitting this general description.

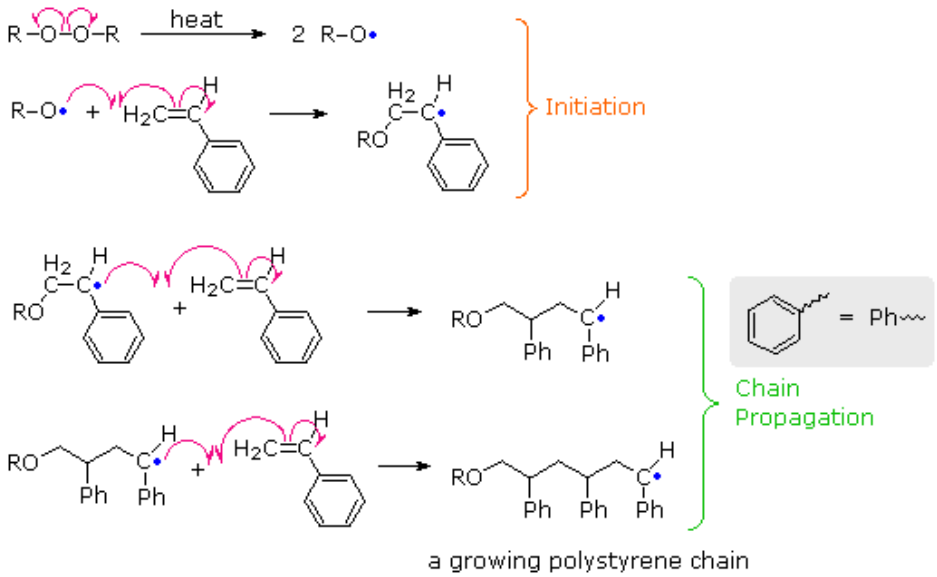
1. Radical Polymerization: The initiator is a radical, and the propagating site of reactivity (*) is a carbon radical.
2. Cationic Polymerization: The initiator is an acid, and the propagating site of reactivity (*) is a carbocation.
3. Anionic Polymerization: The initiator is a nucleophile, and the propagating site of reactivity (*) is a carbanion.
4. 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

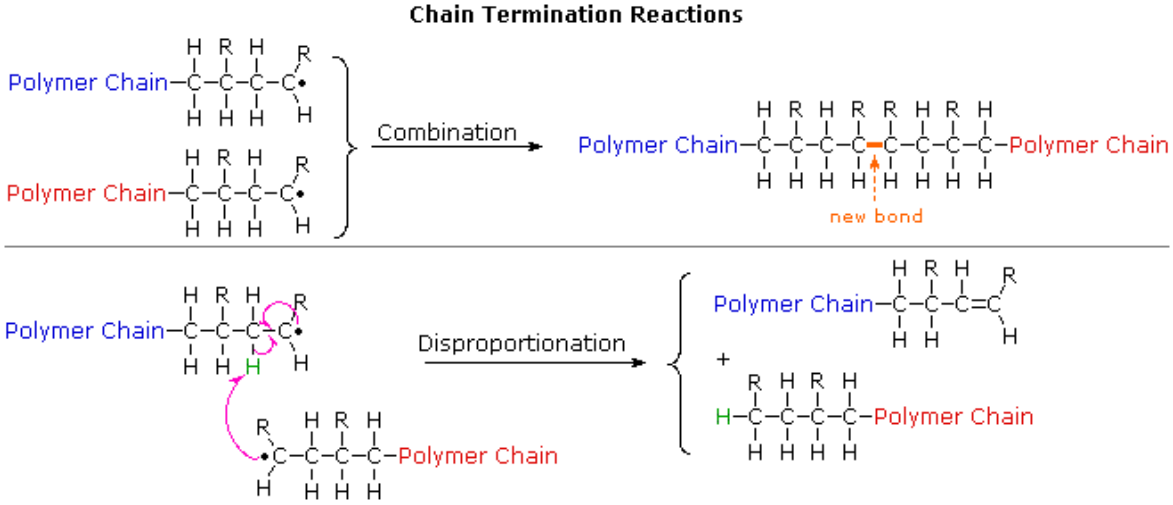
Virtually all of the monomers described above are subject to radical polymerization. Since this can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization 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.

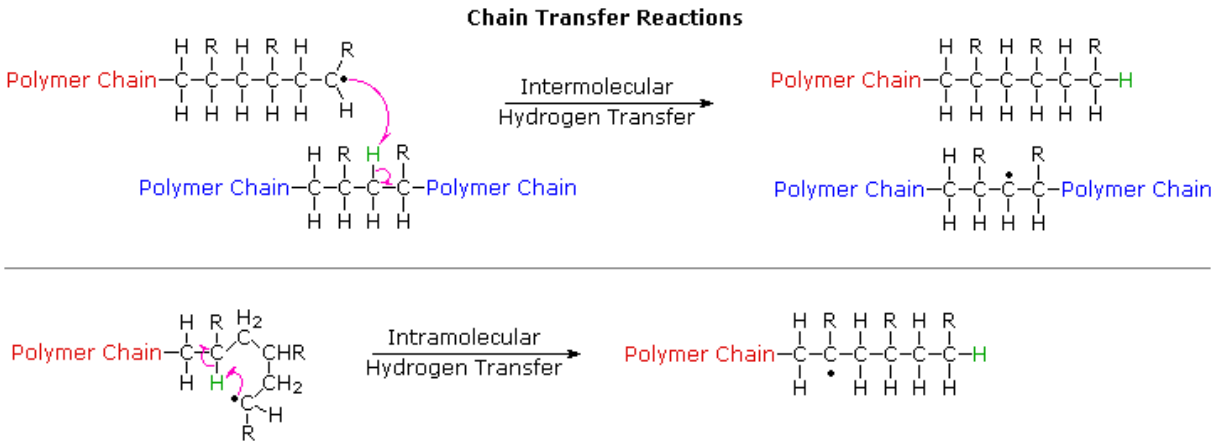


In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination 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.

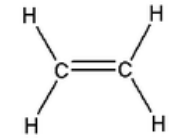
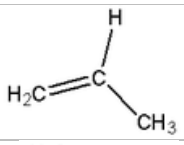
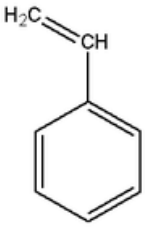
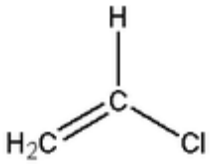
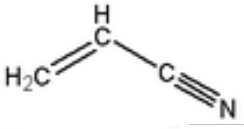
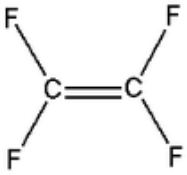


The relative importance of these terminations varies with the nature of the monomer undergoing polymerization. For acrylonitrile and styrene combination is the major process. However, methyl methacrylate and vinyl acetate are terminated chiefly by disproportionation.

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 1°-radical at the end of a growing chain is converted to a more stable 2°-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.

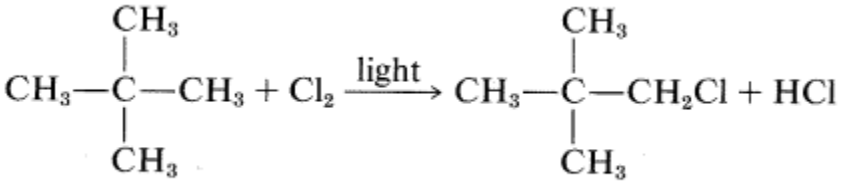
Monomer	Nonsystematic Name	Polymer	Some Typical Uses
	Ethylene	Polyethylene	Film for packaging and bags, toys, bottles, coatings
	Propylene	Polypropylene	Milk cartons, rope, outdoor carpeting
	Styrene	Polystyrene	Transparent containers, plastic glasses, refrigerators, styrofoam
	Vinyl chloride	Polyvinyl chloride, PVC	Pipe and tubing, raincoats, curtains, phonograph records, luggage, floor tiles
	Acrylonitrile	Polyacrylonitrile (Orlon, Acrilan)	Textiles, ruga
	Tetrafluoroethylene	Teflon	Nonstick pan coatings, bearings, gaskets

TOPIC 10: NUCLEOPHILIC SUBSTITION

Substitution reactions involve the replacement of one atom or group (X) by another (Y):

$$RX+Y \rightarrow RY+X$$

We already have described one very important type of substitution reaction, the halogenation of alkanes, in which a hydrogen atom is replaced by a halogen atom (X=H, Y=halogen). The chlorination of 2,2-dimethylpropane is an example:



2,2-dimethylpropane — 1-chloro-2,2-dimethylpropane

Reactions of this type proceed by radical-chain mechanisms in which the bonds are broken and formed by atoms or radicals as reactive intermediates. This mode of bond-breaking, in which one electron goes with R and the other with X, is called **homolytic** bond cleavage:

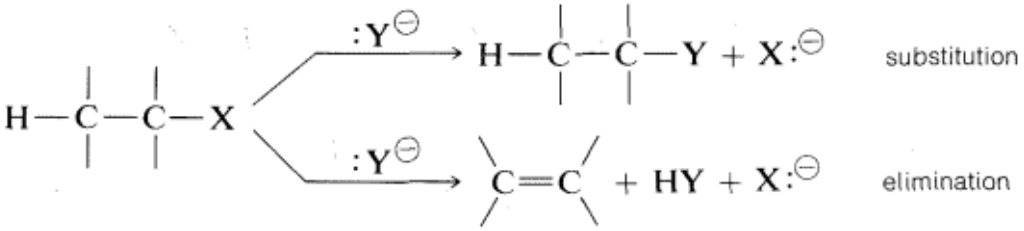
a *homolytic* substitution reaction

There are a large number of reactions, usually occurring in solution, that do *not* involve atoms or radicals but rather involve ions. They occur by **heterolytic** cleavage as opposed to homolytic cleavage of electron-pair bonds. In heterolytic bond cleavage, the electron pair can be considered to go with one or the other of the groups R and X when the bond is broken. As one example, Y is a group such that it has an unshared electron pair and also is a negative ion. A heterolytic substitution reaction in which the R:X bonding pair goes with X would lead to RY and: X⊖,

a *heterolytic* substitution reaction

A specific substitution reaction of this type is that of chloromethane with hydroxide ion to form methanol:

In this chapter, we shall discuss substitution reactions that proceed by ionic or polar mechanisms in which the bonds cleave heterolytically. We also will discuss the mechanistically related **elimination** reactions that result in the formation of carbon-carbon multiple bonds:

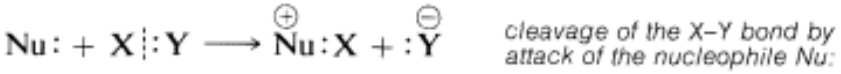


These reactions often are influenced profoundly by seemingly minor variations in the structure of the reactants, in the solvent, or in the temperature. It is our purpose to show how these reactions can be understood and how they can be used to prepare other useful organic compounds. But first it will be helpful to introduce the concepts of **nucleophilic** and **electrophilic** reagents, and to consider the ΔH values for heterolytic bond breaking.

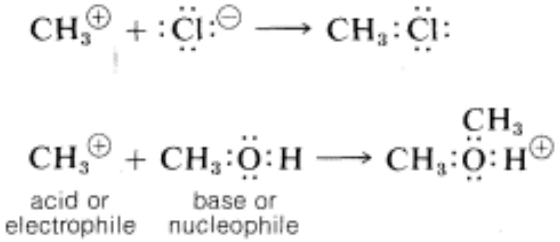
Classification of Reagents as Electrophiles and Nucleophiles: Acids and Bases

To understand ionic reactions, we need to be able to recognize whether a particular reagent will act to *acquire an electron pair* or to *donate an electron pair*. Reagents that acquire an electron pair in chemical reactions are said to be **electrophilic** ("electron-loving"). We can picture this in a general way as a heterolytic bond breaking of compound *X*:*Y* by an electrophile *E* such that *E* becomes bonded to *Y* by the electron pair of the *XY* bond. Thus:

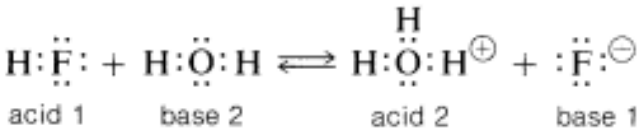
Reagents that donate an electron pair in chemical reactions are said to e **nucleophilic** ("nucleus loving"). Thus the *X*:*Y* bond also can be considered to be broken by the nucleophile *Nu*:, which donates its electron pair to *X* while *Y* leaves as *Y*:⊖ with the electrons of the *X*:*Y* bond:



Thus, by definition, electrophiles are electron-pair acceptors and nucleophiles are electron-pair donors. These definitions correspond closely to definitions used in the generalized theory of acids and bases proposed by G. N. Lewis (1923). According to Lewis, an acid is any substance that can accept an electron pair, and a base is any substance that can donated an electron pair to form a covalent bond. Therefore, acids must be electrophiles and bases must be nucleophiles. For example, the methyl cation may be regarded as a **Lewis acid**, or an electrophile, because it *accepts* electrons from reagents such as chloride ion or methanol. In turn, because chloride ion and methanol donate electrons to the methyl cation they are classified as **Lewis bases**, or nucleophiles:

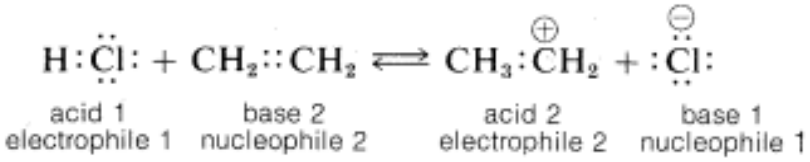


The generalized Lewis concept of acids and bases also includes common proton-transfer reactions. Thus, water acts as a base because one of the electron pairs on oxygen can abstract a proton from a reagent such as hydrogen fluoride:



Alternatively, the hydronium ion ($H_3O^{\oplus}$) is an acid because it can accept electrons from another reagent (e.g., fluoride ion) by donating a proton.

A proton donor can be classified as an electrophile and a proton acceptor as a nucleophile. For example, hydrogen chloride can transfer a proton to ethene to form the ethyl cation. Therefore, hydrogen chloride functions as the electrophile, or acid, and ethene functions as the nucleophile, or base:



What then is the difference between an acid and an electrophile, or between a base and nucleophile? No great difference until we try to use the terms in a *quantitative* sense. For example, if we refer to acid strength, or acidity, this means the position of *equilibrium* in an acid-base reaction. The equilibrium constant *Ka* for the dissociation of an acid *HA*, or the *pKa*, is a quantitative measure of acid strength. The larger the value of *Ka* or the smaller the *pKa*, the stronger the acid.

A summary of the relationships between *Ka* and *pKa* follow, where the quantities in brackets are concentrations:

$$HA + H_2O \rightleftharpoons H_3O^{\oplus} + A^{\ominus}$$

$$K_a = \frac{[H_3O^{\oplus}][A^{\ominus}]}{[HA]}$$

(Notice that the concentration of water does not appear in this expression; it is the solvent and its concentration is large and constant.)

or

$$-\log K_a = -\log [H_3O^{\oplus}] + \log \frac{[HA]}{[A^{\ominus}]}$$

By definition, −log *Ka* =*pKa* and −log[*H*3*O*⊕]=*pH*; hence:

$$pK_a = pH + \log \frac{[HA]}{[A^{\ominus}]}$$

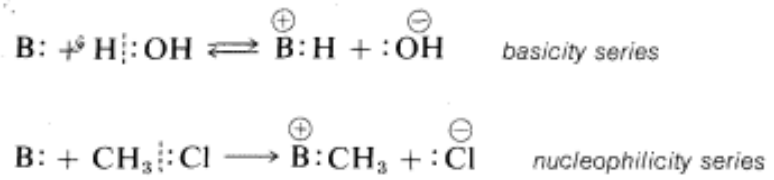
or

$$pK_a = pH + \log \frac{[\text{undissociated acid}]}{[\text{anion of the acid}]}$$

(This sometimes is referred to as the Henderson-Hasselbalch equation.)

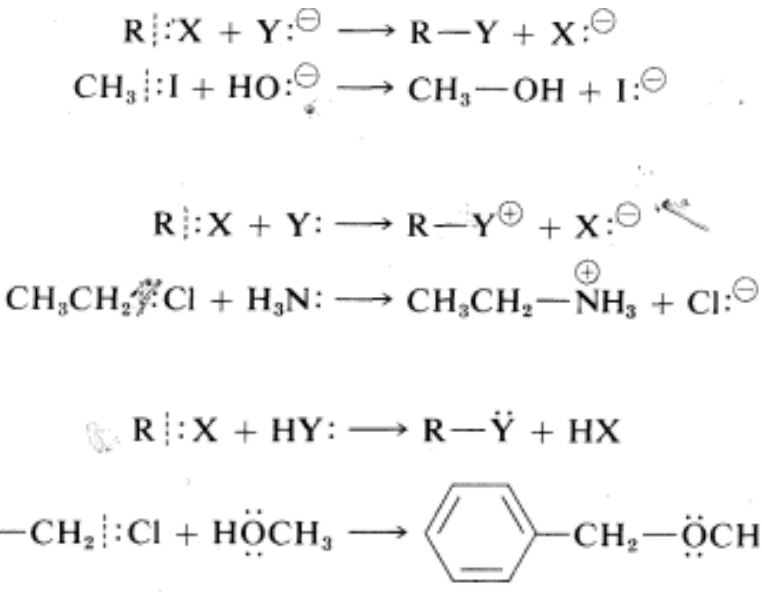
However, in referring to the strength of reagents as electrophiles or nucleophiles we usually are not referring to chemical equilibria but to *reaction rates*. A good nucleophile is a reagent that reacts rapidly with a

particular electrophile. In contrast, a poor nucleophile reacts only slowly with the same electrophile. Consequently, it should not then be taken for granted that there is a parallel between the acidity or basicity of a reagent and its reactivity as an electrophile or nucleophile. For instance, it is incorrect to assume that the strengths of a series of bases, *B*:, in aqueous solution will *necessarily* parallel their nucleophilicities toward a carbon electrophile, such as methyl chloride:

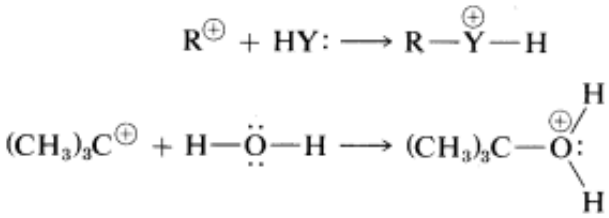


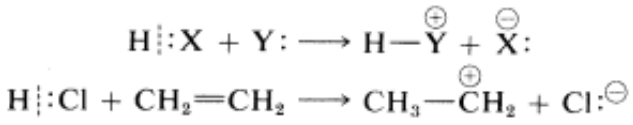
The important difference is that the *strength* of the base, *B*:, is determined in an *equilibrium* reaction, whereas its *nucleophilicity* is determined by its reactivity in slow substitution reactions. To put it another way, the base strength corresponds to the overall energy change of a reaction while the nucleophilicity corresponds to the activation energy of a reaction. Even so, it turns out that most strong bases are good nucleophiles and that most strong proton acids are good electrophiles. We will see that the converse may not be true. Good nucleophiles are not always strong bases [examples are $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, and $(CH_3)_2S$] and good electrophiles are not always strong acids by either the Bronsted-Lowry or Lewis definitions (examples are HOBr, Br_2, Cl_2, I_2).

In what follows we will be concerned with the rates of ionic reactions under *nonequilibrium* conditions. We shall use the term *nucleophilic* repeatedly and we want you to understand that a nucleophile is any neutral or charged reagent that supplies a pair of electrons, either bonding or nonbonding, to form a new covalent bond. In substitution reactions, the nucleophile usually is an anion, *Y*:$^{\ominus}$, or a neutral molecule, *Y*: or *HY*:. The operation of each of these is illustrated in the following equations for reactions of the general compound *RX* and some specific examples:



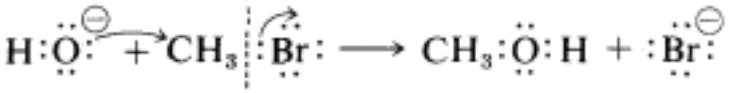
An *electrophile* is any neutral or charged reagent that accepts an electron pair (from a nucleophile) to form a new bond. In the preceding substitution reactions, the electrophile is *RX*. The electrophile in other reactions may be a carbon cation or a proton donor, as in the following examples:





General Considerations of Substitution Reactions

We now wish to discuss displacements by *nucleophilic* reagents (*Y*:) on alkyl derivatives (*RX*). These are *ionic* or *polar* reactions involving attack by a nucleophile at *carbon*. A typical example is the reaction of hydroxide ion with bromomethane to displace bromide ion:



The electron pair of the *C−O* bond can be regarded as having been donated by the hydroxide ion, while the electron pair of the *C−Br* bond departs with the leaving bromide ion. The name for this type of reaction is abbreviated S_N, S for substitution and N for nucleophilic.

Reactions of this type are very useful. They can lead to compounds in which the new bond to carbon in the alkyl group, *R* is to chlorine, bromine, iodine, oxygen, sulfur, carbon, nitrogen, or phosphorus, depending on the nature of the nucleophile used.

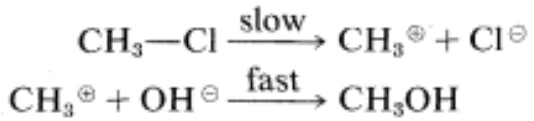
Nucleophilic substitutions are especially important for alkyl halides, but they should not be considered to be confined to alkyl halides. Many other alkyl derivatives such as alcohols, ethers, and esters, also can undergo S_N reactions if conditions are appropriate. The scope of S_N reactions is so broad that it is impossible to include all the various alkyl compounds and nucleophiles that react in this manner. Rather we shall approach the subject here through consideration of the mechanisms of S_N reactions, and then develop the scope of the reactions in later chapters.

The mechanism of an S_N reaction and the reactivity of a given alkyl compound *RX* toward a nucleophile *Y* depend upon the nature of *R*, *X*, and *Y*, and upon the nature of the solvent. For an S_N reaction to occur at a reasonable rate, it is very important to select a solvent that will dissolve both the alkyl compound and the nucleophilic reagent; considerable assistance may be required from both the solvent and the nucleophile to break what usually is a slightly polar *C−X* bond. However, the solvents that best dissolve slightly polar organic compounds seldom will dissolve the common, rather highly polar, nucleophilic agents such as *NaBr*, *NaCN*, and H_2O. In practice, relatively polar solvents, or solvent mixtures, such as 2-propanone (acetone), aqueous 2-propanone, ethanol, aqueous 1,4-dioxacyclohexane (dioxane), and so on, provide the best compromise for reactions between alkyl compounds and salt-like nucleophilic reagents.

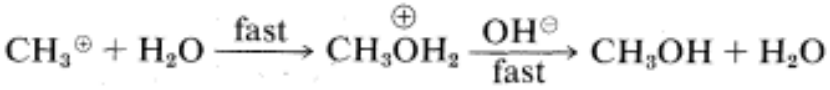
Mechanisms of Nucleophilic Substitution Reactions

Two simple mechanisms can be written for the reaction of chloromethane with hydroxide ion in aqueous solution that differ in the *timing* of bond breaking relative to bond making. In the first mechanism, *A*, the overall reaction is the result of two steps, the first of which involves a *slow* dissociation of chloromethane to solvated methyl **carbocation** and solvated chloride ion. The second step involves a *fast* reaction between the carbocation and hydroxide ion (or water) to yield methanol.

Mechanism A:

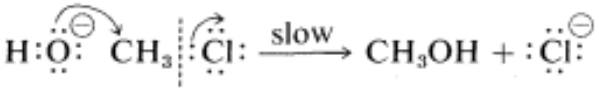


or



In the second mechanism, *B*, the reaction proceeds in a single step. Attack of hydroxide ion at carbon occurs simultaneously with the loss of chloride ion; that is, the carbon-oxygen bond is formed as the carbon-chlorine bond is broken:

Mechanism B:



Both of these mechanisms are important in the displacement reactions of alkyl compounds, although chloromethane appears to react *only* by Mechanism *B*. Now we will discuss the criteria for distinguishing between the concerted and stepwise mechanisms.

Kinetics of Substitution Mechanisms

Of the two mechanisms, *A* requires that the reaction rate be determined solely by the rate of the first step. This means that the rate at which methanol is formed (measured in moles per unit volume per unit time) will depend on the chloromethane concentration, but *not* on the hydroxide ion concentration, because hydroxide ion is not utilized except in a *fast secondary* reaction. In contrast, Mechanism *B* requires the rate to depend on the concentrations of both reagents because the slow step involves collisions between hydroxide ions and chloromethane molecules.

$$v = k_A[CH_3Cl] \qquad \text{(Equation 10.3.1)}$$

$$v = k_B[CH_3Cl][OH^-] \qquad \text{(Equation 10.3.2)}$$

More precisely, the reaction rate (v) may be expressed in terms of Equation 10.3.1 for Mechanism *A* and Equation 10.3.2 for Mechanism *B*.

Customarily, v is expressed in moles of product formed per liter of solution per unit of time (most frequently in seconds). The concentration terms $[CH_3Cl]$ and $[OH^\ominus]$ are then in units of moles per liter, and the proportionality constant k (called the specific rate constant) has the units of sec^{-1} for Mechanism *A* and $mol^{-1} \times L \times sec^{-1}$ for Mechanism *B*.

It is important to recognize the difference between *the order of a reaction with respect to a specific reactant* and the *overall order of a reaction*. The order of a reaction with respect to a *particular* reactant is the power to which the concentration of *that reactant* must be raised to have direct proportionality between concentration and reaction rate. According to Equation 10.3.2 the rate of the chloromethane-hydroxide ion reaction is *first order* with respect to chloromethane and *first order* with respect to hydroxide ion. In Equation 10.3.1 the rate is *first order* with respect to chloromethane and *zero order* with respect to hydroxide ion because $[OH^{\ominus}]^0=1$. The *overall order* of reaction is the *sum* of the orders of the respective reactants. Thus Equations 10.3.1 and 10.3.2 express the rates of overall *first-order* and *second-order* reactions, respectively.

We can use the overall reaction order to distinguish between the two possible mechanisms, *A* and *B*. Experimentally, the rate of formation of methanol is found to be proportional to the concentrations *both* of chloromethane and of hydroxide ion. Therefore, the reaction rate is second order overall and is expressed correctly by Equation 10.3.2. This means that the mechanism of the reaction is the single-step process *B*. Such reactions generally are classified as **bimolecular nucleophilic substitutions**, often designated S_N2, S for substitution, N for nucleophilic, and 2 for bimolecular, because there are *two* reactant molecules in the transition state. To summarize: For an SN2 reaction,

rate: $v=k[RX][Y]$

mechanism: $Y: + R{-}X \longrightarrow Y{-}R + :X^{\ominus}$ (bimolecular transition state)

The stepwise Mechanism *A* is a **unimolecular nucleophilic substitution** and accordingly is designated S_N1. The numeral 1 (or 2) used in these designations does *not* refer to the kinetic order of the reaction, but refers to the number of molecules (not including solvent molecules) that make up the transition state. Thus, for S_N1:

rate: $v=k[RX]$

- **mechanism:** $R{-}X \overset{\text{slow}}{\rightleftharpoons} R^{\oplus} + :X^{\ominus}$ (unimolecular transition state)

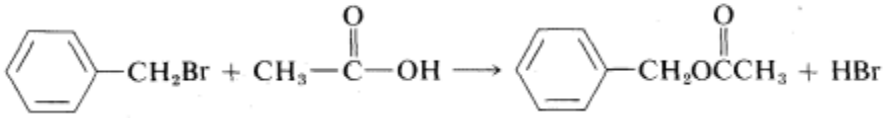
$R^{\oplus} + :Y^{\ominus} \longrightarrow R{-}Y$

or $R^{\oplus} + H{-}\ddot{Y} \longrightarrow R{-}Y + H^{\oplus}$

Solvolysis

Many SN reactions are carried out using the solvent as the nucleophilic agent. They are called solvolysis reactions and involve solvents such as water, ethanol, ethanoic acid, and methanoic acid. Two examples are:

$$(CH_3)_3CCl + H_2O \xrightarrow{\text{aqueous 2-propanone}} (CH_3)_3COH + HCl$$



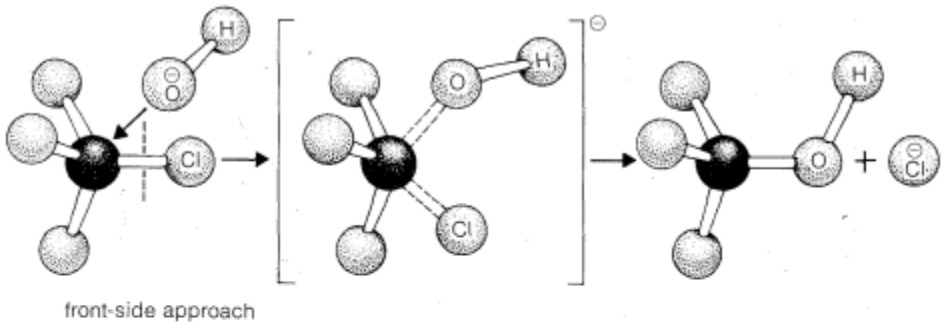
In these examples, solvolysis is necessarily a first-order reaction, because normally the solvent is in such great excess that its concentration does not change appreciably during reaction, and hence its contribution to

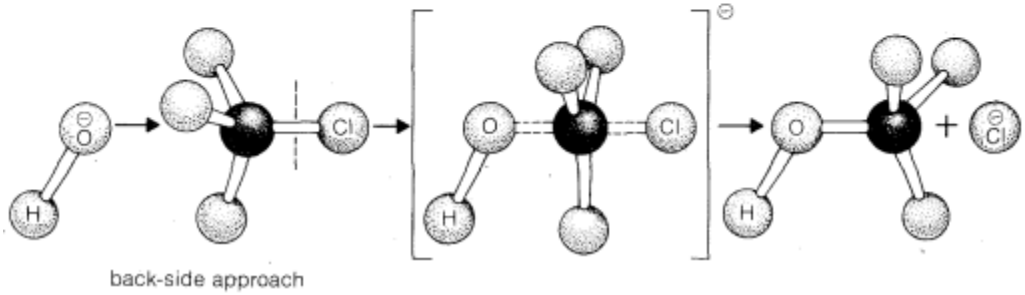
the rate does not change. However, that the *overall* rate is first order does not mean the reaction necessarily proceeds by an S_N1 mechanism, particularly in solvents such as water, alcohols, or amines, which are reasonably good nucleophilic agents. The solvent can act as the displacing agent in an S_N2 reaction.

To distinguish between S_N1 and S_N2 mechanisms *of solvolysis* requires other criteria, notably stereochemistry, and the effect of added nucleophiles on the rate and nature of the reaction products. For example, it often is possible to distinguish between S_N1 and S_N2 solvolysis by adding to the reaction mixture a relatively small concentration of a substance that is expected to be a more powerful nucleophile than the solvent. If the reaction is strictly S_N1, the rate at which *RX* disappears should remain essentially unchanged because it reacts only as fast as $R^{\oplus}$ forms, and the rate of this step is not changed by addition of the nucleophile, even if the nucleophile reacts with $R^{\oplus}$. However, if the reaction is S_N2, the rate of disappearance of *RX* should *increase* because *RX* reacts with the nucleophile in an S_N2 reaction and now the rate depends on both the nature and the concentration of the nucleophile.

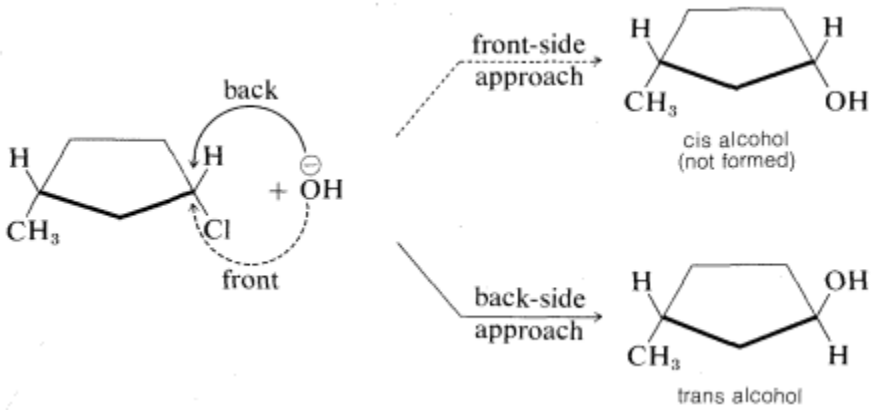
Stereochemistry of S_N2 Reactions

There are two simple ways in which the S_N2 reaction of methyl chloride could occur with hydroxide ion. These differ in the direction of approach of the reagents. The hydroxide ion could attack chloromethane at the **front side** of the carbon where the chlorine is attached or, alternatively, the hydroxide ion could approach the carbon on the side opposite from the chlorine in what is called the **back-side** approach. In either case, the making of the *C−O* bond is essentially *simultaneous* with the breaking of the *C−Cl* bond. The difference is that for the back-side mechanism the carbon and the attached hydrogens become planar in the transition state.

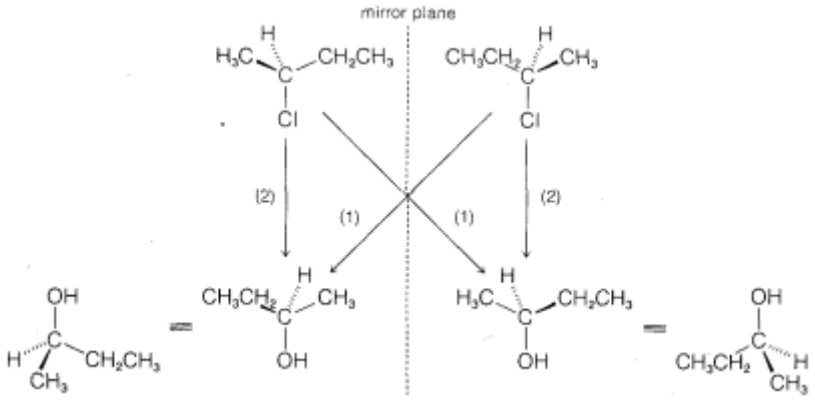




The stereochemical consequences of front- and back-side displacements are different. With cyclic compounds, the two types of displacement lead to *different* products. For example, an S_N2 reaction between *cis*-3-methylcyclopentyl chloride and hydroxide ion would give the cis alcohol by front-side approach but the trans alcohol by back-side approach. The actual product is the trans alcohol, from which we know that reaction occurs by back-side displacement:



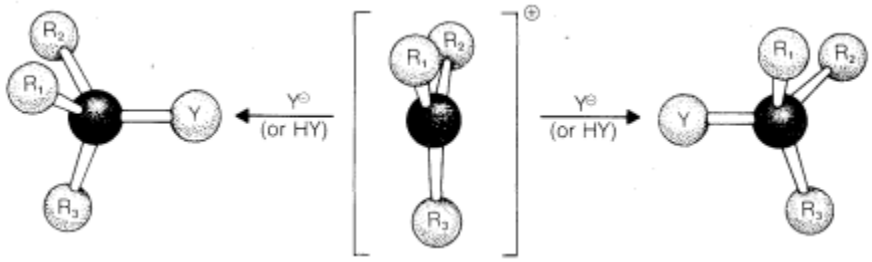
For open-chain compounds, back-side displacement has been established conclusively with the aid of stereoisomers, particularly those with chiral atoms. Inspection of the enantiomers of 2-chlorobutane demonstrates that *front-side* displacement of chloride by hydroxide ion will give an enantiomer of 2-butanol of the *same* configuration as the original chloride, whereas back-side displacement will give the alcohol of the *opposite*, or *inverted*, configuration.



Experiments using either of the two enantiomers show that hydroxide ion attacks 2-chlorobutane exclusively by back-side displacement to give 2-butanol with the inverted configuration. Similar studies of a wide variety of displacements have established that S_N2 reactions invariably proceed with inversion of configuration via back-side attack.

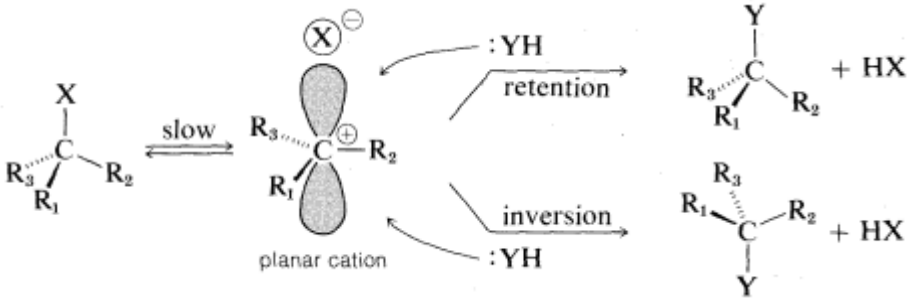
Stereochemistry of S_N1 Reactions

When an S_N1 reaction is carried out starting with a single pure enantiomer, such as *D*-2-chlorobutane, the product usually is a mixture of the enantiomeric substitution products with a slight predominance of that isomer which corresponds to inversion. Theoretically, a carbocation is expected to be most stable in the planar configuration and hence should lead to exactly equal amounts of the two enantiomers, regardless of the chiral configuration of the starting material. However, the extent of configuration change that actually results in an S_N1 reaction depends upon the degree of "shielding" of the front side of the reacting carbon by the leaving group and its associated solvent molecules. If the leaving group does not get away from the carbocation before the product-determining step takes place, there will be some preference for nucleophilic attack at the *back side* of the carbon, which results in a predominance of the product of *inverted* configuration.



Other things being equal, the amount of inversion decreases as the stability of the carbocation intermediate increases, because the more stable the ion the longer is its lifetime, and the more chance it has of getting away from the leaving anion and becoming a relatively "free" ion. The solvent usually has a large influence on the stereochemical results of S_N1 reactions because the stability and lifetime of the carbocations depend upon the nature of the solvent.

An orbital picture of S_N1 ionization leading to a racemic product may be drawn as follows:



It should be clear that *complete* racemization is unlikely to be observed if $X^{\ominus}$ stays in close proximity to the side of the positive carbon that it originally departed from. We can say that $X^{\ominus}$ "shields" the front side, thereby favoring a predominance of inversion. If $X^{\ominus}$ gets far away before :*YH* comes in, then there should be no favoritism for one or the other of the possible substitutions.

If $X^{\ominus}$ and the carbocation, $R^{\oplus}$ stay in close proximity, as is likely to be the case in a solvent that does not promote ionic dissociation, then a more or less "tight" ion pair is formed, $R^{\oplus} \cdots X^{\ominus}$.

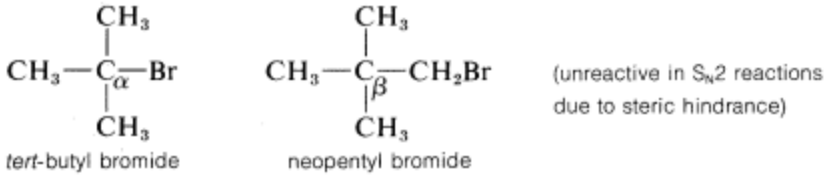
Structural and Solvent Effects in S_N Reactions

We shall consider first the relationship between the structures of alkyl derivatives and their reaction rates toward a given nucleophile. This will be followed by a discussion of the relative reactivities of various nucleophiles toward a given alkyl derivative. Finally, we shall comment in more detail on the role of the solvent in S_N reactions.

Structure of the Alkyl Group, R, in S_N2 Reactions

The rates of S_N2-displacement reactions of simple alkyl derivatives, *RX*, follow the order: *primary R*> *secondary R* $\gg$ *tertiary R*. In practical syntheses involving S_N2 reactions, the primary compounds generally work very well, secondary isomers are fair, and the tertiary isomers are almost completely impractical. Steric hindrance appears to be particularly important in determining S_N2 reaction rates, and the slowness of tertiary halides seems best accounted for by steric hindrance to the back-side approach of an attacking nucleophile by the alkyl groups on the reacting carbon. Pertinent data, which show how alkyl groups affect S_N2 reactivity toward iodide ion, are given in the below. Not only do alkyl groups suppress reactivity when on the same carbon as the leaving group *X*, as in *tert*-butyl bromide, but they also have retarding effects when located one carbon away from the leaving group. This is evident in the data of the following table for 1-bromo-2,2-

dimethylpropane (neopentyl bromide), which is very unreactive in S_N2 reactions. Scale models indicate the retardation to be the result of steric hindrance by the methyl groups located on the adjacent β carbon to the approaching nucleophile:



tert-butyl bromide neopentyl bromide

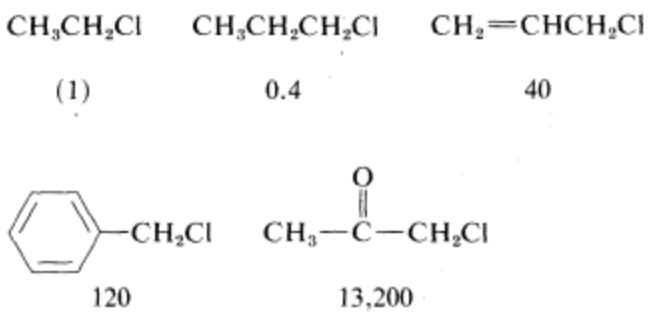
Rates of S_N2 Displacement of Alkyl Bromides with Iodide Ion in 2-Propanone (Acetone) Relative to Ethyl Bromide at 25°

$RBr + I^{\ominus} \longrightarrow RI + Br^{\ominus}$

R: (α substitution)	CH_3-	CH_3CH_2-	$CH_3-CH(CH_3)-$	$CH_3-C(CH_3)_2-$
relative rate:	145	(1)	0.0078	<0.00051

R: (β substitution)	CH_3CH_2-	$CH_3-CH_2-CH_2-$	$CH_3-CH(CH_3)-CH_2-$	$CH_3-C(CH_3)_2-CH_2-$
relative rate:	(1)	0.82	0.036	0.000012

In addition to steric effects, other structural effects of *R* influence the S_N2 reactivity of *RX*. A double bond β to the halogen, as in 2-propenyl, phenylmethyl (benzyl), and 2-oxopropyl chlorides enhances the reactivity of the compounds toward $I^{\ominus}$ in 2-propanone are:



Possible reasons for these high reactivities will be discussed later.

Structure of the Alkyl Group, R, in S_N1 Reactions

The rates of S_N1 reactions of simple alkyl derivatives follow the order: *tertiary R* $\gg$ *secondary R* > *primary R*, which is exactly opposite that of S_N2 reactions. This is evident from the data in following table, which lists the relative rates of hydrolysis of some alkyl bromides; only the secondary and tertiary bromides react at measurable rates, and the tertiary bromide reacts some 10^5 times faster than the secondary bromide.

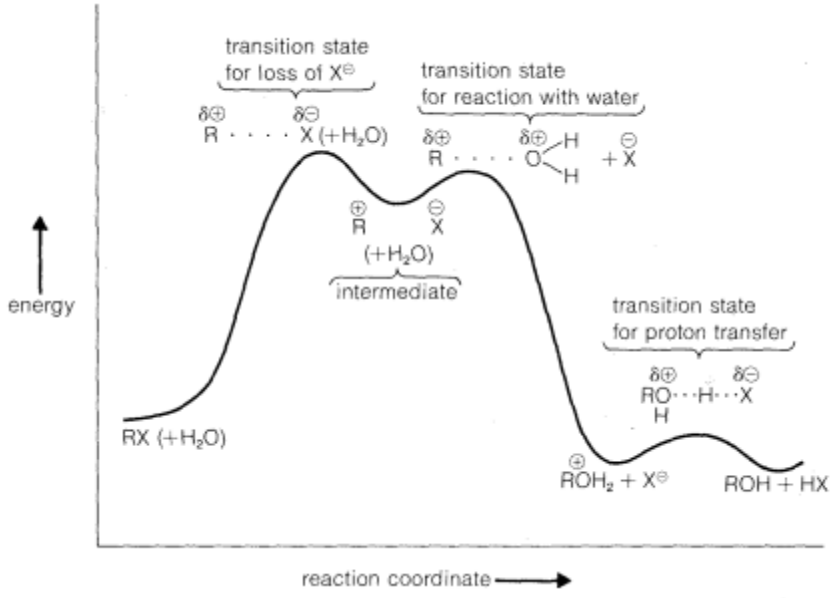
Why do tertiary alkyl compounds ionize so much more rapidly than either secondary or primary compounds? The reason is that tertiary alkyl cations are more *stable* than either secondary or primary cations and therefore are formed more easily. You will appreciate this better by looking at the energy diagram below the table, which shows the profile of energy changes for hydrolysis of an alkyl compound, *RX*, by the S_N1 mechanism.

Rates of Hydrolysis of Alkyl Bromides in Water at 50° Relative to Ethyl Bromide

$$RBr \longrightarrow R^{\oplus} + Br^{\ominus} \xrightarrow{H_2O} ROH + HBr$$

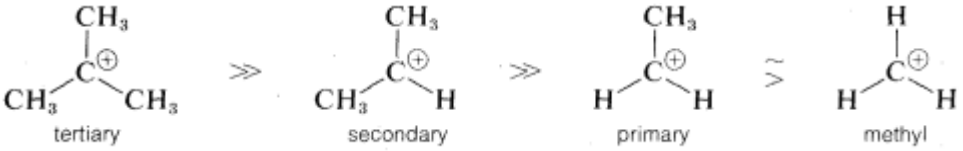
R:	CH_3-	CH_3CH_2-	$CH_3CH(CH_3)-$	$(CH_3)_3C-$
relative rate:	1.05[a]	(1.00)[a]	11.6	1.2×10^6

[a]The reaction mechanism is almost surely S_N2 with solvent acting as the nucleophile because addition of hydroxide ion causes the reaction rate to increase markedly (see Section 8-4B). The relative rate given can be regarded only as an upper limit to the actual S_N1 value, which may be as much as 10^5 times slower.



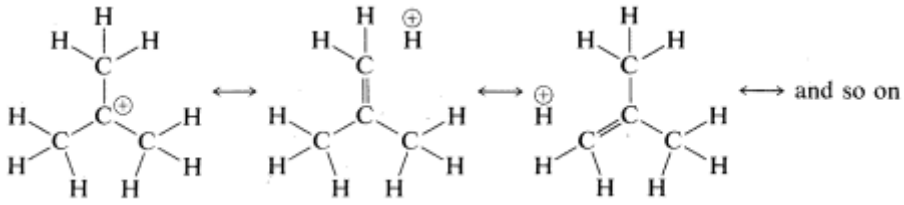
The *rate* of reaction is determined by the ionization step, or by the energy of the transition state relative to that of the reactants. Actually, the energy of the transition state is only slightly higher than the energy of the ionic intermediates $R^{\oplus}X^{\ominus}$. Thus, to a first approximation, we can say that the rate of ionization of *RX* will depend on the energies of the ions formed. Now if we compare the rates for a series of compounds, *RX*, all having the same leaving group, *X*, but differing only in the structure of *R*, their relative rates of ionization will correspond to the relative stabilities of $R^{\oplus}$. The lower energy of $R^{\oplus}$, the faster will be the rate of ionization. Therefore, the experimental results suggest that the sequence of carbocation stabilities is *tertiary* $R^{\oplus} \gg$ *secondary* $R^{\oplus} \gg$ *primary* $R^{\oplus}$.

Just why this sequence is observed is a more difficult question to answer. Notice in the following stability sequence that alkyl cations are more stable the more alkyl groups there are on the positive carbon:

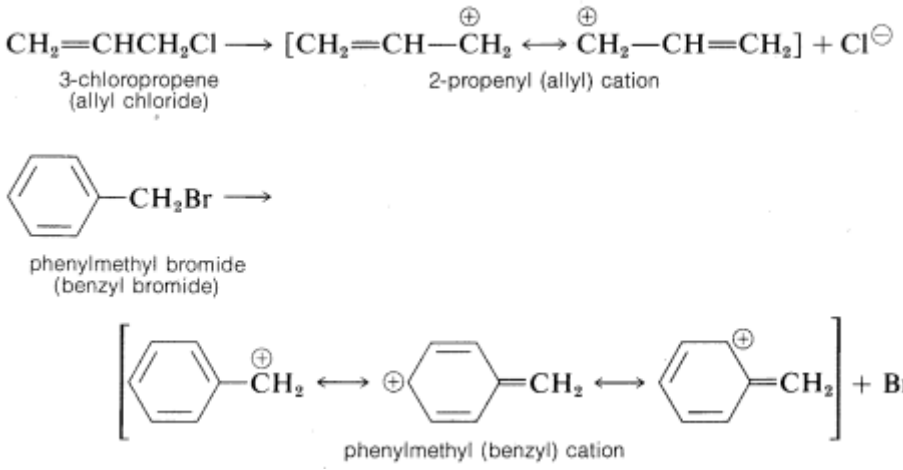


The simplest explanation for why this is so is that alkyl groups are more **polarizable** than hydrogens. In this case, more polarizable means the electrons of the alkyl groups tend to move more readily toward the positive carbon than do those of the hydrogens. Such movements of electrons transfer part of the charge on the cationic carbon to the alkyl groups, thereby spreading the charge over a greater volume. This constitutes *electron delocalization*, which results in enhanced stability.

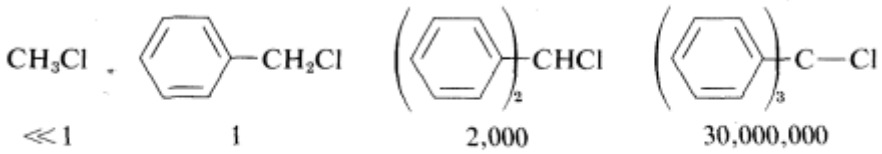
An alternative way of explaining how the cationic charge is spread over the alkyl groups of a tertiary cation, such as the *tert*-butyl cation, is to write the cation as a hybrid of the following structures:



Other organohalogen compounds besides secondary and tertiary alkyl compounds can react by S_N1 mechanisms provided they have the ability to form reasonably stabilized carbon cations. Examples include 2-propenyl (allylic) and phenylmethyl (benzylic) compounds, which on ionization give cations that have delocalized electrons:

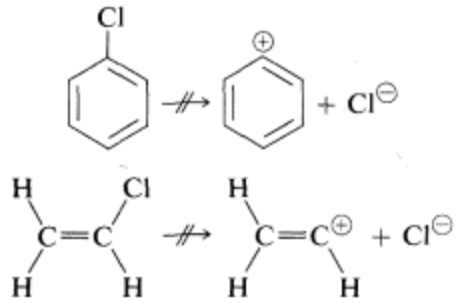


In general, the more stabilized the carbon cation from an alkyl halide, the more reactive the compound will be in S_N1-type reactions. This is especially apparent in the reactivities of compounds with phenyl groups on the reacting carbon. As the number of phenyl groups increases from zero to three, the S_N1 reactivity of the chlorides increases by more than 10^7 because of increasing stabilization of the carbon cation by the phenyl groups:

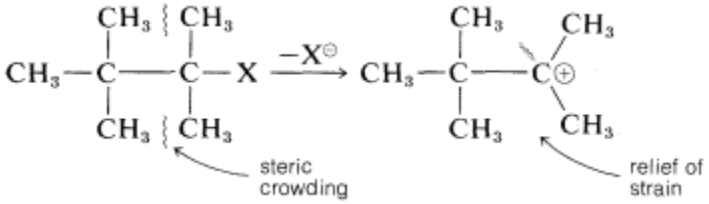


relative rates of solvolysis in 40% ethanol–60% ether solution

In contrast, compounds such as chlorobenzene and chloroethene, in which the halogen is attached directly to a multiply bonded carbon atom, do *not* exhibit S_N1-type reactions. Evidently then, unsaturated carbon cations such as phenyl or ethenyl are appreciably less stable (more difficult to form) than *tert*-alkyl cations:



Steric hindrance is relatively unimportant in S_N1 reactions because the rate is independent of the nucleophile. In fact, steric acceleration is possible in the solvolysis of highly branched alkyl halides through relief of steric compression between the alkyl groups in the halide by formation of a planar cation:



Along with the effect *R* has on the *rate* at which an alkyl compound *RX* reacts by an S_N1 mechanism, the group *R* also affects the nature of the products obtained. The intermediate alkyl cations $R^{\oplus}$ may react in various ways to give products of substitution, elimination, and rearrangement.

The Leaving Group

The reactivity of a given alkyl derivative, *RX*, in either S_N1 or S_N2 reactions, is influenced strongly by the leaving group, *X*. The choice of leaving group is therefore an important consideration in any synthesis involving S_N reactions.

From the foregoing discussion of structural effects in the *R* group on S_N reactivity, particularly in S_N1 reactions, we might expect the *stability* of :*X* as an ion or neutral molecule to play a major role in determining how good or poor *X* is as a leaving group. The stability of :*X* is indeed important - the problem is that there are several factors that contribute to the stability and hence the lability of the leaving group.

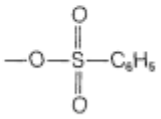
For the purpose of initially identifying good and poor leaving groups, consider development of a practical synthesis of diethyl ether. One route is by way of S_N2 displacement using an ethyl compound, CH_3CH_2X, and ethoxide ion:

$$CH_3CH_2X + CH_3CH_2O^{\ominus} \longrightarrow CH_3CH_2OCH_2CH_3 + X^{\ominus}$$

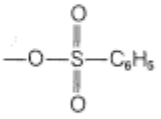
Many CH_3CH_2X compounds have X groups that are quite unsatisfactory in this reaction. They include compounds such as ethane, propane, ethanol, ethyl methyl ether, ethylamine, and ethyl ethanoate; the respective groups, $H^{\ominus}$, $CH_3^{\ominus}$, $HO^{\ominus}$, $CH_3O^{\ominus}$, $NH_2^{\ominus}$, and $CH_3CO_2^{\ominus}$ all can be classified as *very poor* leaving groups. The more reactive ethyl derivatives include the halides, particularly ethyl iodide, and sulfonic acid derivatives; the corresponding anions $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, and $RS(O_2)O^{\ominus}$ therefore are *moderate to good* leaving groups. The table below includes pertinent data for the rates of ether formation from various alkyl compounds and illustrates that the relative abilities of groups to leave are about the same in S_N1 reactions as they are in S_N2 reactions.

Dependence of Rate of S_N Reactions on the Leaving Group, X

S_N2 reaction: $CH_3CH_2X + C_2H_5O^{\ominus} \xrightarrow[25^\circ]{C_2H_5OH} CH_3CH_2OCH_2CH_3 + X^{\ominus}$

X:		—I	—Br	—Cl	—F
relative rate[a]:	5.8	1.9	(1.0)	0.024[b]	–
C—X bond energy (kcal):	–	53	69	82	109

S_N1 reaction: $(CH_3)_2CHX + C_2H_5OH \xrightarrow[50^\circ]{80\%\ C_2H_5OH} (CH_3)_2CHOCH_2CH_3 + HX$

X		—I	—Br	—Cl
relative rate[a]	76.3	–	(1.0)	0.0131

[a]The rates are relative to the bromo compound as 1.0. [b]At 40°.

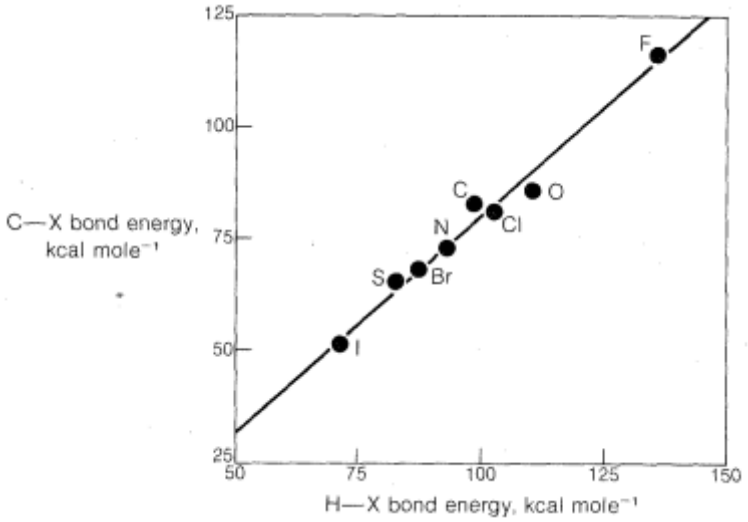
Why are groups such as $I^{\ominus}$ and $RSO_3^{\ominus}$ good leaving groups, whereas others such as $H^{\ominus}$, $HO^{\ominus}$ and $NH_2^{\ominus}$ are poor? The simplest correlation is with the strength of HX as an *acid*. This is very reasonable because the ease of loss of $X^{\ominus}$, as from $(CH_3)C{-}X$ in an S_N1 reaction, would be expected to be related, to some degree at least, to the ease of ionization of $H{-}X$ to $H^{\oplus}$ and $X^{\ominus}$. Therefore, the stronger HX is as an acid, the better X will be as a leaving group. Thus, HF is a relatively weak acid and $F^{\ominus}$ is not a very good leaving group; $H{-}I$ is a very strong acid and $I^{\ominus}$ is a good leaving group. The usual order of reactivity of alkyl halides, $R{-}I > R{-}Br > R{-}Cl > R{-}F$ (when R is the same group throughout), is in accord with the acid strengths of the halogen acids. Similarly, $CF_3CO_2{-}$ is a much better leaving group than $CH_3CO_2{-}$, and we find that trifluoroethanoic acid, CF_3CO_2H is a several thousand times stronger acid than ethanoic acid, CH_3CO_2H. For the same reason, $CF_3SO^{\ominus}$ is a better leaving group than $CH_3XO_3^{\ominus}$.

This correlation can be extended easily to groups that leave as neutral X:. For example, $ROH_2^{\oplus} \rightarrow R^{\oplus} + H_2O$ occurs far more readily than $ROH \rightarrow R^{\oplus} + OH^{\ominus}$ and we know that $H_3O^{\oplus}$ is a stronger acid (or better proton donor) than H_2O.

The relationship between $X^{\ominus}$ as a leaving group and *HX* as an acid is very useful because much information is available on acid strengths. However, it is not a very fundamental explanation unless we can explain why some acids are strong acids and others are weak acids. One factor is the strength of the *H–X* bond, but here we need to remember that the usual bond strengths are for dissociation to radicals or atoms, not ions, and for the gas, not for solutions. If we write the steps relating the bond-dissociation energy to the energy of ionic dissociation in solution, we see that for variations in *X*, in addition to the bond energy, the electron affinity of $X\cdot$, the solvation energy of $X^{\ominus}$, and the solvation energy of *HX*, also will be contributing factors.

$H{-}X(g) \longrightarrow H\cdot(g) + X\cdot(g)$	bond-dissociation energy
$X\cdot(g) + e^{\ominus} \longrightarrow X{:}^{\ominus}(g)$	electron affinity of X·
$H\cdot(g) \longrightarrow H^{\oplus}(g) + e^{\ominus}$	ionization energy of H·
$H{-}X(g) \longrightarrow H^{\oplus}(g) + X{:}^{\ominus}(g)$	energy of ionic dissociation in the gas
$H{-}X(aq) \longrightarrow H{-}X(g)$	− energy of solution of HX
$H^{\oplus}(g) \longrightarrow H^{\oplus}(aq)$	solvation energy of $H^{\oplus}$
$X{:}^{\ominus}(g) \longrightarrow X{:}^{\ominus}(aq)$	solvation energy of $X^{\ominus}$
$H{-}X(aq) \longrightarrow H^{\oplus}(aq) + X{:}^{\ominus}(aq)$	energy of ionic dissociation in water

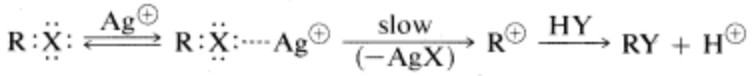
Pauling has shown for the halogen acids that the bond dissociation energy, which is highest for *H–F* and lowest for *H–I*, can be regarded as the most important factor in determining the energy of dissociation in solution. The above energy equations can be written in the same way with *RX* in place of *HX*, and we would expect to reach the same conclusion about the ease of *X* leaving carbon, because *C–X* bond energies are reasonably closely proportional to *H–X* bond energies.



Enhancement of Leaving Group Abilities by Electrophilic Catalysis

In general, a leaving group that leaves as a neutral molecule is a much better leaving group than one that leaves as an anion. Alcohols, *ROH*, are particularly *unreactive* in S_N reactions because $OH^{\ominus}$ is a very poor leaving group. However, if a strong acid is present, the reactivity of the alcohol is enhanced greatly. The acid functions by donating a proton to the oxygen of the alcohol, thereby transforming the hydroxyl function into $ROH_2^{\oplus}$, which has a much better leaving group, H_2O, in place of $OH^{\ominus}$. The S_N reactions of ethers and esters are acid-catalyzed for the same reason. Heavy-metal salts, particularly those of silver, mercury, and copper, catalyze S_N1 reactions of alkyl halides in much the same way that acids catalyze the S_N reactions of alcohols. A heavy-metal ion functions by complexing with the unshared electrons of the halide, thereby making the

leaving group a metal halide rather than a halide ion. This acceleration of the rates of halide reactions is the basis for a qualitative test for alkyl halides with silver nitrate in ethanol solution:



Silver halide precipitates at a rate that depends upon the structure of the alkyl group, *tertiary* > *secondary* > *primary*. Tertiary halides usually react immediately at room temperature, whereas primary halides require heating. That complexes actually are formed between organic halides and silver ion is indicated by an increase in water solubility in the presence of silver ion for those halides that are slow in forming carboncations.

The Nucleophilic Reagent

The nucleophilicty of a particular reagent (:*Y*, :*Y*$^{\ominus}$, or *HY*¨) can be defined as its ability to donate an electron pair to another atom. In fact, the S_N2 reactivity of a reagent toward a methyl derivative can be taken to measure its nucleophilicity toward carbon. The relative reaction rates of some nucleophiles toward methyl bromide are listed in order of increasing nucleophilicity in the table below, together with their basicities as measured by K_b. Important generalizations can be made from these data provided that one recognizes that they may apply only to hydroxylic solvents.

Table 8-4
Reactivities of Various Nucleophiles toward Methyl Bromide in Water at 50°

Nucleophile	Approximate reaction half-time, hr[a]	Rate relative to water	K_b^c
H_2O	1,100[b]	(1)	10^{-16}
$CH_3CO_2^{\ominus}$	2.1	5.2×10^2	10^{-11}
$Cl^{\ominus}$	1	1.1×10^3	$\sim 10^{-20}$
$Br^{\ominus}$	0.17	7.8×10^3	$< 10^{-20}$
$N_3^{\ominus}$	0.11	1.0×10^4	10^{-11}
$HO^{\ominus}$	0.07	1.6×10^4	55
$C_6H_5NH_2$	0.04	3.1×10^4	10^{-10}
$SCN^{\ominus}$	0.02	5.9×10^4	10^{-14}
$I^{\ominus}$	0.01	1.1×10^5	$< 10^{-22}$

[a]Time in hours required for half of methyl bromide to react at constant (1*M*) concentration of nucleophile.
[b]Calculated from data for pure water, assuming water to be 55*M*.
[c]Defined as the equilibrium constant for $X^{\ominus} + H_2O \rightleftharpoons HX + OH^{\ominus}$ or $X + H_2O \rightleftharpoons HX^{\oplus} + OH^{\ominus}$.

1. For the atoms representing any one group of the periodic table, nucleophilicty *increases* with increasing atomic number: $I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$; $HS^{\ominus} > HO^{\ominus}$; $PH_3 > NH_3$. Thus, other things being equal, larger atoms are better nucleophiles.

2. For nucleophiles having the same atomic number of the entering atom (e.g., oxygen nucleophiles), there is usually a good correlation between the basicity of the reagent and its nucleophilicity. Thus, a weak base such as $CH_3CO_2^{\ominus}$ is a poorer nucleophile than a strong base such as $OH^{\ominus}$. The poorer $X^{\ominus}$ is as a leaving group, the better it is as an entering group.

3. For nucleophiles of different atomic numbers, nucleophilicity usually does *not* parallel basicity. For example, for the halogens the reactivity sequence $I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$ is opposite to the sequence for basicity $Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$. Similarly, sulfur anions such as $HS^{\ominus}$ are better nucleophiles but *weaker* bases than corresponding oxyanions such as $HO^{\ominus}$.

4. A number of nucleophilic agents, which are very reactive in S_N2 reactions, are of the type $X{-}Y$, where both atoms have unshared electron pairs. Examples include $HOO^{\ominus}$, $H_2NO^{\ominus}$, $ClO^{\ominus}$, and H_2NNH_2, all of which are more reactive than the closely related nucleophiles $HO^{\ominus}$ and NH_3.

Why is the correlation between basicity and nucleophilcity so poor for atoms of different atomic number? it is now clear from much research that the dominant effect is associated with differences in the solvation energies of the ions, as defined for halide ions by the following equations:

$$\begin{aligned} F^{\ominus}(g) &\longrightarrow F^{\ominus}(aq) \qquad \Delta H^{\circ} = -117 \text{ kcal} \\ Cl^{\ominus}(g) &\longrightarrow Cl^{\ominus}(aq) \qquad \Delta H^{\circ} = -85 \text{ kcal} \\ Br^{\ominus}(g) &\longrightarrow Br^{\ominus}(aq) \qquad \Delta H^{\circ} = -78 \text{ kcal} \\ I^{\ominus}(g) &\longrightarrow I^{\ominus}(aq) \qquad \Delta H^{\circ} = -68 \text{ kcal} \end{aligned}$$

The solvation energies of small ions with concentrated charge always are greater than those of large ions with diffuse charge.

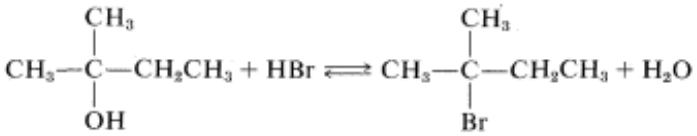
When an ion participates in a nucleophilic attack on carbon, it must slough off some of the solvent molecules that stabilize it in solution. Otherwise, the ion cannot get close enough to the carbon, to which it will become attached, to begin forming a bond. Sloughing off solvent molecules will be less favorable for a small ion than a large ion. Consequently, we expect $Cl^{\ominus}$ to be less reactive than $I^{\ominus}$.

Strong evidence for solvation effects on reactivity is provided by the fact that chloride ion is *more* reactive than iodide in solvents that have low solvation energies for anions. Furthermore, in the gas phase where solvation effects are absent, $F^{\ominus}$ is more reactive than any of the other halide ions toward chloromethane:

$$X^{\ominus}(g) + CH_3Cl(g) \longrightarrow CH_3X(g) + Cl^{\ominus}(g)$$

(gas-phase reactivity sequence $F^{\ominus} > Br^{\ominus} > I^{\ominus}$)

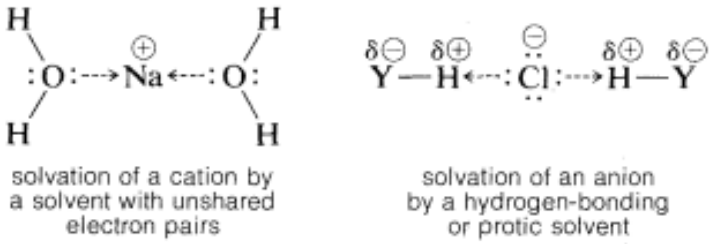
It should be recognized that SN reactions may be reversible when both the leaving group *X* and the entering group *Y* are good entering and leaving groups, respectively. In such circumstances, the position of the equilibrium often can be changed by suitably adjusting the reaction conditions. Thus, 48% aqueous hydrogen bromide can convert alcohols to alkyl bromides (forward direction), whereas the reverse reaction (hydrolysis) is achieved by high water concentration:



The Nature of the Solvent

The rates of S_N reactions are sensitive to the nature and composition of the solvent. This is easy to understand for S_N1 reactions because the ionizing power of a solvent is crucial to the ease of formation of ions $R^{\oplus}$ and $X^{\ominus}$ from *RX*.

Actually, two factors are relevant in regard to the ionizing ability of solvents. First, a high-dielectric constant increases ionizing power by making it easier to separate ions. This is because the force between charged particles varies inversely with the dielectric constant of the medium. Thus water, with a dielectric constant of 80, is 40 times more effective than a hydrocarbon with a dielectric constant of 2. Second, and usually more important, is the ability of the solvent to solvate the separated ions. Cations are solvated most effectively by compounds of elements in the first row of the periodic table that have unshared electron pairs. Examples are ammonia, water, alcohols, carboxylic acids, sulfur dioxide, and methylsulfinylmethane [dimethyl sulfoxide, $(CH_3)_2SO$]. Anions are solvated most efficiently by solvents having hydrogen attached to a strongly electronegative element *Y* so the *H*–*Y* bond is strongly polarized as $H\delta^{\oplus} \cdots Y\delta^{\ominus}$. Such solvents usually are called **protic solvents**. Protic solvents form hydrogen bonds to the leaving group, which assist ionization in much the same way that silver ion catalyzes ionization of alkyl halides. We can represent solvation by the following structural formulas, but it must be recognized that the number of solvent molecules involved in close interacitons can be as large as four or six, or as small as one:



solvation of a cation by a solvent with unshared electron pairs

solvation of an anion by a hydrogen-bonding or protic solvent

The most effective ionizing solvents are those that effectively solvate both anions and cations. Water strikes an excellent compromise with regard to the structural features that make up ionizing power, that is, dielectric constant *and* solvating ability. From this, we expect *tert*-butyl chloride to ionize much more readily in water than in ether, because ethers can solvate only cations effectively, whereas water can solvate both anions and cations. The fact is that S_N1 ionizations usually are so difficult that S_N1 reactions seldom occur in solvents that cannot effectively solvate *both* anions and cations, even if the dielectric constant of the solvent is high. Solvation by hydrogen bonding is especially helpful in assisting ionization. Solvents that cannot provide such hydrogen bonding [e.g., CH_3OCH_3, $(CH_3)_3N$, CH_3NO_2, CH_3CN, $(CH_3)_2SO$] generally are poor for S_N1 reactions. These solvents are called **aprotic** solvents. An important exception is liquid sulfur dioxide, SO_2, which promotes S_N1 ionization by having a high dielectric constant and being able to solvate both anions and cations.

A list of protic and aprotic solvents, their dielectric constants, boiling points, and melting points is given below. This table will be useful in selecting solvents for nucleophilic substitution reactions.

Solvent Properties

Compound	Formula	Dielectric constant, ϵ^{20}	bp, °C	mp, °C	Solubility in water
hydrogen cyanide	HCN	115	26	−14	+
methanamide (formamide)	$HCONH_2$	84	210.5	2.5	+
hydrogen fluoride	HF	84[a]	19.7	−83.7	+
water	H_2O	80	100	0	+
methanoic (formic) acid	HCO_2H	58	100	8.5	+
methylsulfinylmethane (dimethyl sulfoxide)	$(CH_3)_2SO$	45	189	18	+
1,2,3-propanetriol (glycerol)	$HOCH_2CHOHCH_2OH$	42.5	290 (dec)	17.8	+
ethanenitrile (acetonitrile)	CH_3CN	38.8	81.6	−45	+
N,N-dimethylmethanamide (dimethylformamide)	$HCON(CH_3)_2$	–	153	−61	+
nitromethane	CH_3NO_2	38	101.2	−29	+[b]
methanol	CH_3OH	32.6	64.7	−97.8	+
ethanol	CH_3CH_2OH	24	78.5	−118	+
2-propanone (acetone)	CH_3COCH_3	21	56.5	−94	+
ammonia	NH_3	17	−33	−78	+
sulfur dioxide	SO_2	17.6[c]	−10	−72	[d]
azabenzene (pyridine)	C_5H_5N	12.3	115	−42	+
dichloromethane	CH_2Cl_2	9.1	40	−95	−
ethanoic (acetic) acid	CH_3CO_2H	6.2	118	16.7	+
trichloromethane (chloroform)	$CHCl_3$	4.8	61	−64	−
diethyl ether	$(C_2H_5)_2O$	4.3	35	−116	−
carbon disulfide	CS_2	2.6	46.5	−111.6	−
1,4-dioxacyclohexane (dioxane)	$O[(CH_2)_2]_2O$	2.2	101	11.8	+
tetrachloromethane (carbon tetrachloride)	CCl_4	2.2	76.7	−23	−
benzene	C_6H_6	2.3	80.1	5.5	−
cyclohexane	C_6H_{12}	2.0	80.7	6.5	−

[a]At 0°. [b]Slightly soluble. [c]At −20°. [d]Reacts with water.

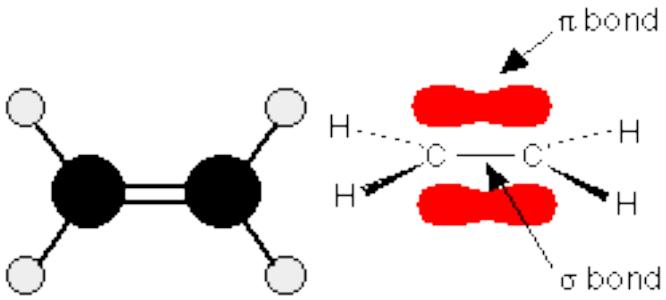
With regard to S_N2 reactions, the solvent can affect profoundly the reactivity of a given nucleophile. Thus, anions such as $Cl^{\ominus}$ and $CN^{\ominus}$, which are weakly nucleophilic in hydroxylic solvents and in poor ionizing solvents such as 2-propanone (acetone), become very significantly nucleophilic in polar aprotic sovlents such as $(CH_3)_2SO$. The reason is that for salts such as *NaCl* and *NaCN* the aprotic solvent preferentially solvates the cation, leaving the anion relatively bare. This dissociation of the anion from the cation together with its poor solvation makes the anion abnormally reactive as a nucleophile.

TOPIC 11: ELECTROPHILIC ADDITION

Electrophilic addition is a reaction between an electrophile and nucleophile, adding to double or triple bonds. An electrophile is defined by a molecule with a tendency to react with other molecules containing a donatable pair of electrons. Thus, it is an "electron lover." A nucleophile is one that possesses a lone pair of electrons that can be easily shared. In essence, all nucleophiles are Lewis bases that attack non-hydrogen atoms (Lewis acids).

In a general electrophilic addition reaction, one of the pi bonds is removed and creates two new sigma bonds. There are a variety of electrophilic reactions, and therefore a variety of different products that are very useful. It simply depends on which reagents are used to determine the final product.

We are going to start by looking at ethene, because it is the simplest molecule containing a carbon-carbon double bond. What is true of C=C in ethene will be equally true of C=C in more complicated alkenes.



Ethene, C_2H_4, is often modeled as shown on the right. The double bond between the carbon atoms is, of course, two pairs of shared electrons. What the diagram doesn't show is that the two pairs aren't the same as each other. One of the pairs of electrons is held on the line between the two carbon nuclei as you would expect, but the other is held in a molecular orbital above and below the plane of the molecule. A molecular orbital is a region of space within the molecule where there is a high probability of finding a particular pair of electrons.

In this diagram, the line between the two carbon atoms represents a normal bond - the pair of shared electrons lies in a molecular orbital on the line between the two nuclei where you would expect them to be. This sort of bond is called a sigma bond.

The other pair of electrons is found somewhere in the shaded part above and below the plane of the molecule. This bond is called a pi bond. The electrons in the pi bond are free to move around anywhere in this shaded region and can move freely from one half to the other. The pi electrons are not as fully under the control of the carbon nuclei as the electrons in the sigma bond and, because they lie exposed above and below the rest of the molecule, they are relatively open to attack by other things.

Electrophiles

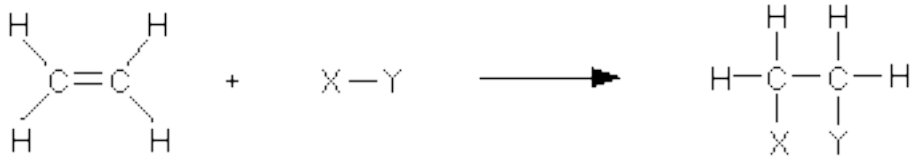
An electrophile is something which is attracted to electron-rich regions in other molecules or ions. Because it is attracted to a negative region, an electrophile must be something which carries either a full positive charge, or has a slight positive charge on it somewhere.

Ethene and the other alkenes are attacked by electrophiles. The electrophile is normally the slightly positive (δ +) end of a molecule like hydrogen bromide, HBr.

Electrophiles are strongly attracted to the exposed electrons in the pi bond and reactions happen because of that initial attraction - as you will see shortly.

You might wonder why fully positive ions like sodium, Na+, don't react with ethene. Although these ions may well be attracted to the pi bond, there is no possibility of the process going any further to form bonds between sodium and carbon, because sodium forms ionic bonds, whereas carbon normally forms covalent ones.

In a sense, the pi bond is an unnecessary bond. The structure would hold together perfectly well with a single bond rather than a double bond. The pi bond often breaks and the electrons in it are used to join other atoms (or groups of atoms) onto the ethene molecule. In other words, ethene undergoes addition reactions.
For example, using a general molecule X-Y . . .



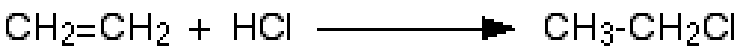
There are four common types of Electrophilic Addition reactions:

1. Hydrohalogenation
2. Hydrogenation
3. Hydration
4. Halogenation

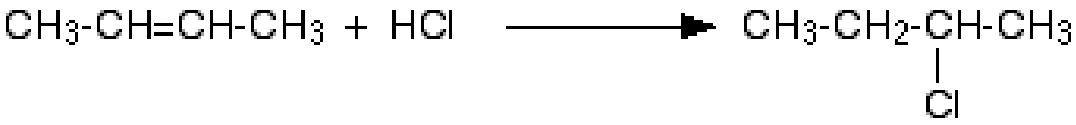
Hydrohalogenation

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:



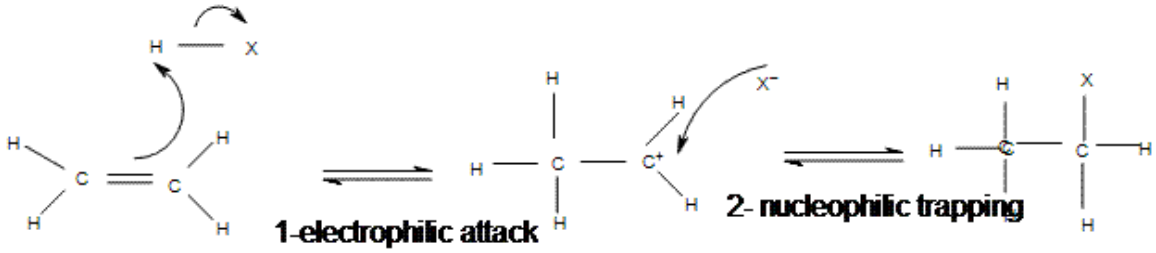
What happens if you add the hydrogen to the carbon atom at the right-hand end of the double bond, and the chlorine to the left-hand end? You would still have the same product.

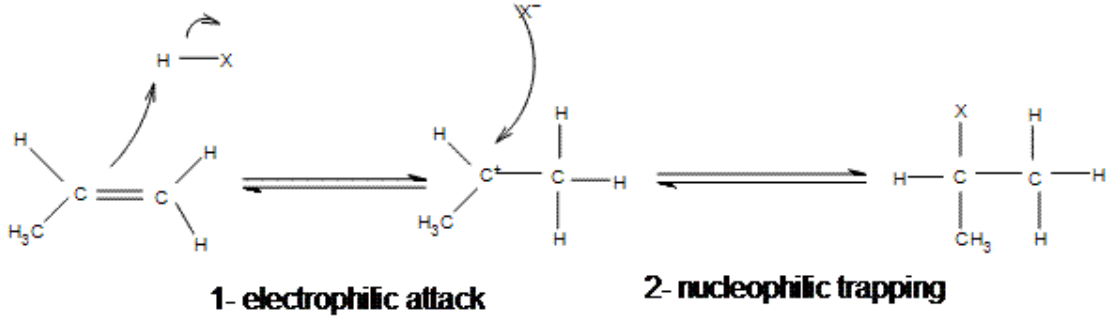
The chlorine would be on a carbon atom next to the end of the chain - you would simply have drawn the molecule flipped over in space.

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 π electrons, attaching it to the molecule. This is basically the reverse of the last step in the E1 reaction. 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. The second step will only occur if a good nucleophile is used.





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).

Reaction rates

Variation of rates when you change the halogen

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.

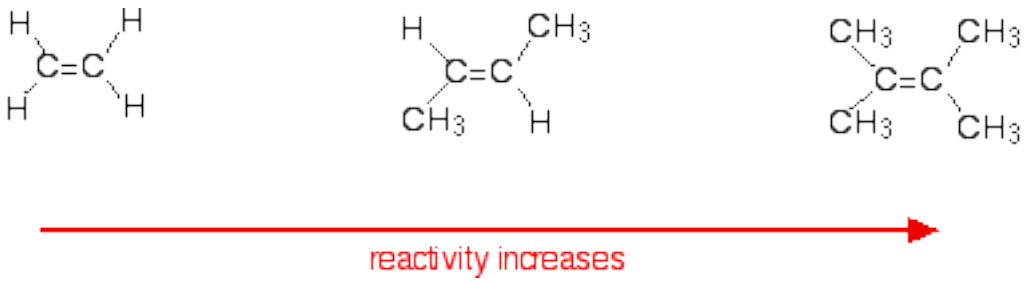
When the hydrogen halides react with alkenes, the hydrogen-halogen bond has to be broken. The bond strength falls as you go from HF to HI, and the hydrogen-fluorine bond is particularly strong. Because it is difficult to break the bond between the hydrogen and the fluorine, the addition of HF is bound to be slow.

Variation of rates when you change the alkene

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:



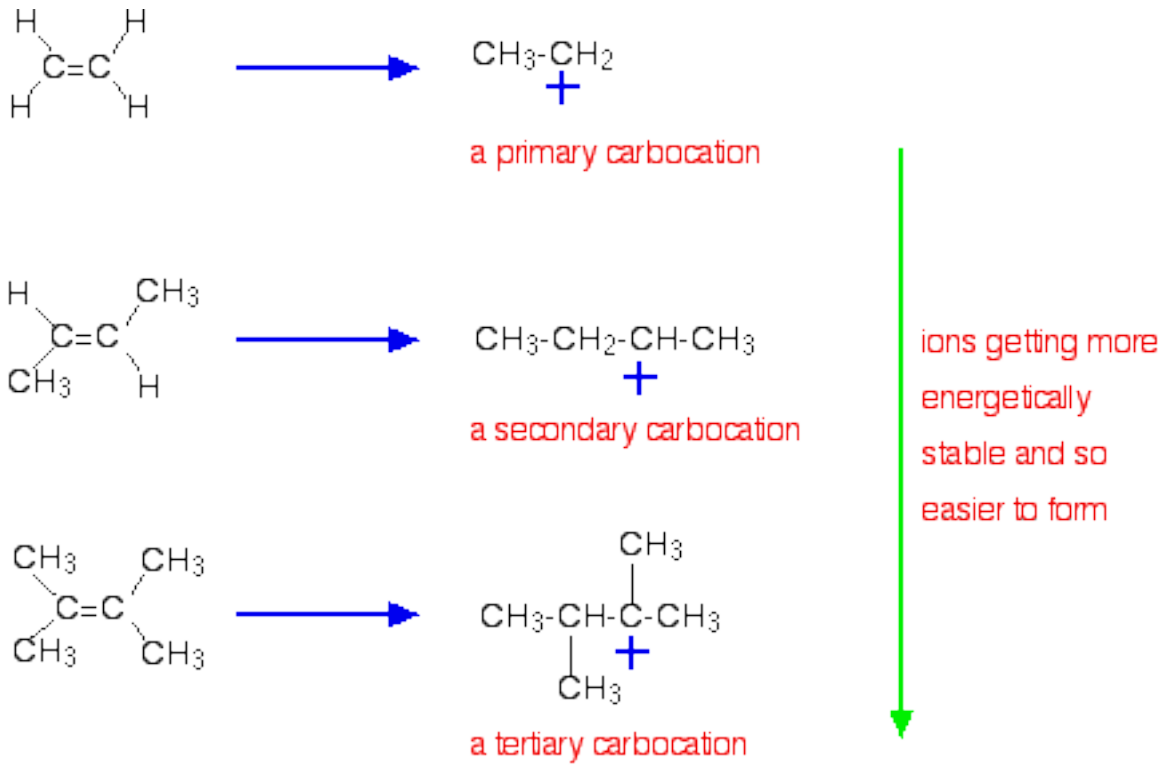
There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

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.

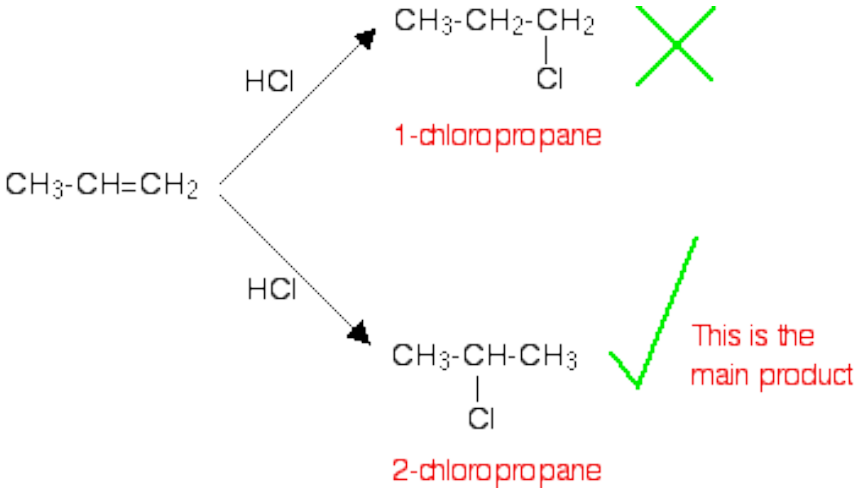
Addition to unsymmetrical alkenes

What happens?

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.

Orientation of addition

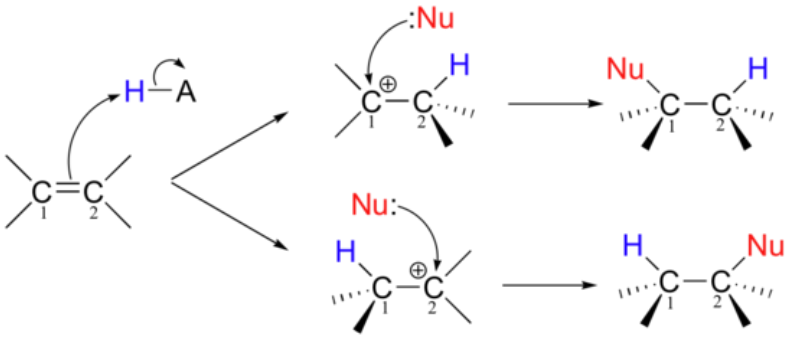
If HCl adds to an unsymmetrical alkene like propene, there are two possible ways it could add. However, in practice, there is only one major product.



This is in line with **Markovnikov's Rule**, also called **regioselectivity.**

Markovnikov's Rule (Regioselectivity)

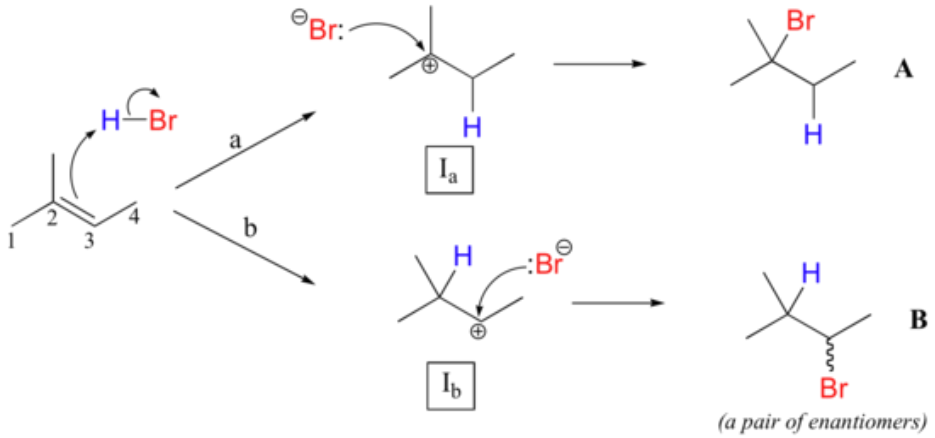
Something very important with electrophilic addition reactions is that if the starting alkene is asymmetrical, there are two possible courses that could be followed, depending on which of the two alkene carbons forms the new sigma bond in the first step.



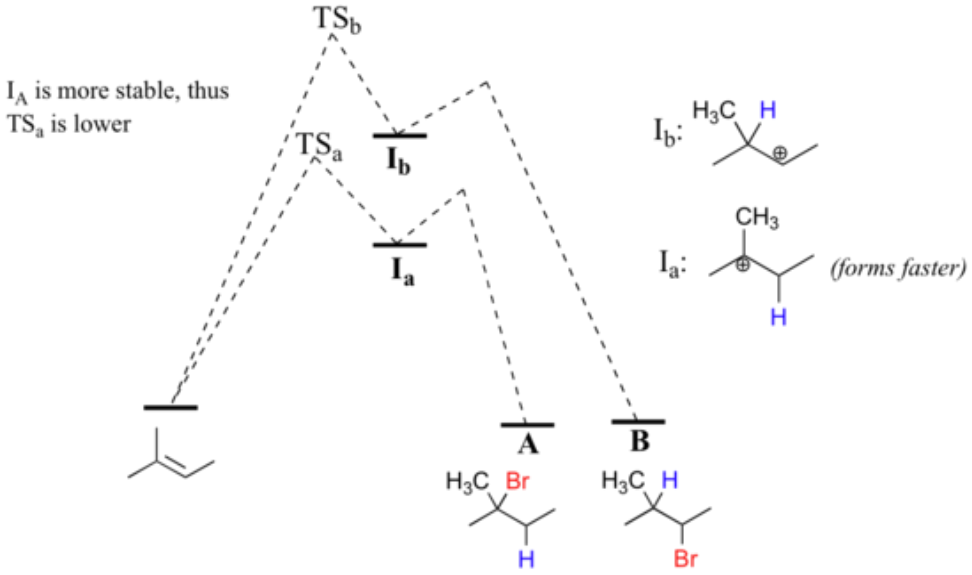
Of course, the two reaction courses involve two different carbocation intermediates, which may have different energy levels. Two different products are possible, and in general *the product which predominates will be the one that is derived from the lower-energy carbocation intermediate*.

This important regiochemical principle is nicely illustrated by a simple electrophilic addition that is commonly carried out in the organic laboratory: the conversion of an alkene to an alkyl bromide by

electrophilic addition of HBr to the double bond. Let's look at a hypothetical addition of HBr to 2-methyl-2-butene, pictured below. Two different regiochemical outcomes are possible:



The initial protonation step could follow two different pathways, resulting in two different carbocation intermediates: pathway '**a**' gives a tertiary carbocation intermediate (I_a), while pathway '**b**' gives a secondary carbocation intermediate (I_b). We know already that the tertiary carbocation is more stable (in other words, lower in energy). According to the Hammond postulate, this implies that the activation energy for pathway **a** is lower than in pathway **b**, meaning in turn that I_a forms *faster*.



Because the protonation step is the rate determining step for the reaction, the tertiary alkyl bromide A will form much faster than the secondary alkyl halide B, and thus A will be the predominant product observed in this reaction. This is a good example of a non-enzymatic organic reaction that is highly regiospecific.

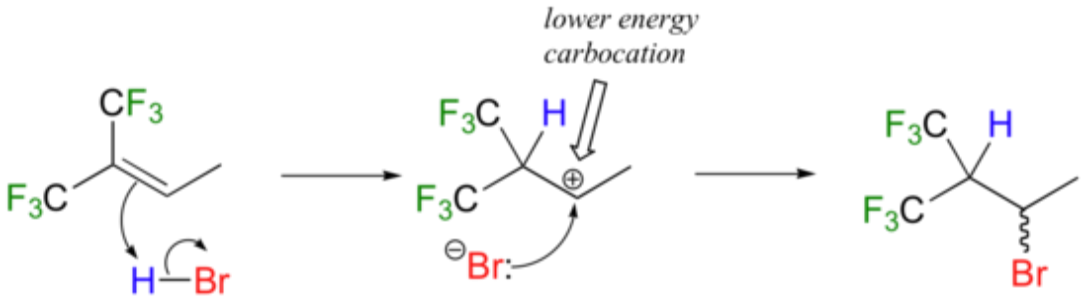
In the example above, the difference in carbocation stability can be accounted for by the electron-donating effects of the extra methyl group on one side of the double bond. It is generally observed that, in electrophilic addition of acids (including water) to asymmetrical alkenes, the *more substituted* carbon is the one that ends up bonded to the heteroatom of the acid, while the less substituted carbon is protonated.

This rule of thumb is known as **Markovnikov's rule**, after the Russian chemist Vladimir Markovnikov who proposed it in 1869.

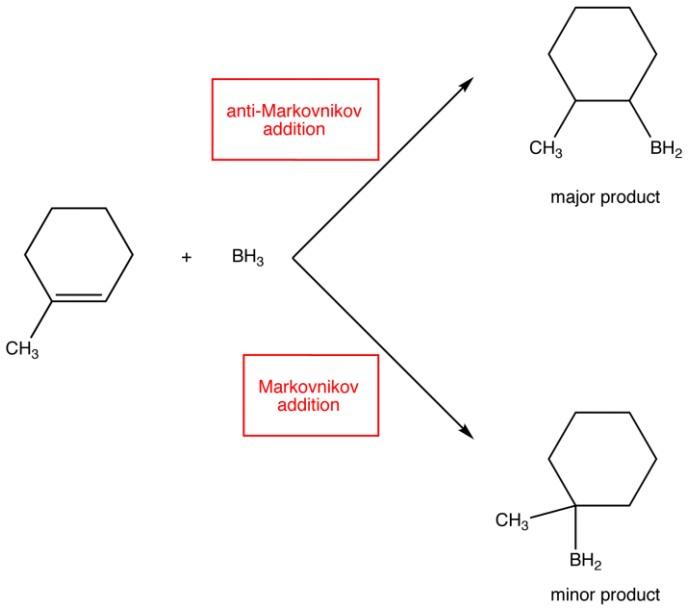
While it is useful in many cases, Markovikov's rule does not apply to all possible electrophilic additions. It is more accurate to use the more general principle that has already been stated above:

When an asymmetrical alkene undergoes electrophilic addition, the product that predominates is the one that results from the more stable of the two possible carbocation intermediates.

How is this different from Markovnikov's original rule? Consider the following hypothetical reaction, which is similar to the HBr addition shown above except that the six methyl hydrogens on the left side of the double bond have been replaced by highly electron-withdrawing fluorines.



Now when HBr is added, it is the *less* substituted carbocation that forms faster in the rate-determining protonation step, because in this intermediate the carbon bearing the positive charge is located further away from the electron-withdrawing, *cation-destabilizing* fluorines. As a result, the predominant product is the secondary rather than the tertiary bromoalkane. This would be referred to as an 'anti-Markovnikov' addition product, because it 'breaks' Markovnikov's rule.

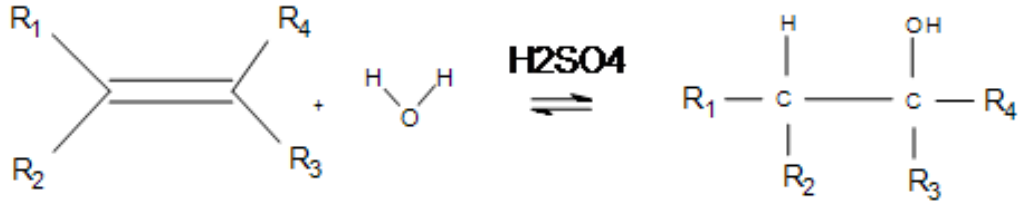


Hydration

Electrophilic hydration is the act of adding electrophilic hydrogen from a non-nucleophilic strong acid (a reusable catalyst, examples of which include sulfuric and phosphoric acid) and applying appropriate

temperatures to break the alkene's double bond. After a carbocation is formed, water bonds with the carbocation to form a 1º, 2º, or 3º alcohol on the alkane.

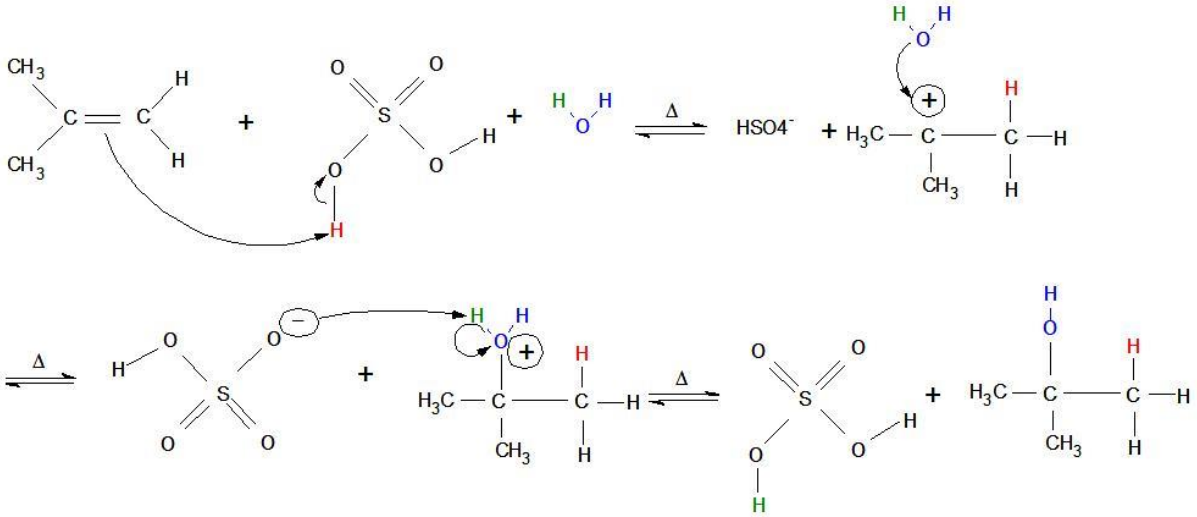
Electrophilic hydration is the reverse dehydration of alcohols and has practical application in making alcohols for fuels and reagents for other reactions. The basic reaction under certain temperatures (given below) is the following:



The phrase "electrophilic" literally means "electron loving" (whereas "nucleophilic" means "nucleus loving"). Electrophilic hydrogen is essentially a proton: a hydrogen atom stripped of its electrons. Electrophilic hydrogen is commonly used to help break double bonds or restore catalysts.

How Does Electrophilic Hydration Work?

Mechanism for 3º Alcohol (1º and 2º mechanisms are similar):



Temperatures for Types of Alcohol Synthesis

Heat is used to catalyze electrophilic hydration; because the reaction is in equilibrium with the dehydration of an alcohol, which requires higher temperatures to form an alkene, lower temperatures are required to form an alcohol. *The exact temperatures used are highly variable and depend on the product being formed.*

- Primary Alcohol: Less than 170ºC
- Secondary Alcohol: Less than 100ºC
- Tertiary Alcohol: Less than 25ºC

But...Why Does Electrophilic Hydration Work?

- An alkene placed in an aqueous non-nucleophilic strong acid immediately "reaches out" with its double bond and attacks one of the acid's hydrogen atoms (meanwhile, the bond between oxygen and

hydrogen performs heterolytic cleavage toward the oxygen—in other words, both electrons from the oxygen/hydrogen single bond move onto the oxygen atom).

- A carbocation is formed on the original alkene (now alkane) in the more-substituted position, where the oxygen end of water attacks with its 4 non-bonded valence electrons (oxygen has 6 total valence electrons because it is found in Group 6 on the periodic table and the second row down: two electrons in a 2s-orbital and four in 2p-orbitals. Oxygen donates one valence electron to each bond it forms, leaving four 4 non-bonded valence electrons).
- After the blue oxygen atom forms its third bond with the more-substituted carbon, it develops a positive charge (3 bonds and 2 valence electrons give the blue oxygen atom a formal charge of +1).
- The bond between the green hydrogen and the blue oxygen undergoes heterolytic cleavage, and both the electrons from the bond move onto the blue oxygen. The now negatively-charged strong acid picks up the green electrophilic hydrogen.
- Now that the reaction is complete, the non-nucleophilic strong acid is regenerated as a catalyst and an alcohol forms on the most substituted carbon of the current alkane. At lower temperatures, more alcohol product can be formed.

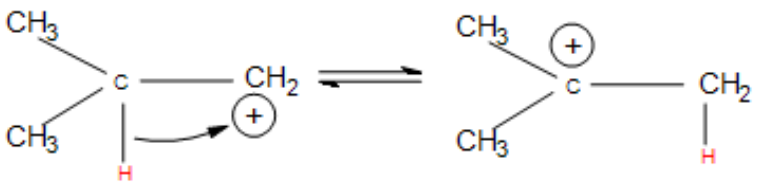
How Does Regiochemistry Apply?

Regiochemistry deals with where the substituent bonds on the product. **Zaitsev**'s (explained more later in Elimination Reactions) and **Markovnikov**'s rules address regiochemistry, but Zaitsev's rule applies when synthesizing an alkene while Markovnikov's rule describes where the substituent bonds onto the product. In the case of electrophilic hydration, Markovnikov's rule is the only rule that *directly* applies.

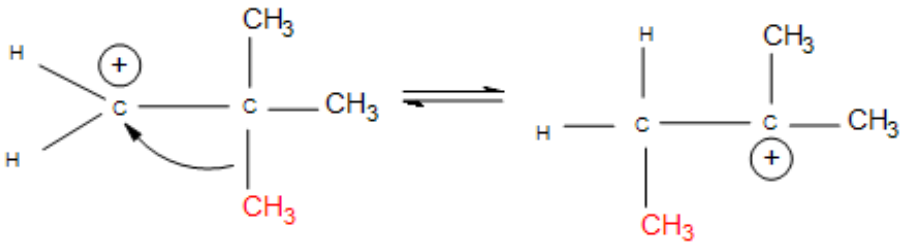
In the mechanism for a 3º alcohol shown above, the red H is added to the least-substituted carbon connected to the nucleophilic double bonds (it has less carbons attached to it). This means that the carbocation forms on the 3º carbon, causing it to be highly stabilized by *hyperconjugation*—electrons in nearby sigma (single) bonds help fill the empty p-orbital of the carbocation, which lessens the positive charge. More substitution on a carbon means more sigma bonds are available to "help out" (by using overlap) with the positive charge, which creates greater *carbocation stability*. In other words, carbocations form on the most substituted carbon connected to the double bond. Carbocations are also stabilized by resonance, but resonance is not a large factor in this case because any carbon-carbon double bonds are used to initiate the reaction, and other double bonded molecules can cause a completely different reaction.

If the carbocation does originally form on the less substituted part of the alkene, carbocation rearrangements occur to form more substituted products:

- **Hydride shifts:** a hydrogen atom bonded to a carbon atom next to the carbocation leaves that carbon to bond with the carbocation (after the hydrogen has taken both electrons from the single bond, it is known as a hydride). This changes the once neighboring carbon to a carbocation, and the former carbocation becomes a neighboring carbon atom.



- **Alkyl shifts:** if no hydrogen atoms are available for a hydride shift, an entire methyl group performs the same shift.

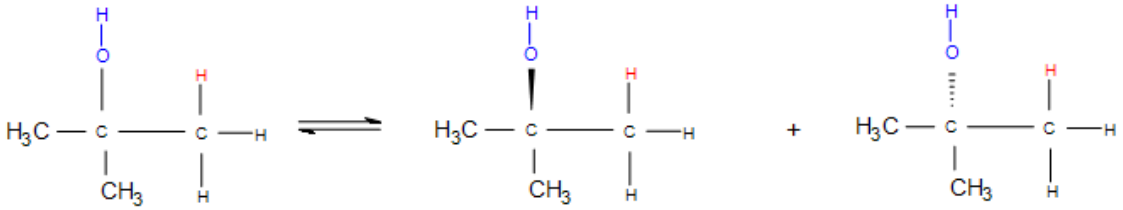


The nucleophile attacks the positive charge formed on the most substituted carbon connected to the double bond, because the nucleophile is seeking that positive charge. In the mechanism for a 3º alcohol shown above, water is the nucleophile. When the green H is removed from the water molecule, the alcohol attached to the most substituted carbon. Hence, electrophilic hydration follows Markovnikov's rule.

How Does Stereochemistry Apply?

Stereochemistry deals with how the substituent bonds on the product directionally. Dashes and wedges denote stereochemistry by showing whether the molecule or atom is going into or out of the plane of the board. Whenever the bond is a simple single straight line, the molecule that is bonded is equally likely to be found going into the plane of the board as it is out of the plane of the board. This indicates that the product is a racemic mixture.

Electrophilic hydration adopts a stereochemistry wherein the substituent is equally likely to bond pointing into the plane of the board as it is pointing out of the plane of the board. The 3º alcohol product could look like either of the following products:



Note: Whenever a straight line is used along with dashes and wedges on the same molecule, it could be denoting that the straight-line bond is in the same plane as the board. Practice with a molecular model kit and attempting the practice problems at the end can help eliminate any ambiguity.

Is this a Reversible Synthesis?

Electrophilic hydration is reversible because an alkene in water is in equilibrium with the alcohol product. To sway the equilibrium one way or another, the temperature or the concentration of the non-nucleophilic strong acid can be changed. For example:

- Less sulfuric or phosphoric acid and an excess of water help synthesize more alcohol product.
- Lower temperatures help synthesize more alcohol product.

Halogenation

Halogens can act as electrophiles to attack a double bond in alkene. Double bond represents a region of electron density and therefore functions as a nucleophile. How is it possible for a halogen to obtain positive charge to be an electrophile?

As halogen molecule, for example Br_2, approaches a double bond of the alkene, electrons in the double bond repel electrons in bromine molecule causing polarization of the halogen bond. This creates a dipolar moment in the halogen molecule bond. Heterolytic bond cleavage occurs and one of the halogens obtains positive charge and reacts as an electrophile. The reaction of the addition is not regioselective but stereoselective. Stereochemistry of this addition can be explained by the mechanism of the reaction. In the first step, electrophilic halogen with a positive charge approaches the double carbon bond and 2p orbitals of the halogen, bond with two carbon atoms and create a cyclic ion with a halogen as the intermediate step. In the second step, halogen with the negative charge attacks any of the two carbons in the cyclic ion from the back side of the cycle as in the S_N2 reaction. Therefore, stereochemistry of the product is **vicinial dihalides through anti** addition.

$$\mathbf{R_2C{=}CR_2{+}X_2{\rightarrow}R_2CX{-}CR_2XR_2C{=}CR_2{+}X_2{\rightarrow}R_2CX{-}CR_2X}$$

Halogens that are commonly used in this type of the reaction are: Br and Cl. In thermodynamic terms II is too slow for this reaction because of the size of its atom, and FF is too vigorous and explosive.

Solvents that are used for this type of electrophilic halogenation are inert (e.g., CCl_4) can be used in this reaction.

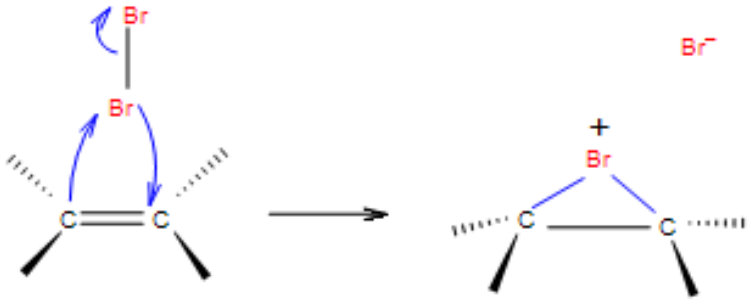
Because halogen with negative charge can attack any carbon from the opposite side of the cycle it creates a mixture of steric products. Optically inactive starting material produce optically inactive achiral products (meso) or a racemic mixture.

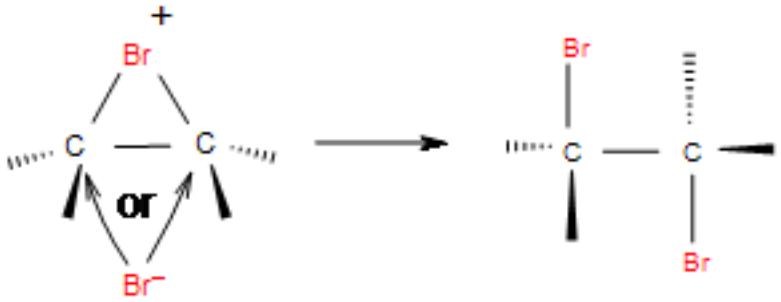
Electrophilic Addition Mechanism Consists of Two Steps

Before constructing the mechanism let us summarize conditions for this reaction. We will use Br_2 in our example for halogenation of ethylene.

Nucleophile	**Double bond in alkene**
Electrophile	Br_2, Cl_2
Regiochemistry	not relevant
Stereochemistry	**ANTI**

Step 1: In the first step of the addition the Br-Br bond polarizes, heterolytic cleavage occurs and Br with the positive charge forms an intermediate cycle with the double bond.





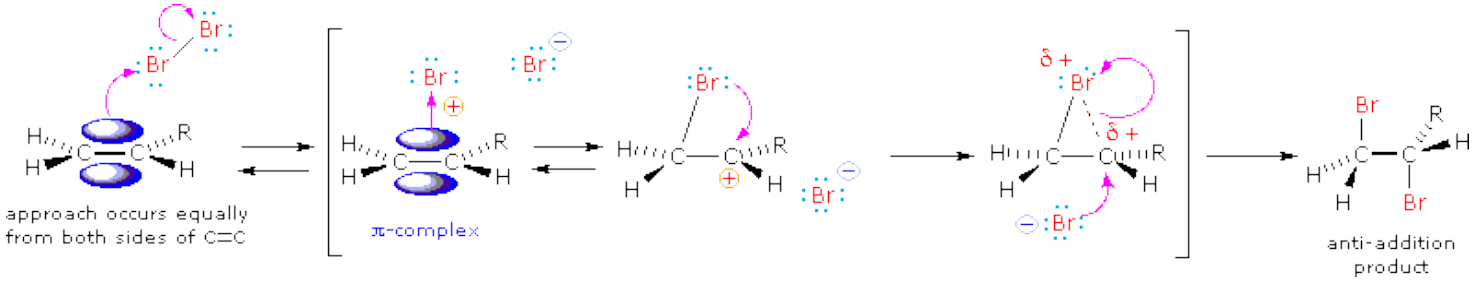
Step 2: In the second step, bromide anion attacks any carbon of the bridged bromonium ion from the back side of the cycle. Cycle opens up and two halogens are in the position **anti**.

Halogens can act as electrophiles due to polarizability of their covalent bond. Addition of halogens is stereospecific and produces vicinal dihalides with anti-addition. Cis starting material will give mixture of enantiomers and trans produces a meso compound.

Stereochemistry

The halogens chlorine and bromine add rapidly to a wide variety of alkenes without inducing the kinds of structural rearrangements (carbocation shifts) noted for strong acids - this is because a discreet carbocation intermediate does not form in these reactions.

We can account both for the high stereoselectivity and the lack of rearrangement in these reactions by proposing a stabilizing interaction between the developing carbocation center and the electron rich halogen atom on the adjacent carbon. This interaction delocalizes the positive charge on the intermediate and blocks halide ion attack from the *syn*-location.

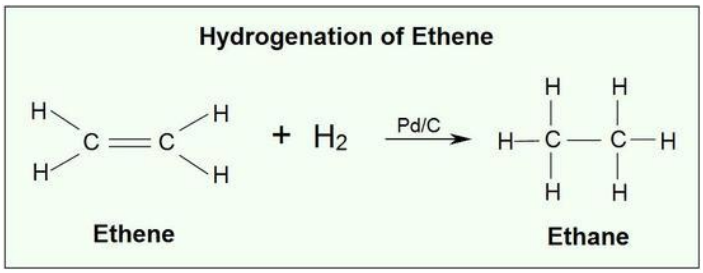


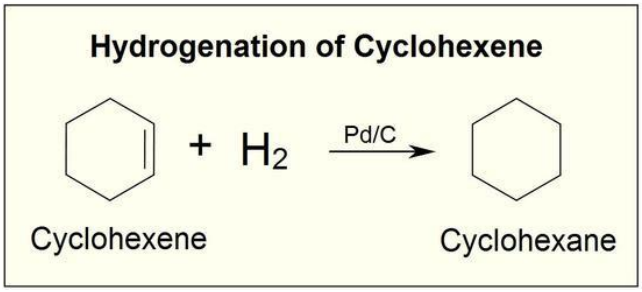
The stabilization provided by the halogen-carbocation bonding makes rearrangement unlikely, and in a few cases three-membered cyclic halonium cations have been isolated and identified as true intermediates. A resonance description of such a bromonium ion intermediate is shown below. The positive charge is delocalized over all the atoms of the ring, but should be concentrated at the more substituted carbon (where positive charge is more stable), and this is the site to which the nucleophile will bond. This means that halogen addition is always anti-addition.

Hydrogenation

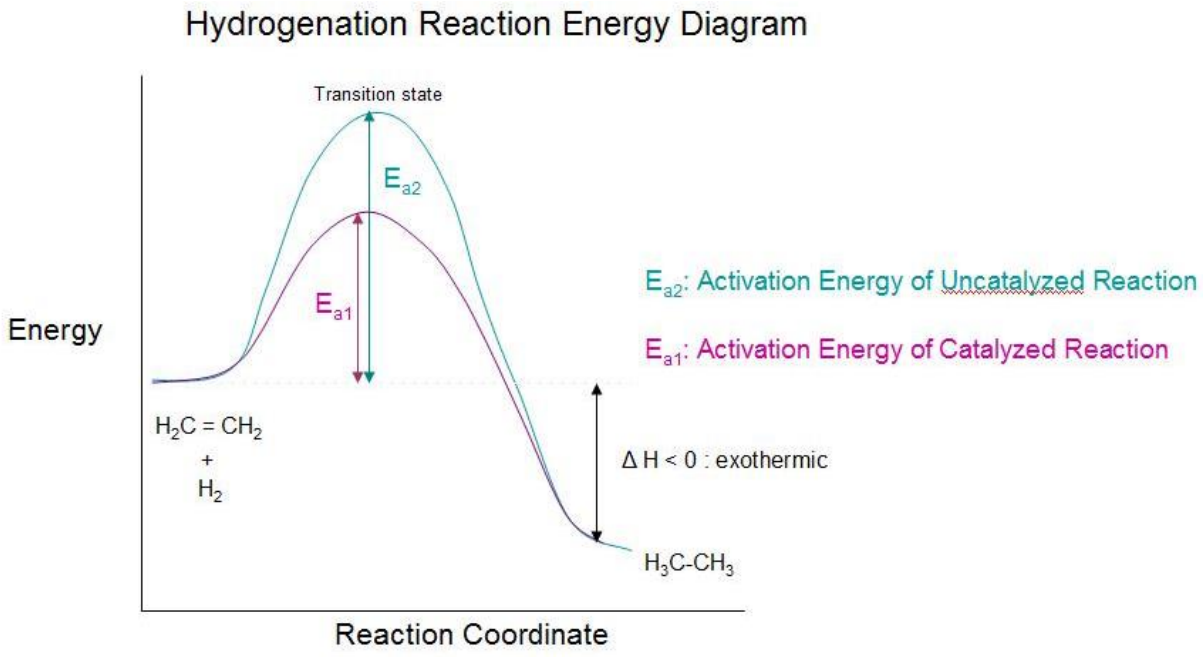
Addition of hydrogen to a carbon-carbon double bond is called hydrogenation. The overall effect of such an addition is the reductive removal of the double bond functional group. Regioselectivity is not an issue, since the same group (a hydrogen atom) is bonded to each of the double bond carbons. The simplest source of two hydrogen atoms is molecular hydrogen (H_2), but mixing alkenes with hydrogen does not result in any discernible reaction. Although the overall hydrogenation reaction is exothermic, a high activation energy prevents it from taking place under normal conditions. This restriction may be circumvented by the use of a catalyst, as shown in the following diagram.

An example of an alkene addition reaction is a process called hydrogenation. In a hydrogenation reaction, two hydrogen atoms are added across the double bond of an alkene, resulting in a saturated alkane. Hydrogenation of a double bond is a thermodynamically favorable reaction because it forms a more stable (lower energy) product. In other words, the energy of the product is lower than the energy of the reactant; thus, it is exothermic (heat is released). The heat released is called the heat of hydrogenation, which is an indicator of a molecule's stability.





Catalysts are substances that changes the rate (velocity) of a chemical reaction without being consumed or appearing as part of the product. Catalysts act by lowering the activation energy of reactions, but they do not change the relative potential energy of the reactants and products. Finely divided metals, such as platinum, palladium and nickel, are among the most widely used hydrogenation catalysts. Catalytic hydrogenation takes place in at least two stages, as depicted in the diagram. First, the alkene must be adsorbed on the surface of the catalyst along with some of the hydrogen. Next, two hydrogens shift from the metal surface to the carbons of the double bond, and the resulting saturated hydrocarbon, which is more weakly adsorbed, leaves the catalyst surface. The exact nature and timing of the last events is not well understood.

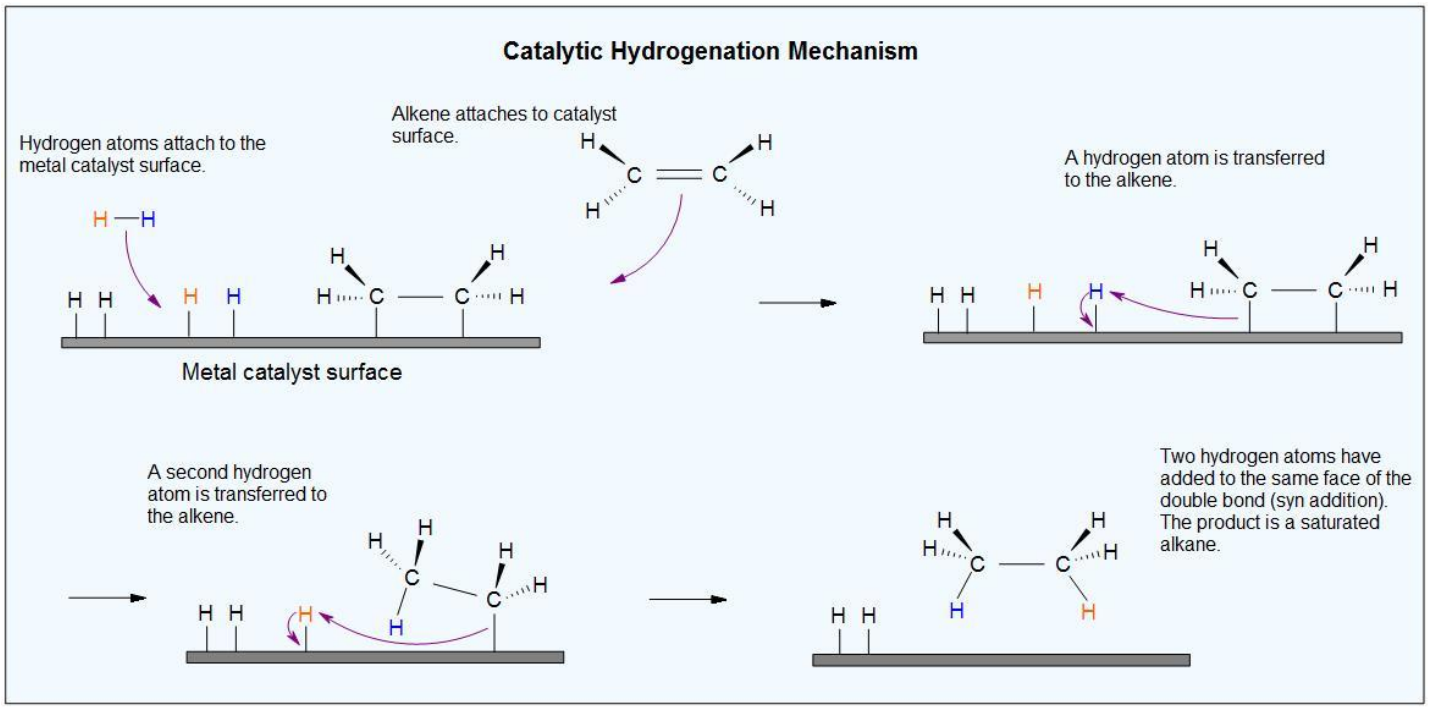


A catalyst lowers the activation energy needed for the reacting molecules to reach the transition state. The addition of a catalyst enables the hydrogenation reaction to occur, that otherwise, would not.

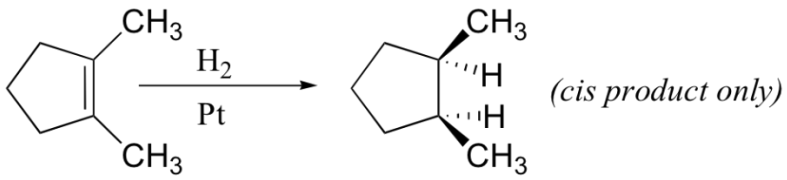
As shown in the energy diagram, the hydrogenation of alkenes is exothermic, and heat is released corresponding to the ΔE (colored green) in the diagram. This heat of reaction can be used to evaluate the

thermodynamic stability of alkenes having different numbers of alkyl substituents on the double bond. For example, the following table lists the heats of hydrogenation for three C_5H_{10} alkenes which give the same alkane product (2-methylbutane). Since a large heat of reaction indicates a high energy reactant, these heats are inversely proportional to the stabilities of the alkene isomers. To a rough approximation, we see that each alkyl substituent on a double bond stabilizes this functional group by a bit more than 1 kcal/mole.

Alkene Isomer	$(CH_3)_2CHCH=CH_2$ 3-methyl-1-butene	$CH_2=C(CH_3)CH_2CH_3$ 2-methyl-1-butene	$(CH_3)_2C=CHCH_3$ 2-methyl-2-butene
Heat of Reaction (ΔH°)	–30.3 kcal/mole	–28.5 kcal/mole	–26.9 kcal/mole



From the mechanism shown here we would expect the addition of hydrogen to occur with **syn-stereoselectivity**. This is often true, but the hydrogenation catalysts may also cause isomerization of the double bond prior to hydrogen addition, in which case stereoselectivity may be uncertain.



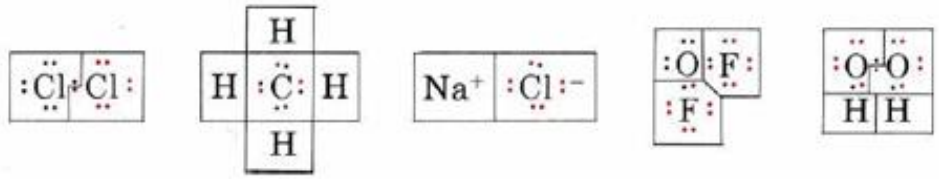
Oxidation

Oxidation Numbers Review

We can obtain oxidation numbers by arbitrarily assigning the electrons of each covalent bond to the more electronegative atom in the bond. This is in contrast to the Formal Charge which divides each bonding pair equally without concern for which atom may be more electronegative. When this division has been done for

all bonds, the charge remaining on each atom is said to be its oxidation number. If two like atoms are joined, each atom is assigned half the bonding electrons.

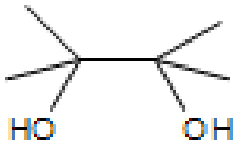
In each case we begin by drawing a Lewis diagram:



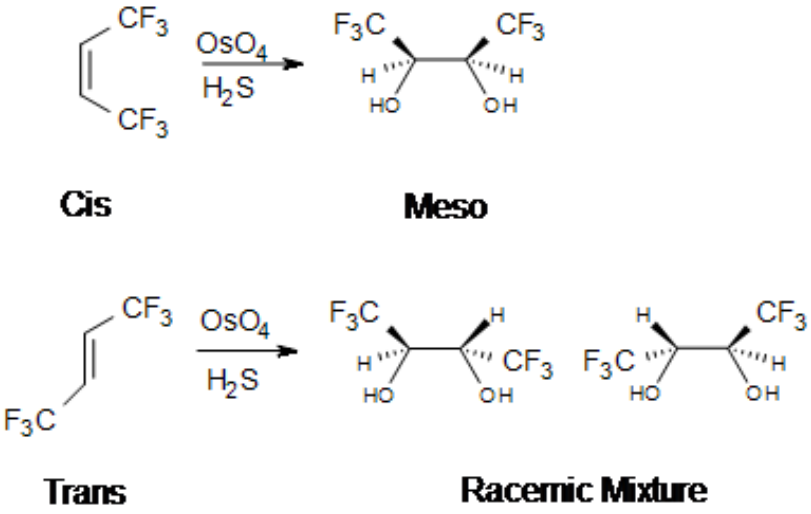
In each Lewis diagram, electrons have been color coded to indicate the atom from which they came originally. The boxes enclose electrons assigned to a given atom by the rules for determining oxidation number.

Syn Dihydroxylation

Osmium tetroxide oxidizes alkenes to give glycols through syn addition. A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.



The reaction with OsO_4 is a concerted process that has a cyclic intermediate and no rearrangements. Vicinal syn dihydroxylation complements the epoxide-hydrolysis sequence which constitutes an *anti* dihydroxylation of an alkene. When an alkene reacts with osmium tetroxide, stereocenters can form in the glycol product. Cis alkenes give meso products and trans alkenes give racemic mixtures.



OsO_4 is formed slowly when osmium powder reacts with gaseous O_2 at ambient temperature. Reaction of bulk solid requires heating to 400 °C:

$$Os_{(s)} + 2O_{2(g)} \rightarrow OS_4$$

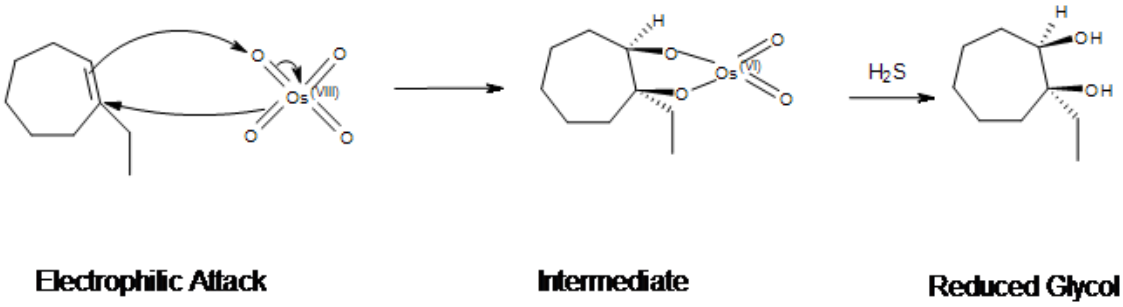
Since Osmium tetroxide is expensive and highly toxic, the reaction with alkenes has been modified. Catalytic amounts of OsO_4 and stoichiometric amounts of an oxidizing agent such as hydrogen peroxide are now used to eliminate some hazards. Also, an older reagent that was used instead of OsO_4 was potassium

permanganate, *$KMnO_4$*. Although syn diols will result from the reaction of $KMnO_4$ and an alkene, potassium permanganate is less useful since it gives poor yields of the product because of *overoxidation*.

Mechanism

- Electrophilic attack on the alkene
  Pi bond of the alkene acts as the nucleophile and reacts with osmium (VIII) tetroxide (OsO_4)
  2 electrons from the double bond flows toward the osmium metal
  In the process, 3 electron pairs move simultaneously
  Cyclic ester with Os (VI) is produced
- Reduction
  H2S reduces the cyclic ester
  $NaHSO_4$ with H_2O may be used
  Forms the syn-1,2-diol (glycol)

Example: Dihydroxylation of 1-ethyl-1-cycloheptene



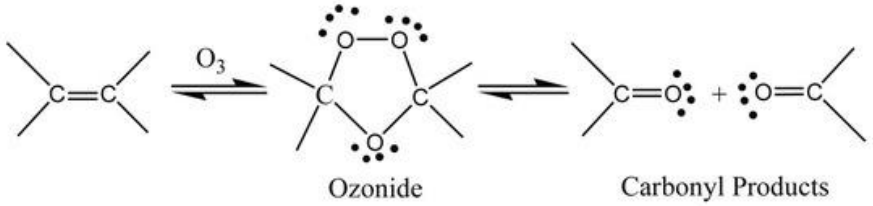
Hydroxylation of Alkenes

Dihydroxylated products (glycols) are obtained by reaction with aqueous potassium permanganate (pH > 8) or osmium tetroxide in pyridine solution. Both reactions appear to proceed by the same mechanism; the metallocyclic intermediate may be isolated in the osmium reaction. In basic solution, the purple permanganate anion is reduced to the green manganate ion, providing a nice color test for the double bond functional group. From the mechanism shown here we would expect syn-stereoselectivity in the bonding to oxygen, and regioselectivity is not an issue.

When viewed in context with the previously discussed addition reactions, the hydroxylation reaction might seem implausible. Permanganate and osmium tetroxide have similar configurations, in which the metal atom occupies the center of a tetrahedral grouping of negatively charged oxygen atoms. How, then, would such a species interact with the nucleophilic pi-electrons of a double bond? A possible explanation is that an empty d-orbital of the electrophilic metal atom extends well beyond the surrounding oxygen atoms and initiates electron transfer from the double bond to the metal, in much the same fashion noted above for platinum. Back-bonding of the nucleophilic oxygens to the antibonding π*-orbital completes this interaction.

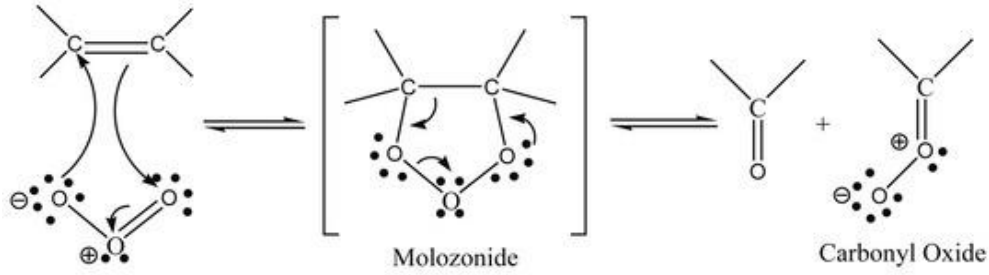
Ozonolysis of Alkenes

Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (*O_3*), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen. This reaction is often used to identify the structure of unknown alkenes by breaking them down into smaller, more easily identifiable pieces. Ozonolysis also occurs naturally and would break down repeated units used in rubber and other polymers. On an industrial scale, azelaic acid and pelargonic acids are produced from ozonolysis.



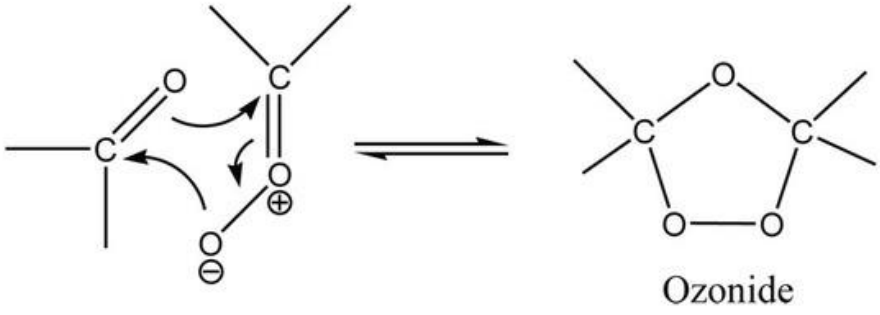
The gaseous ozone is first passed through the desired alkene solution in either methanol or dichloromethane. The first intermediate product is an ozonide molecule which is then further reduced to carbonyl products. This results in the breaking of the Carbon-Carbon double bond and is replaced by a Carbon-Oxygen double bond instead.

Step 1:



The first step in the mechanism of ozonolysis is the initial electrophilic addition of ozone to the Carbon-Carbon double bond, which then form the molozonide intermediate. Due to the unstable molozonide molecule, it continues further with the reaction and breaks apart to form a carbonyl and a carbonyl oxide molecule.

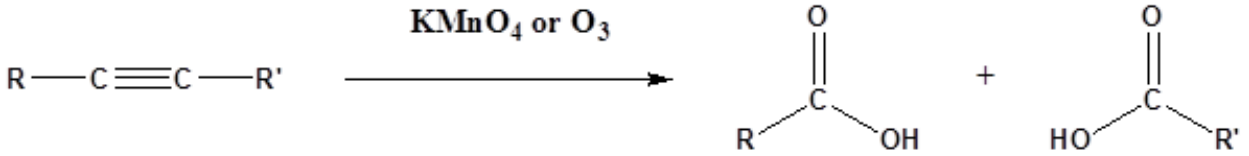
Step 2:



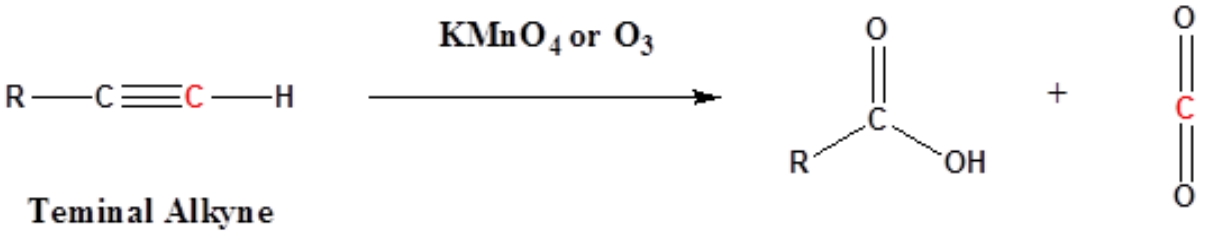
The carbonyl and the carbonyl oxide rearranges itself and reforms to create the stable ozonide intermediate. A reductive workup could then be performed to convert convert the ozonide molecule into the desired carbonyl products.

Oxidative Cleavage of Alkynes

Alkynes, much like alkene, can be cleaved with as powerful oxidizing agents such as ozone or $KMnO_4$. Because triple bonds are generally less reactive than double bonds the yields of the is reaction are sometimes low.



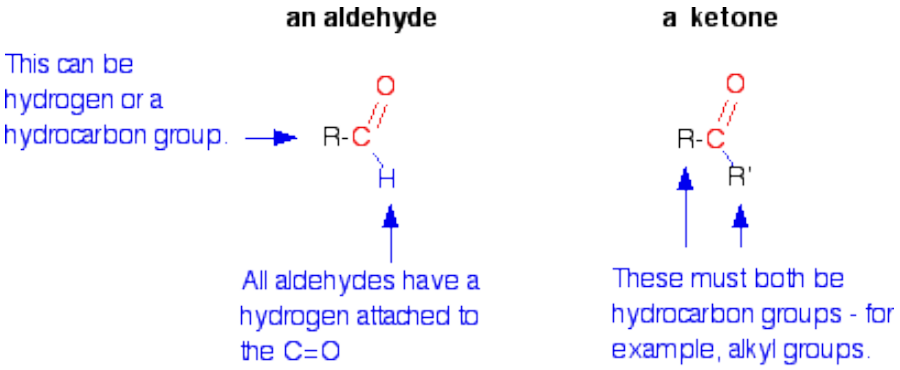
Internal Alkyne



Teminal Alkyne

Oxidation of Aldehydes

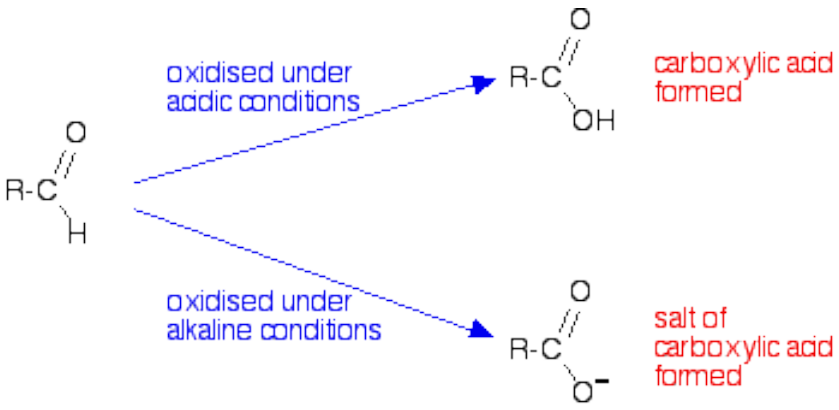
Why do aldehydes and ketones behave differently? You will remember that the difference between an aldehyde and a ketone is the presence of a hydrogen atom attached to the carbon-oxygen double bond in the aldehyde. Ketones don't have that hydrogen.



The presence of that hydrogen atom makes aldehydes very easy to oxidize. Or, put another way, they are strong reducing agents. However, because ketones do not have that particular hydrogen atom, they are resistant to oxidation, and only very strong oxidizing agents like potassium manganate(VII) solution (potassium permanganate solution) oxidize ketones. However, they do it in a destructive way, breaking carbon-carbon bonds.

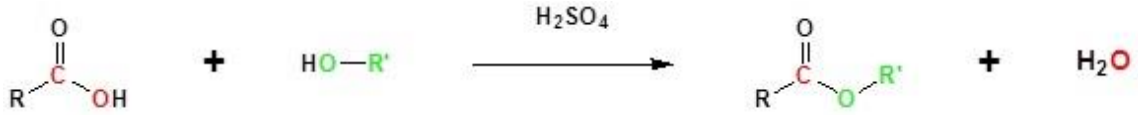
Provided you avoid using these powerful oxidizing agents, you can easily tell the difference between an aldehyde and a ketone. Aldehydes are easily oxidized by all sorts of different oxidizing agents and ketones are not.

What is formed when aldehydes are oxidized? It depends on whether the reaction is done under acidic or alkaline conditions. Under acidic conditions, the aldehyde is oxidized to a carboxylic acid. Under alkaline conditions, this couldn't form because it would react with the alkali. A salt is formed instead.

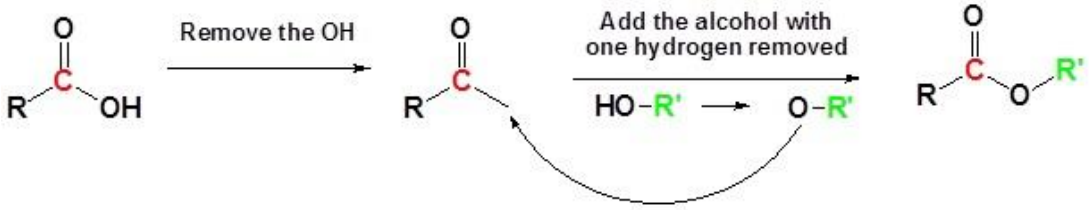


Fischer Esterification

Fischer esterification is the esterification of a Carboxylic acid by heating it with an alcohol in the presence of a strong acid as the catalyst.



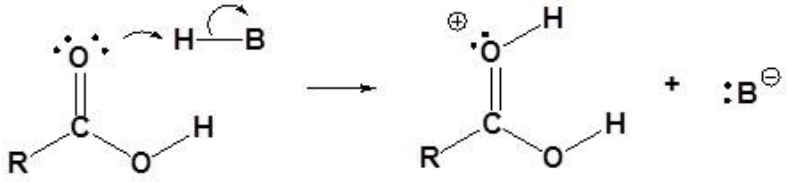
Going from reactants to products simplified.



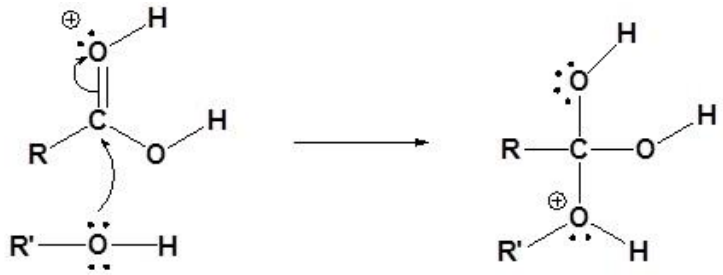
Mechanism

The overall reaction is reversible; to drive the reaction to completion, it is necessary to exploit Le Châteliers principle, which can be done either by continuously removing the water formed from the system or by using a large excess of the alcohol.

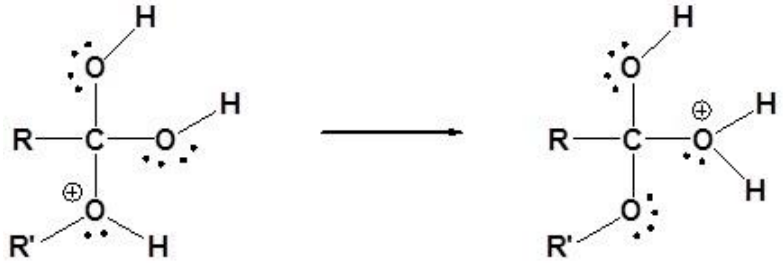
1) Protonation of the carbonyl by the acid. The carbonyl is now activated toward nucleophilic attack.



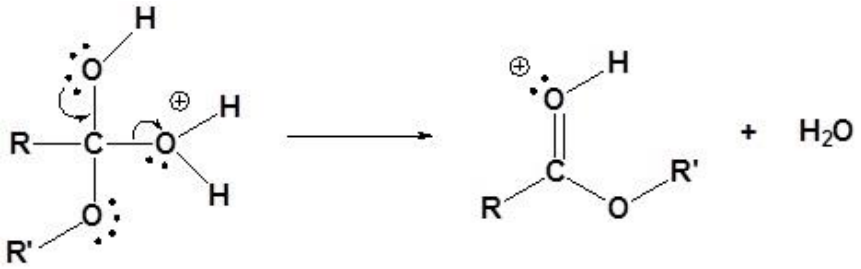
2) Nucleophilic attack on the carbonyl



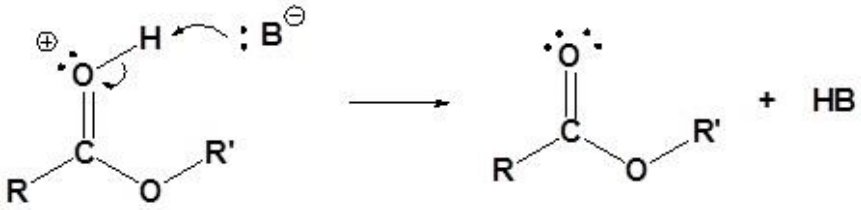
3) Proton transfer



4) Water leaves

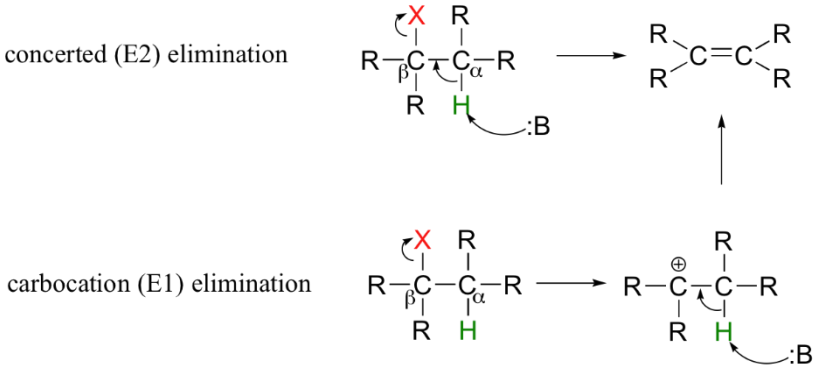


5) Deprotonation



TOPIC 12: ELIMINATION REACTIONS

Elimination reactions are possible at positions that are isolated from carbonyls or any other electron-withdrawing groups. This type of elimination can be described by two model mechanisms: it can occur in a single concerted step (proton abstraction at C_α occurring at the same time as C_β-X bond cleavage), or in two steps (C_β-X bond cleavage occurring first to form a carbocation intermediate, which is then 'quenched' by proton abstraction at the alpha-carbon).

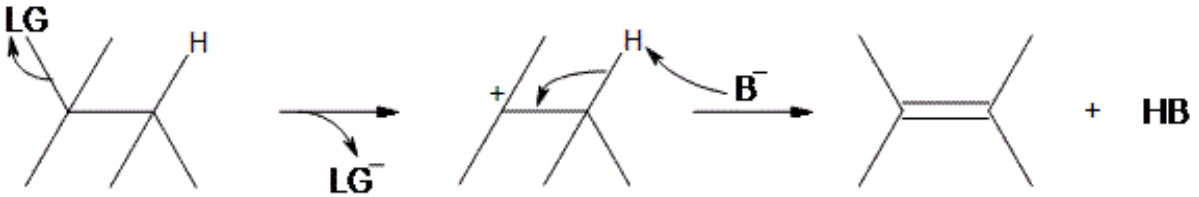


These mechanisms, termed E2 and E1, respectively, are important in laboratory organic chemistry, but are less common in biological chemistry. As explained below, which mechanism actually occurs in a laboratory reaction will depend on the identity of the R groups (i.e., whether the alkyl halide is primary, secondary, tertiary, etc.) as well as on the characteristics of the base.

E1 Reactions

Unimolecular Elimination (E1) is a reaction in which the removal of an HX substituent results in the formation of a double bond. It is similar to a unimolecular nucleophilic substitution reaction (S_N1) in various ways. One being the formation of a carbocation intermediate. Also, the only rate determining (slow) step is the dissociation of the leaving group to form a carbocation, hence the name unimolecular. Thus, since these two reactions behave similarly, they compete against each other. Many times, both these reactions will occur simultaneously to form different products from a single reaction. However, one can be favored over another through thermodynamic control.

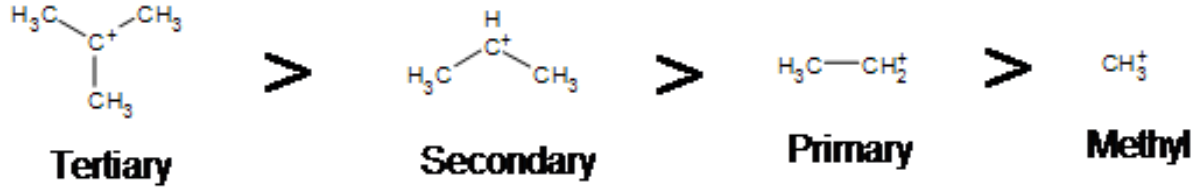
An E1 reaction involves the deprotonation of a hydrogen nearby (usually one carbon away, or the beta position) the carbocation resulting in the formation of an alkene product. In order to accomplish this, a Lewis base is required. For a simplified model, we'll take B to be a Lewis base, and LG to be a halogen leaving group.



As can be seen above, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base (*B*–) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond, forming a double bond.

Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct.

Reactivity
Due to the fact that E1 reactions create a carbocation intermediate, rules present in S_N1 reactions still apply.



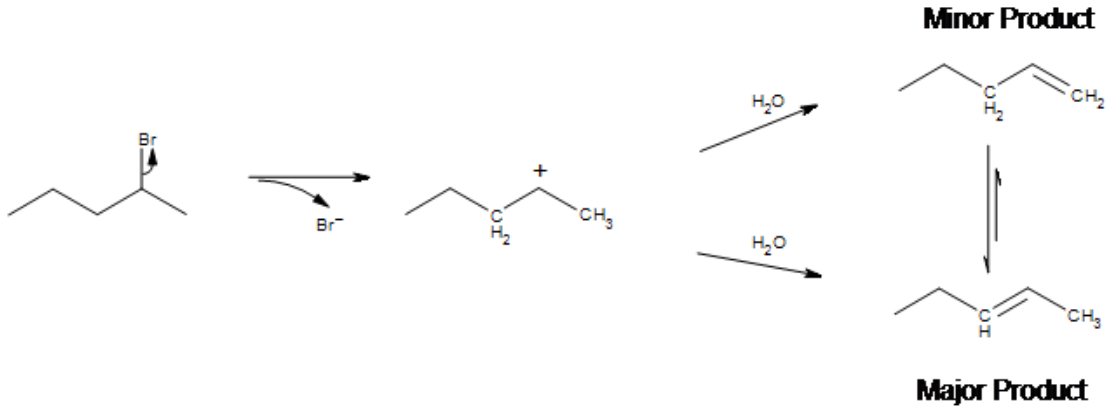
As expected, tertiary carbocations are favored over secondary, primary and methyl's. This is due to the phenomena of hyperconjugation, which essentially allows a nearby C-C or C-H bond to interact with the p orbital of the carbon to bring the electrons down to a lower energy state. Thus, this has a stabilizing effect on the molecule as a whole. In general, primary and methyl carbocations do not proceed through the E1 pathway for this reason, unless there is a means of carbocation rearrangement to move the positive charge to a nearby carbon. Secondary and Tertiary carbons form more stable carbocations, thus this formation occurs quite rapidly.

Secondary carbocations can be subject to the E2 reaction pathway, but this generally occurs in the presence of a good/strong base. Adding a weak base to the reaction disfavors E2, essentially pushing towards the E1 pathway. In many instances, solvolysis occurs rather than using a base to deprotonate. This means heat is added to the solution, and the solvent itself deprotonates a hydrogen. The medium can affect the pathway of the reaction as well. Polar protic solvents may be used to hinder nucleophiles, thus disfavoring E2 / S_N2 from occurring.

How are Regiochemistry & Stereochemistry Involved?

In terms of regiochemistry, Zaitsev's rule (defined later in this chapter) states that although more than one product can be formed during alkene synthesis, the more substituted alkene is the major product. This infers that the hydrogen on the most substituted carbon is the most probable to be deprotonated, thus allowing for the most substituted alkene to be formed.

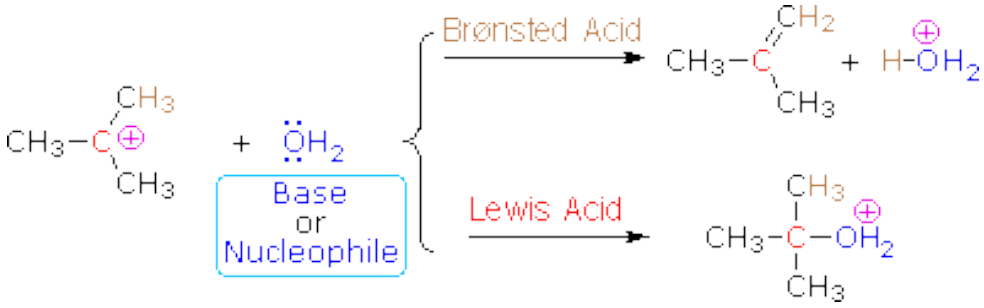
Unlike E2 reactions, E1 is not stereospecific. Thus, a hydrogen is not required to be anti-periplanar to the leaving group.



In this mechanism, we can see two possible pathways for the reaction. One in which the methyl on the right is deprotonated, and another in which the CH_2 on the left is deprotonated. Either one leads to a plausible resultant product, however, only one forms a major product. As stated by **Zaitsev's rule**, deprotonation of the most substituted carbon results in the most substituted alkene. This then becomes the most stable product due to hyperconjugation, and is also more common than the minor product.

The Connection Between S_N1 and E1

The E1 mechanism is nearly identical to the S_N1 mechanism, differing only in the course of reaction taken by the carbocation intermediate. As shown by the following equations, a carbocation bearing beta-hydrogens may function either as a Lewis acid (electrophile), as it does in the S_N1 reaction, or a Brønsted acid, as in the E1 reaction.



Thus, hydrolysis of tert-butyl chloride in a mixed solvent of water and acetonitrile gives a mixture of 2-methyl-2-propanol (60%) and 2-methylpropene (40%) at a rate independent of the water concentration. The alcohol is the product of an S_N1 reaction and the alkene is the product of the E1 reaction. The characteristics of these two reaction mechanisms are similar, as expected. They both show first order kinetics; neither is much influenced by a change in the nucleophile/base; and both are relatively non-stereospecific.

$$\mathbf{(CH_3)_3C–Cl \;+\; H_2O \;\longrightarrow\; [\,(CH_3)_3C(+)\,] \;+\; Cl(–) \;+\; H_2O \;\longrightarrow}$$

$$\mathbf{(CH_3)_3C–OH \;+\; (CH_3)_2C{=}CH_2 \;+\; HCl \;+\; H_2O}$$

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

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

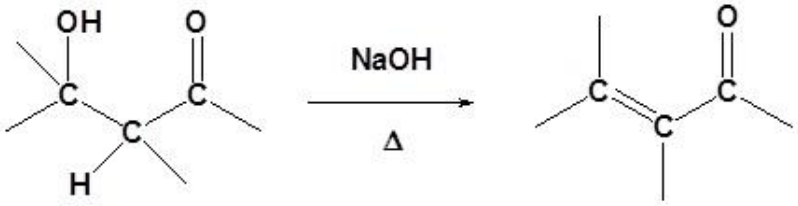
Since the S_N1 and E1 reactions proceed via the same carbocation intermediate, the product ratios are difficult to control and both substitution and elimination usually take place.

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**. The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br, or I. In cases where both S_N2 and E2 reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

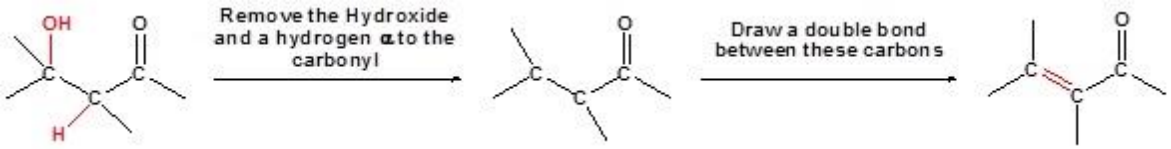
The E1cB Reaction

Although E1 reactions typically involves a carbocation intermediate, the E1cB reaction utilizes a carbanion intermediate. This reaction is generally utilized when a poor leaving group, such an and alcohol, is involved. This poor leaving group makes the direct E1 or E2 reactions difficult. This reaction is used later in a reaction called an aldol condensation.

The product of this ***β*-elimination** reaction is an α,β-unsaturated aldehyde or ketone. Base-catalyzed elimination occurs with heating. The additional stability provided by the conjugated carbonyl system of the product makes some aldol reactions thermodynamically and mixtures of stereoisomers (E & Z) are obtained from some reactions.

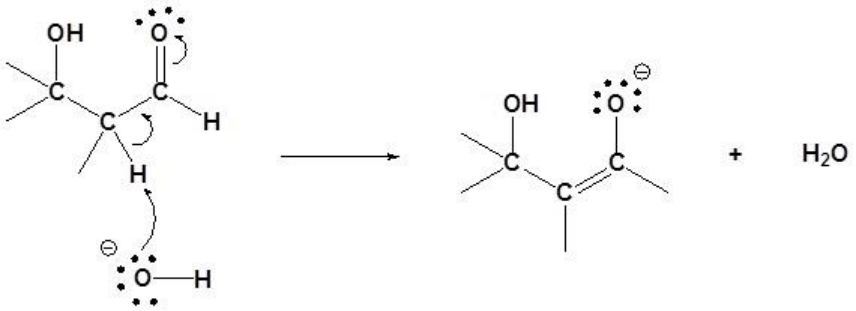


Going from reactants to products simply

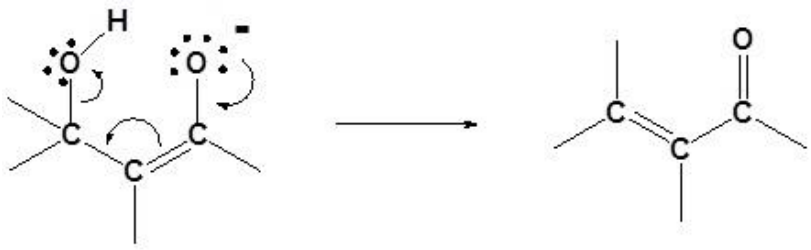


E1cB Mechanism

1) Form resonance stabilized anion



2) Form for conjugated alkene

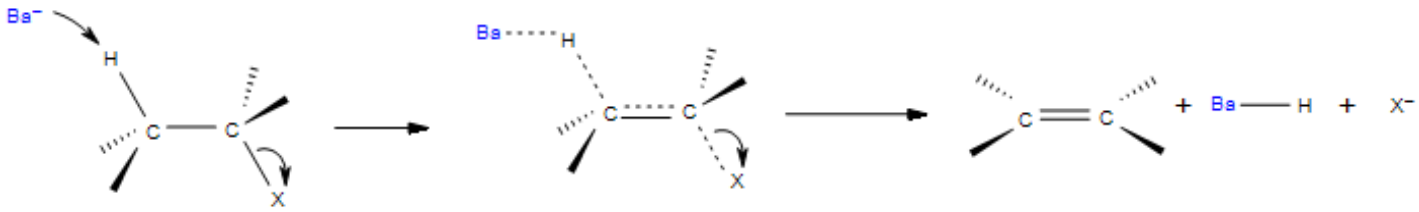


Note! The double bond always forms in conjugation with the carbonyl.

E2 Reactions

E2, bimolecular elimination, was proposed in the 1920s by British chemist Christopher Kelk Ingold. Unlike E1 reactions, E2 reactions remove two substituents with the addition of a strong base, resulting in an alkene.

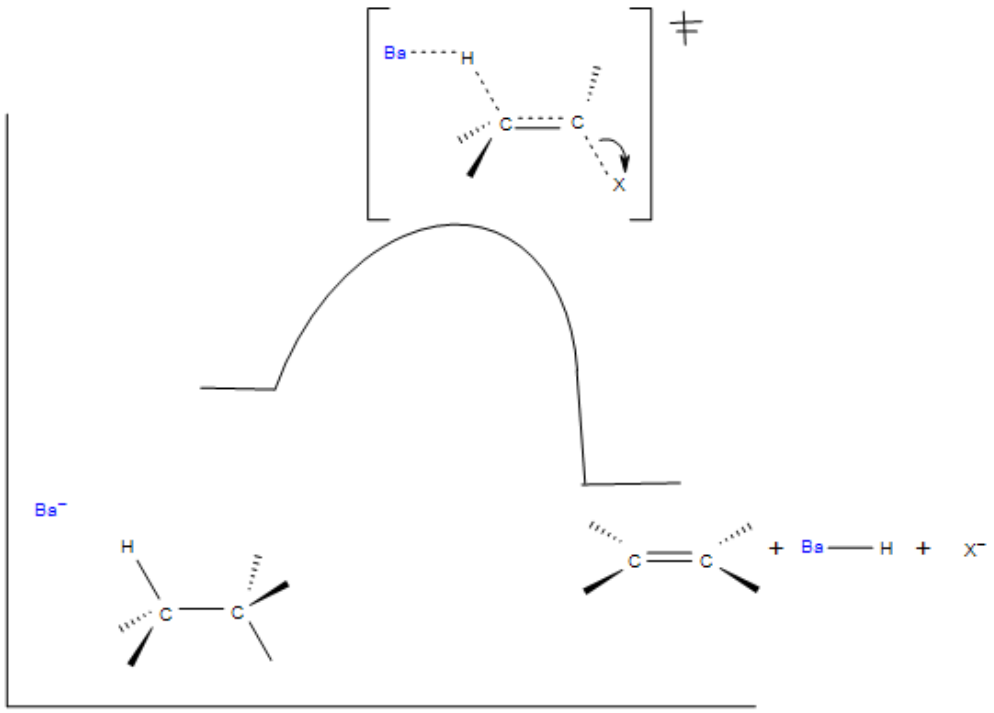
E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step concerted reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp3 to sp2 hybridization states.



In this reaction Ba represents the base and X represents a leaving group, typically a halogen. There is one transition state that shows the concerted reaction for the base attracting the hydrogen and the halogen taking the electrons from the bond. The product be both eclipse and staggered depending on the transition states. Eclipsed products have a synperiplanar transition states, while staggered products have antiperiplanar transition states. Staggered conformation is usually the major product because of its lower energy confirmation.

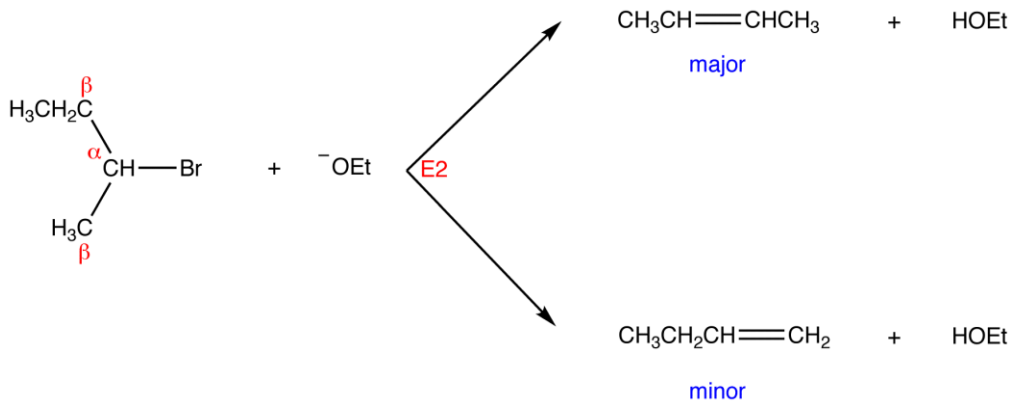
An E2 reaction has certain requirements to proceed:

- A strong base is necessary especially necessary for primary alkyl halides. Secondary and tertiary primary halides will proceed with E2 in the precedence of a base (OH-, RO-, R2N-)
- Both leaving groups should be on the same plane, this allows the double bond to form in the reaction. In the reaction above you can see both leaving groups are in the plane of the carbons.
- Follows Zaitsev's rule, the most substituted alkene is usually the major product.
- Hofmann Rule (see 12.3), if a sterically hindered base will result in the least substituted product.

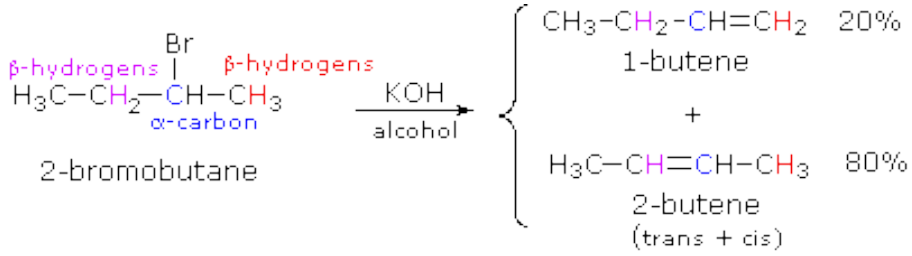


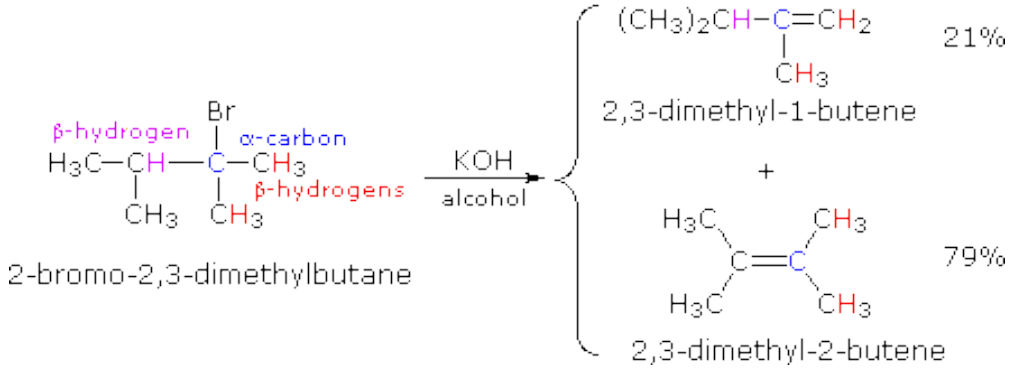
Zaitsev's Rule

Zaitsev's or Saytzev's (anglicized spelling) rule is an empirical rule used to predict regioselectivity of 1,2-elimination reactions occurring via the E1 or E2 mechanisms. It states that in a regioselective E1 or E2 reaction the major product is the more stable alkene, (i.e., the alkene with the more highly substituted double bond). For example:



If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.



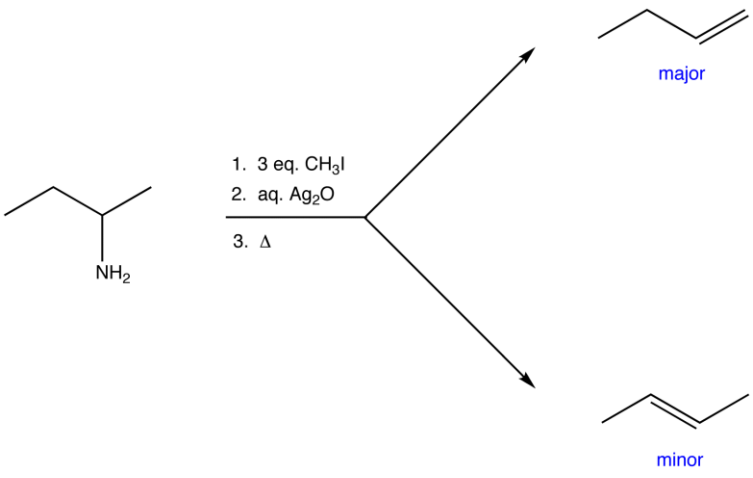


By using the strongly basic hydroxide nucleophile, we direct these reactions toward elimination. In both cases there are two different sets of beta-hydrogens available to the elimination reaction (these are colored red and magenta and the alpha carbon is blue). If the rate of each possible elimination was the same, we might expect the amounts of the isomeric elimination products to reflect the number of hydrogens that could participate in that reaction. For example, since there are three 1º-hydrogens (red) and two 2º-hydrogens (magenta) on beta-carbons in 2-bromobutane, statistics would suggest a 3:2 ratio of 1-butene and 2-butene in the products. This is not observed, and the latter predominates by 4:1. This departure from statistical expectation is even more pronounced in the second example, where there are six 1º-beta-hydrogens compared with one 3º-hydrogen. These results point to a strong regioselectivity favoring the more highly substituted product double bond, an empirical statement generally called the **Zaitsev Rule**.

Hofmann's Rule (or Hofmann Elimination)

When a primary amine bearing one or more beta hydrogens is treated with methyl iodide, followed by aqueous silver oxide, followed by heat, the primary amine is converted to an alkene. This reaction is known as Hofmann elimination.

Hofmann elimination is regioselective. Since the 1,2-elimination in Stage 3 occurs via E1cB mechanism, Hofmann rule is used to predict the major product. e.g.:



The key different between Hofmann and Zaitsev's rule is controlling which product is major and minor.

The larger leaving groups like $-NR_3^+$ and $-SR_2^+$ give more Hoffmann product than smaller groups like halogens. The bulkiness of the base also increases the Hoffmann product at the cost

of the Zaitsev product. The situation appears to be more complex. When the base strength was increased without increasing the bulk at the reaction site ($X\text{-}C_6H_4\text{-}O^-$), the Hoffmann product increased at the cost of the Zaitsev product. This suggests an E1cB mechanism, where the acidity of the β proton is important. Thus, the mechanism (and therefore the products composition) could be altered by factors such as the size of the leaving group, size of the base, nature of the leaving group and the strength of the base.

Elimination from Unsymmetrical Halogenoalkenes

2-bromobutane is an unsymmetrical halogenoalkane in the sense that it has a CH_3 group one side of the C-Br bond and a CH_2CH_3 group the other.

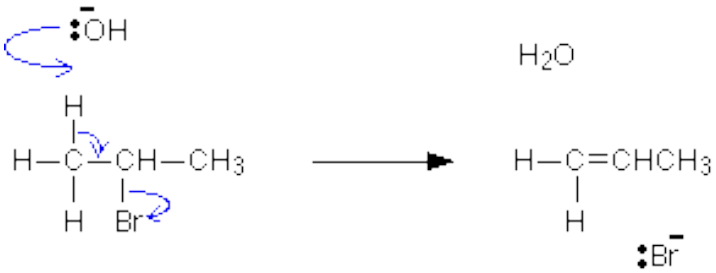
The basic facts and mechanisms for these reactions are exactly the same as with simple halogenoalkanes like 2-bromopropane. This page only deals with the extra problems created by the possibility of more than one elimination product.

Background to the mechanism

You will remember that elimination happens when a hydroxide ion (from, for example, sodium hydroxide) acts as a base and removes a hydrogen as a hydrogen ion from the halogenoalkane.

For example, in the simple case of elimination from 2-bromopropane:

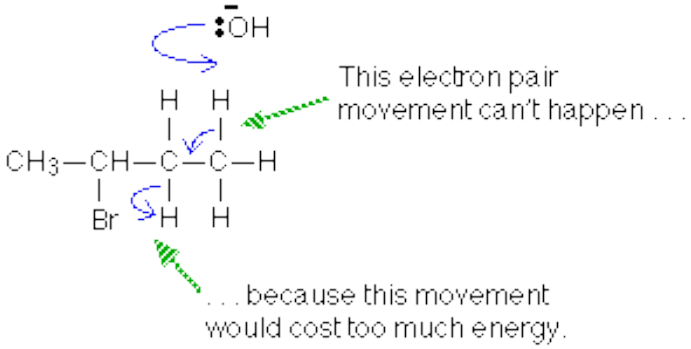
The hydroxide ion removes a hydrogen from one of the carbon atoms next door to the carbon-bromine bond, and the various electron shifts then lead to the formation of the alkene - in this case, propene.



With an unsymmetrical halogenoalkane like 2-bromobutane, there are several hydrogens which might possibly get removed. You need to think about each of these possibilities.

Where does the hydrogen get removed from?

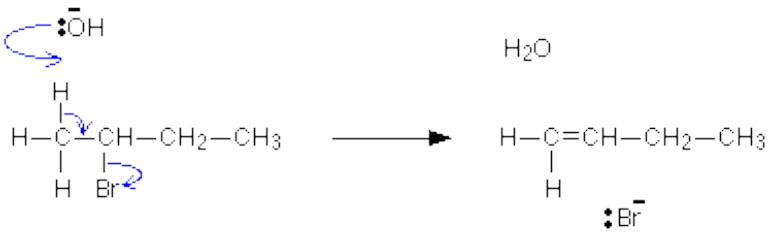
The hydrogen has to be removed from a carbon atom adjacent to the carbon-bromine bond. If an OH- ion hit one of the hydrogens on the right-hand CH_3 group in the 2-bromobutane (as we've drawn it), there's nowhere for the reaction to go.



To make room for the electron pair to form a double bond between the carbons, you would have to expel a hydrogen from the CH_2 group as a hydride ion, H-. That is energetically much too difficult, and so this reaction doesn't happen.

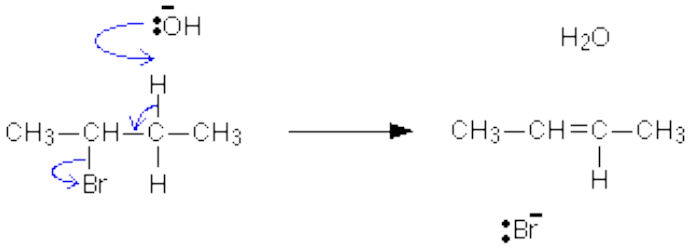
That still leaves the possibility of removing a hydrogen either from the left-hand CH_3 or from the CH_2 group.

If it was removed from the CH3 group:



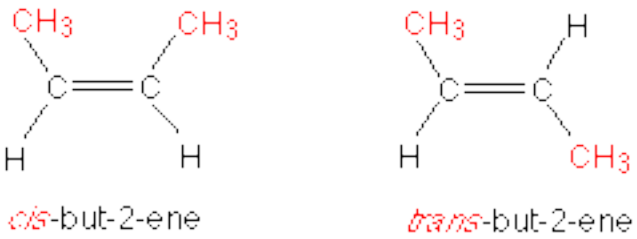
The product is but-1-ene, $CH_2=CHCH_2CH_3$.

If it was removed from the CH2 group:



This time the product is but-2-ene, $CH_3CH=CHCH_3$.

In fact, the situation is even more complicated than it looks, because but-2-ene exhibits geometric isomerism. You get a mixture of two isomers formed - cis-but-2-ene and trans-but-2-ene.



Cis-but-2-ene is also known as (Z)-but-2-ene; trans-but-2-ene is also known as (E)-but-2-ene. For an explanation of the two ways of naming these two compounds, follow the link in the box below.

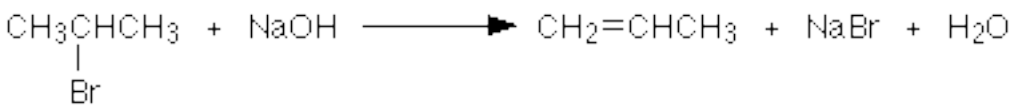
Which isomer gets formed is just a matter of chance.

The overall result

Elimination from 2-bromobutane leads to a mixture containing but-1-ene, cis-but-2-ene (also known as (Z)-but-2-ene), and trans-but-2-ene (also known as (E)-but-2-ene).

Example: Elimination Reaction Involving 2-bromopropane and Hydroxide Ions

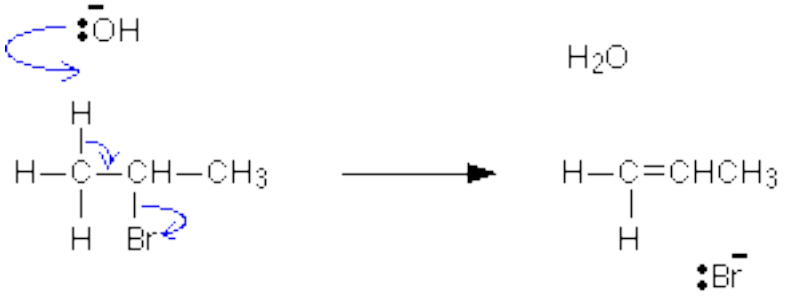
2-bromopropane is heated under reflux with a concentrated solution of sodium or potassium hydroxide in ethanol. Heating under reflux involves heating with a condenser placed vertically in the flask to avoid loss of volatile liquids. Propene is formed and, because this is a gas, it passes through the condenser and can be collected.



Everything else present (including anything formed in the alternative substitution reaction) will be trapped in the flask.

The mechanism

In elimination reactions, the hydroxide ion acts as a base - removing a hydrogen as a hydrogen ion from the carbon atom next door to the one holding the bromine. The resulting re-arrangement of the electrons expels the bromine as a bromide ion and produces propene.



TOPIC 13: SUMMARY OF REACTIVITY AND REACTION EXCEPTIONS

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**. In general, in order for an S_N1 or E1 reaction to occur, the relevant carbocation intermediate must be relatively stable. Strong nucleophile favor substitution, and strong bases, especially strong hindered bases (such as tert-butoxide) favor elimination.

The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I. In cases where both S_N2 and E2 reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

The following table summarizes the expected outcome of alkyl halide reactions with nucleophiles. It is assumed that the alkyl halides have one or more beta-hydrogens, making elimination possible. **Note that halogens bonded to sp^2 or sp hybridized carbon atoms do not normally undergo substitution or elimination reactions with nucleophilic reagents**.

Nucleophile **Alkyl Group**	**Anionic Nucleophiles** (Weak Bases: I^-, Br^-, SCN^-, N_3^-, $CH_3CO_2^-$, RS^-, CN^-etc.) pK_a's from -9 to 10 (left to right)	**Anionic Nucleophiles** (Strong Bases: HO^-, RO^-) pK_a's > 15	**Neutral Nucleophiles** (H_2O, ROH, RSH, R_3N) pK_a's ranging from -2 to 11
Primary RCH_2–	Rapid S_N2 substitution. The rate may be reduced by substitution of β-carbons, as in the case of neopentyl.	Rapid S_N2 substitution. E2 elimination may also occur. *e.g.* $ClCH_2CH_2Cl + KOH$ ——> $CH_2=CHCl$	S_N2 substitution. (N ≈ S >>O)
Secondary R_2CH–	S_N2 substitution and / or E2 elimination (depending on the basicity of the nucleophile). Bases weaker than acetate (pK_a = 4.8) give less elimination. The rate of substitution may be reduced by branching at the β-carbons, and this will increase elimination.	E2 elimination will dominate.	S_N2 substitution. (N ≈ S >>O)
Tertiary R_3C–	E2 elimination will dominate with most nucleophiles (even if they are weak bases). No S_N2 substitution due to steric hindrance	E2 elimination will dominate. No S_N2 substitution will occur.	E2 elimination with nitrogen nucleophiles (they are bases). No S_N2 substitution.

Allyl $H_2C=CHCH_2–$	Rapid S_N2 substitution for 1º and 2º-halides. For 3º-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2 elimination	Rapid S_N2 substitution for 1º halides. E2 elimination will compete with substitution in 2º-halides, and dominate in the case of 3º-halides.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1º and 2º-halides. 3º-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases).
Benzyl $C_6H_5CH_2–$	Rapid S_N2 substitution for 1º and 2º-halides. For 3º-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2	Rapid S_N2 substitution for 1º halides (note there are no β hydrogens). E2 elimination will compete with substitution in 2º-halides, and dominate in the case of 3º-halides.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1º and 2º-halides. 3º-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases).

What decides whether you get substitution or elimination?

The reagents you are using are the same for both substitution and elimination - the halogenoalkane and either sodium or potassium hydroxide solution. In all cases, you will get a mixture of both reactions happening - some substitution and some elimination. What you get most of depends on a number of factors.

The Type of Halogenoalkane

This is the most important factor.

Type of Halogenoalkane	Substitution or Elimination?
primary	mainly substitution
secondary	both substitution and elimination
tertiary	mainly elimination

For example, whatever you do with tertiary halogenoalkanes, you will tend to get mainly the elimination reaction, whereas with primary ones you will tend to get mainly substitution. However, you can influence things to some extent by changing the conditions.

The Solvent

The proportion of water to ethanol in the solvent matters.

- Water encourages substitution.
- Ethanol encourages elimination.

The Temperature

Higher temperatures encourage elimination.

Concentration of the sodium or potassium hydroxide solution
Higher concentrations favor elimination.

In Summary

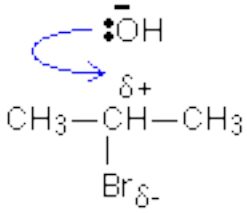
For a given halogenoalkane, to favour elimination rather than substitution, use:

- heat
- a concentrated solution of sodium or potassium hydroxide
- pure ethanol as the solvent

The role of the Hydroxide Ions

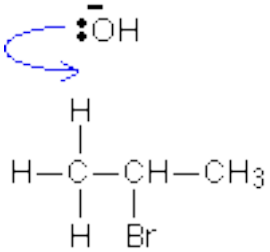
The role of the hydroxide ion in a substitution reaction

In the substitution reaction between a halogenoalkane and OH- ions, the hydroxide ions are acting as nucleophiles. For example, one of the lone pairs on the oxygen can attack the slightly positive carbon. This leads on to the loss of the bromine as a bromide ion, and the -OH group becoming attached in its place.



The role of the hydroxide ion in an elimination reaction

Hydroxide ions have a very strong tendency to combine with hydrogen ions to make water - in other words, the OH- ion is a very strong base. In an elimination reaction, the hydroxide ion hits one of the hydrogen atoms in the CH_3 group and pulls it off. This leads to a cascade of electron pair movements resulting in the formation of a carbon-carbon double bond, and the loss of the bromine as Br-.



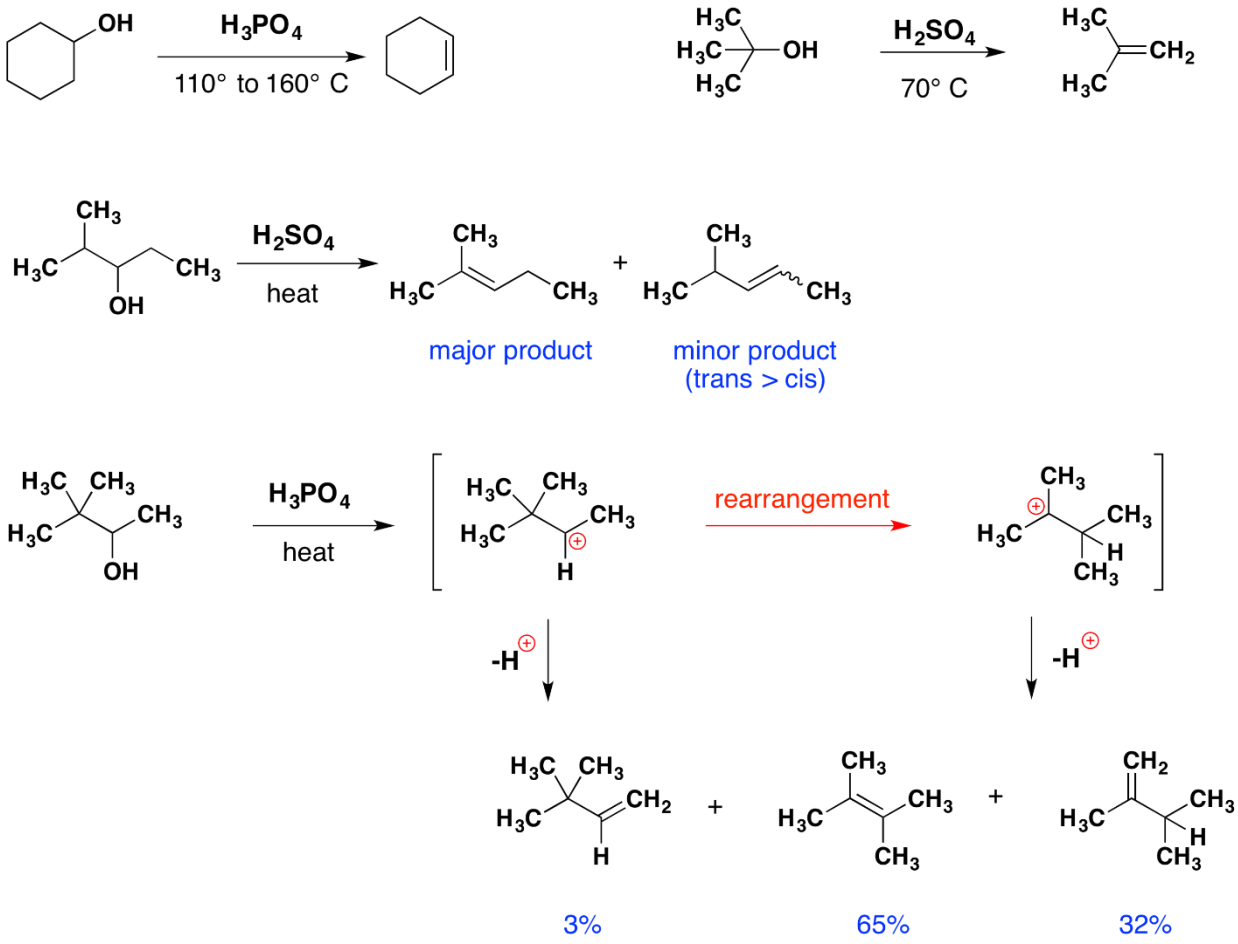
Alcohols

Elimination Reactions of Alcohols: Dehydration

The discussion of alkyl halide reactions noted that 2º and 3º-alkyl halides experience rapid E2 elimination when treated with strong bases such as hydroxide and alkoxides. Alcohols do not undergo such base-induced elimination reactions and are, in fact, often used as solvents for such reactions. This is yet another example of how leaving-group stability influences the rate of a reaction. When an alcohol is treated with sodium hydroxide, the following acid-base equilibrium occurs. Most alcohols are slightly weaker acids than water, so the left side is favored.]

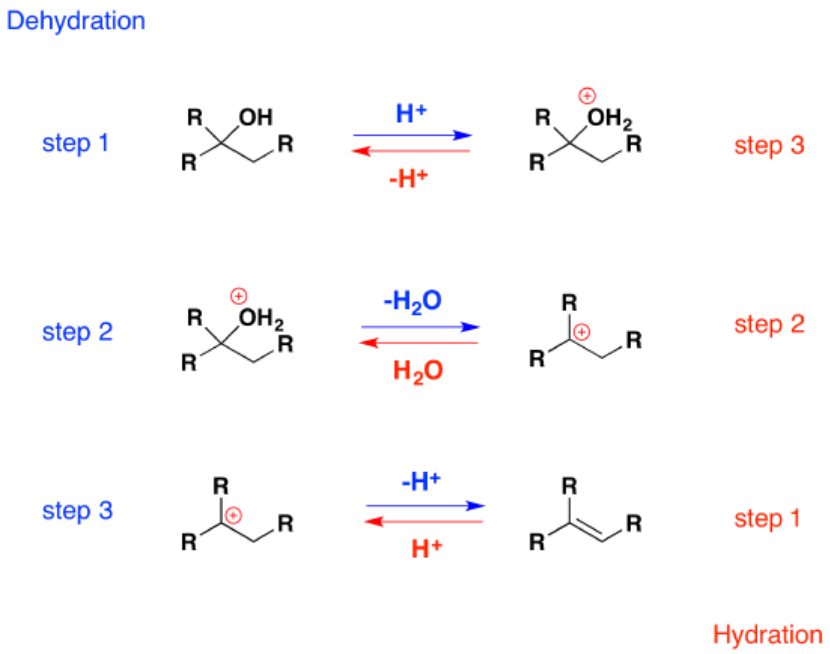
$$\text{R–O–H} \quad + \quad \text{Na(+) OH(–)} \rightleftharpoons \text{R–O(–) Na(+)} \quad + \quad \text{H–OH}$$

The elimination of water from an alcohol is called **dehydration**. Recalling that water is a much better leaving group than hydroxide ion, it is sensible to use acid-catalysis rather than base-catalysis in such reactions. Four examples of this useful technique are shown below. Note that hydrohalic acids (HX) are not normally used as catalysts because their conjugate bases are good nucleophiles and may create substitution products. The conjugate bases of sulfuric and phosphoric acids are not good nucleophiles, and do not participate in substitution under typical conditions.



The first two examples (in the top row) are typical, and the more facile elimination of the 3º-alcohol suggests the predominant E1 character for the reaction. This agrees with the tendency of branched 1º and 2º-alcohols to yield rearrangement products, as shown in the last example. The last two reactions also demonstrate that the Zaitsev rule applies to alcohol dehydrations, as well as to alkyl halide eliminations. Therefore, the more highly-substituted double bond isomer is favored among the products.

It should be noted that the acid-catalyzed dehydrations discussed here are the reverse of the acid-catalyzed hydration reactions of alkenes. Indeed, for these types of reversible reactions, the laws of thermodynamics require that the mechanism in both directions proceed by the same reaction path. This is known as **the principle of microscopic reversibility**. To illustrate, the following diagram lists the three steps in each transformation. The dehydration reaction is shown by the blue arrows; the hydration reaction by magenta arrows. The intermediates in these reactions are common to both, and common transition states are involved. This can be seen clearly in the energy diagrams depicted by clicking the button beneath the equations.



About Primary Alcohols

E1 reactions involve an unstable carbocations, and the transition state has lower energy with primary alcohols. Protonating the alcohol is required to create a good leaving group. Then, a weak base can break the C–H bond, creating an alkene. At that point, a standard E2 reaction can occur.

Oxidation of the Different Types of Alcohol

The oxidizing agent used in these reactions is normally a solution of sodium or potassium dichromate(VI) acidified with dilute sulfuric acid. If oxidation occurs, then the orange solution containing the dichromate(VI) ions is reduced to a green solution containing chromium(III) ions. The electron-half-equation for this reaction is as follows:

$$\mathbf{Cr_2O_2^{7-} + 14H^+ + 6e- \rightarrow 2Cr_3^+ + 7H_2O}$$

Primary Alcohols

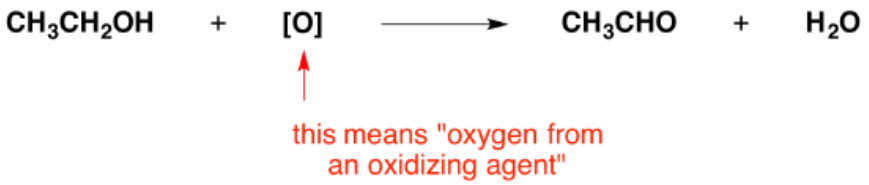
Primary alcohols can be oxidized to either aldehydes or carboxylic acids, depending on the reaction conditions. In the case of the formation of carboxylic acids, the alcohol is first oxidized to an aldehyde, which is then oxidized further to the acid.

An aldehyde is obtained if an excess amount of the alcohol is used, and the aldehyde is distilled off as soon as it forms. An excess of the alcohol means that there is not enough oxidizing agent present to carry out the second stage, and removing the aldehyde as soon as it is formed means that it is not present to be oxidized anyway!

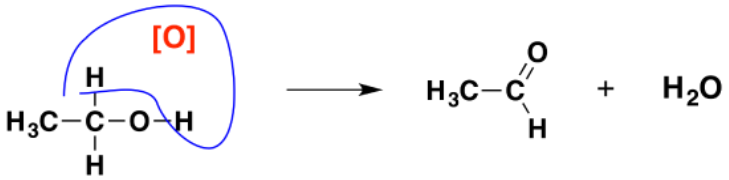
If you used ethanol as a typical primary alcohol, you would produce the aldehyde ethanal, (CH_3CHO). The full equation for this reaction is fairly complicated, and you need to understand the electron-half-equations in order to work it out.

$$\mathbf{3CH_3CH_2OH + Cr_2O_2^{7-} + 8H^+ \rightarrow 3CH_3CHO + 2Cr_3^+ + 7H_2O}$$

In organic chemistry, simplified versions are often used that concentrate on what is happening to the organic substances. To do that, oxygen from an oxidizing agent is represented as [*O*]. That would produce the much simpler equation:



It also helps in remembering what happens. You can draw simple structures to show the relationship between the primary alcohol and the aldehyde formed.



Full Oxidation to Carboxylic Acids

An excess of the oxidizing agent must be used, and the aldehyde formed as the half-way product should remain in the mixture. The alcohol is heated under reflux with an excess of the oxidizing agent. When the reaction is complete, the carboxylic acid is distilled off. The full equation for the oxidation of ethanol to ethanoic acid is as follows:

$$3CH_3CH_2OH + 2Cr_2O_2^{7-} + 16H^+ \rightarrow 3CH_3COOH + 4Cr_3^+ + 11H_2O$$

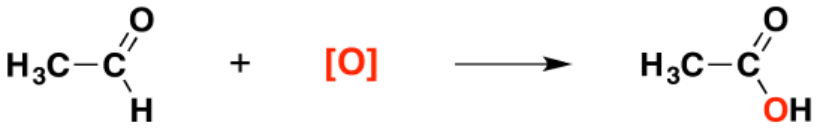
The more typical simplified version looks like this:

$$CH_3CH_2OH + 2[O] \rightarrow CH_3COOH + H_2O$$

Alternatively, you could write separate equations for the two stages of the reaction - the formation of ethanal and then its subsequent oxidation.

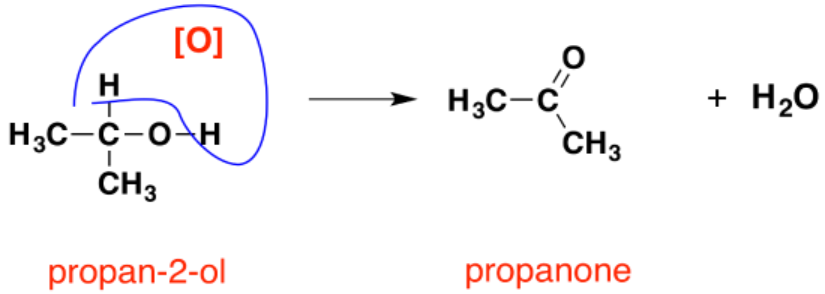
$$CH_3CH_2OH + [O] \rightarrow CH_3CHO + H_2O$$

This is what is happening in the second stage:



Secondary Alcohols

Secondary alcohols are oxidized to ketones - and that's it. For example, if you heat the secondary alcohol propan-2-ol with sodium or potassium dichromate (VI) solution acidified with dilute sulfuric acid, propanone is formed. Changing the reaction conditions makes no difference to the product. Following is the simple version of the equation, showing the relationship between the structures:

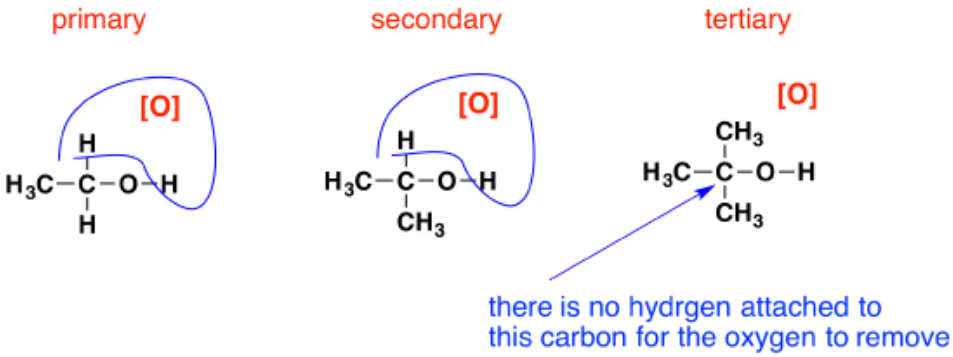


If you look back at the second stage of the primary alcohol reaction, you will see that an oxygen inserted between the carbon and the hydrogen in the aldehyde group to produce the carboxylic acid. In this case, there is no such hydrogen - and the reaction has nowhere further to go.

Tertiary Alcohols

Tertiary alcohols are not oxidized by acidified sodium or potassium dichromate (VI) solution - there is no reaction whatsoever. If you look at what is happening with primary and secondary alcohols, you will see that the oxidizing agent is removing the hydrogen from the -OH group, and a hydrogen from the carbon atom is attached to the -OH. Tertiary alcohols don't have a hydrogen atom attached to that carbon.

You need to be able to remove those two particular hydrogen atoms in order to set up the carbon-oxygen double bond.

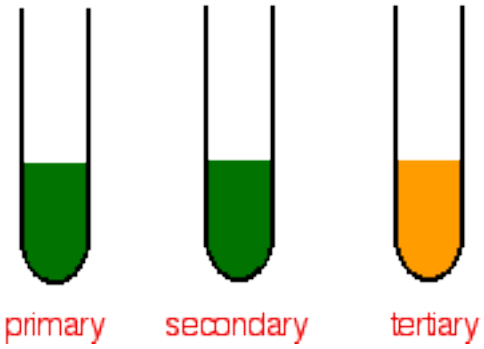


Using these reactions as a test for the different types of alcohols

First, the presence of an alcohol must be confirmed by testing for the -OH group. The liquid would need to be verified as neutral, free of water and that it reacted with solid phosphorus (V) chloride to produce a burst of acidic steamy hydrogen chloride fumes. A few drops of the alcohol would be added to a test tube containing potassium dichromate (VI) solution acidified with dilute sulfuric acid. The tube would be warmed in a hot water bath.

Determining the tertiary alcohol

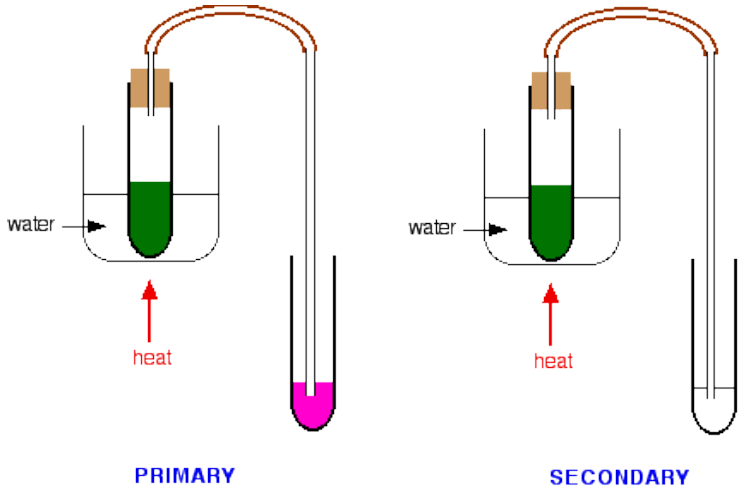
In the case of a primary or secondary alcohol, the orange solution turns green. With a tertiary alcohol, there is no color change. After heating, the following colors are observed:



Distinguishing Between the Primary and Secondary Alcohols
A sufficient amount of the aldehyde (from oxidation of a primary alcohol) or ketone (from a secondary alcohol) must be produced to be able to test them. There are various reactions that aldehydes undergo that ketones do not. These include the reactions with Tollens' reagent, Fehling's solution and Benedict's solution, and these reactions are covered on a separate page.

These tests can be difficult to carry out, and the results are not always as clear-cut as the books say. A much simpler but fairly reliable test is to use *Schiff's reagent*. Schiff's reagent is a fuchsine dye decolorized by passing sulfur dioxide through it. In the presence of even small amounts of an aldehyde, it turns bright magenta.

It must, however, be used absolutely cold, because ketones react with it very slowly to give the same color. If you heat it, obviously the change is faster - and potentially confusing. While you are warming the reaction mixture in the hot water bath, you can pass any vapors produced through some Schiff's reagent.



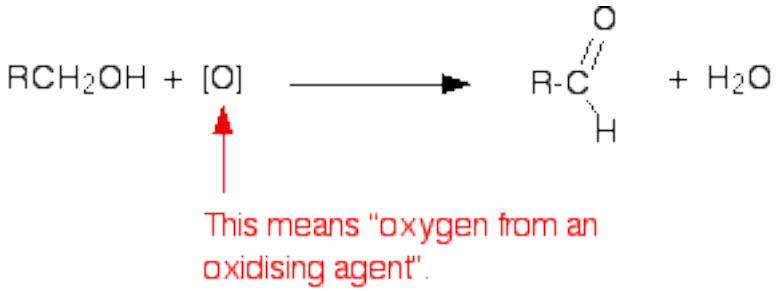
- If the Schiff's reagent quickly becomes magenta, then you are producing an aldehyde from a primary alcohol.
- If there is no color change in the Schiff's reagent, or only a trace of pink color within a minute or so, then you are not producing an aldehyde; therefore, no primary alcohol is present.

Because of the color change to the acidified potassium dichromate (VI) solution, you must, therefore, have a secondary alcohol. You should check the result as soon as the potassium dichromate (VI) solution turns green - if you leave it too long, the Schiff's reagent might start to change color in the secondary alcohol case as well.

Primary Alcohols and Aldehydes to Carboxylic Acids

Primary alcohols and aldehydes are normally oxidized to carboxylic acids using potassium dichromate (VI) solution in the presence of dilute sulfuric acid. During the reaction, the potassium dichromate (VI) solution turns from orange to green. The potassium dichromate (VI) can just as well be replaced with sodium dichromate (VI). Because what matters is the dichromate (VI) ion, all the equations and color changes would be identical.

Primary alcohols are oxidized to carboxylic acids in two stages - first to an aldehyde and then to the acid. We often use simplified versions of these equations using "[O]" to represent oxygen from the oxidizing agent. The formation of the aldehyde is shown by the simplified equation:



"R" is a hydrogen atom or a hydrocarbon group such as an alkyl group. The aldehyde is then oxidized further to give the carboxylic acid:

If you start with an aldehyde, you are obviously just doing this second stage. Starting from the primary alcohol, you could combine these into one single equation to give:

$$\mathbf{RCH_2OH + 2[O] \rightarrow RCOOH + H_2O}$$

For example, if you were converting ethanol into ethanoic acid, the simplified equation would be:

$$\mathbf{CH_3CH_2OH + 2[O] \rightarrow CH_3COOH + H_2O}$$

It is possible that you might want to write proper equations for these reactions rather than these simplified ones. You can work these out from electron-half-equations. How you do this is described in detail elsewhere on the site.

The complete equation for the conversion of a primary alcohol to a carboxylic acid is:

$$\mathbf{3RCH_2OH + 2Cr_2O_2^{7-} + 16H^+ \rightarrow 3RCOOH + 4Cr_3^+ + 11H_2O}$$

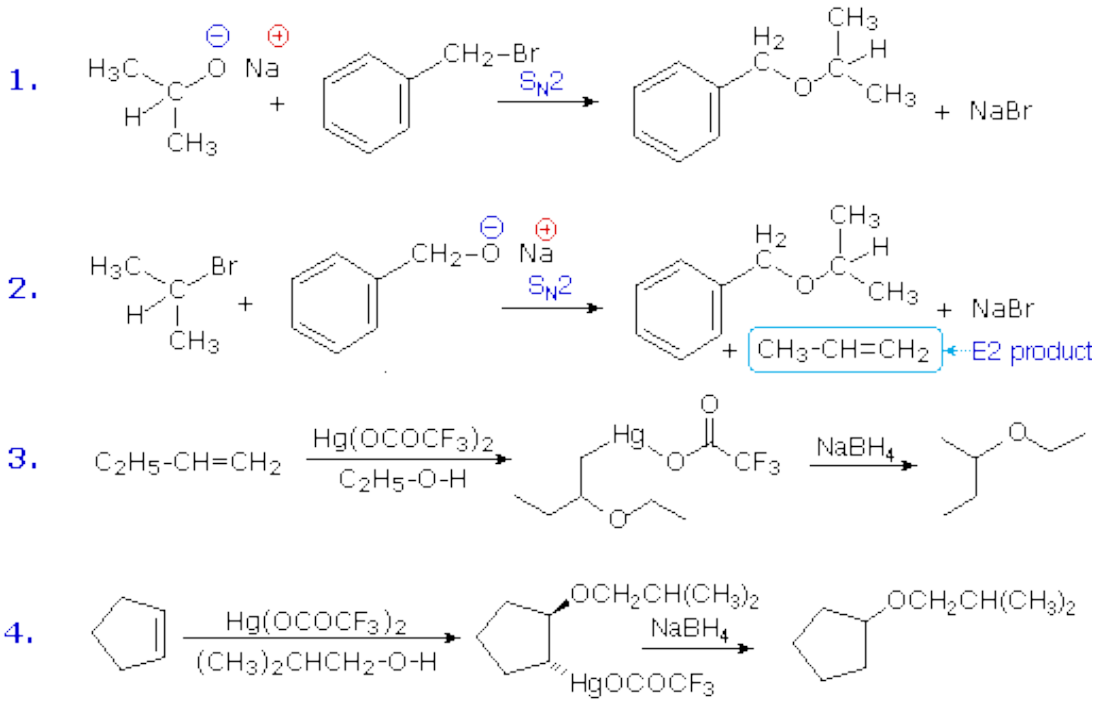
or if you were starting from an aldehyde is:

$$\mathbf{3RCHO + Cr_2O_2^{7-} + 8H^+ \rightarrow 3RCOOH + 3Cr_3^+ + 4H_2O}$$

Ethers

Williamson Ether Synthesis

Ethers are usually prepared from alcohols or their conjugate bases. One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with an alkyl halide. Reactions #1 and #2 below are two examples of this procedure. When applied to an unsymmetrical ether, as in this case, there are two different combinations of reactants are possible. Of these one is usually better than the other. Since alkoxide anions are strong bases, the possibility of a competing E2 elimination must always be considered. Bearing in mind the factors that favor substitution over elimination, a 1º-alkyl halide should be selected as a preferred reactant whenever possible. Thus, reaction #1 gives a better and cleaner yield of benzyl isopropyl ether than does reaction #2, which generates considerable elimination product.



A second general ether synthesis, **alkoxymercuration**, is patterned after the oxymercuration reaction. Reactions #3 and #4 are examples of this two-step procedure. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the acetate (trifluoroacetate anion is a poorer nucleophile than acetate). The mechanism of alkoxymercuration is similar to that of oxymercuration, with an initial anti-addition of the mercuric species and alcohol being followed by reductive demercuration.

Acid-catalyzed dehydration of small 1º-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. As shown in the following two equations, the success of this procedure depends on the temperature. At 110º to 130ºC, an SN2 reaction of the alcohol conjugate acid leads to an ether product.

$$2CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{130^oC} CH_3CH_2{-}O{-}CH_2CH_3 + H2O$$

At higher temperatures (over 150ºC), an E2 elimination takes place.

$$CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{150^oC} CH_2{=}CH_2 + H_2O$$

This reaction **cannot** be employed to prepare unsymmetrical ethers. It is because a mixture of products is likely to be obtained.

Thiols and Sulfides

Oxidation States of Sulfur Compounds

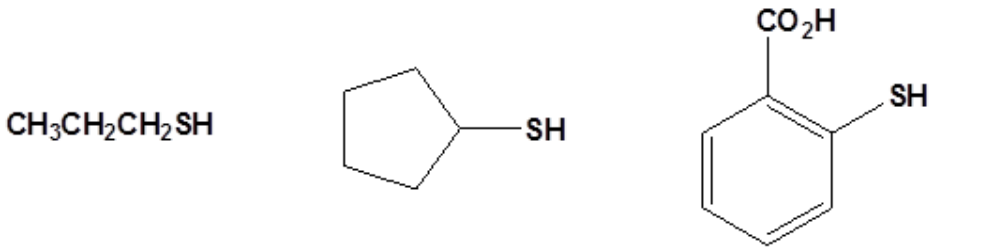
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

Sulfur Oxidation States in Organic Compounds

-2	-1	0	+2	+4	+6
H_2S R–S–H thiols R–S–R sulfides R–S(⊕)(R)–R sulfonium ions	R–S–S–R disulfides	S elemental R–S(=O)–R sulfoxides R–S–OH sulfenic acids	R–S(=O)(=O)–R sulfones R–S(=O)–OH sulfinic acids	SO_2 R–S(=O)(=O)–OH sulfonic acids R-O–S(=O)–O-R sulfite esters	SO_3 R-O–S(=O)(=O)–O-R sulfate esters

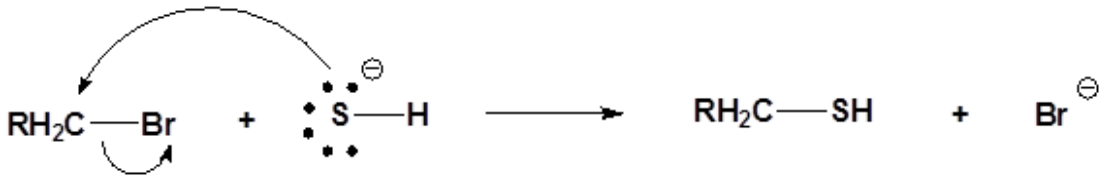
Thiols

Thiols, which are also called *mercaptans*, are analogous to alcohols. They are named in a similar fashion as alcohols except the suffix *-thiol* is used in place of *-ol*. By itself the -SH group is called a *mercapto* group.



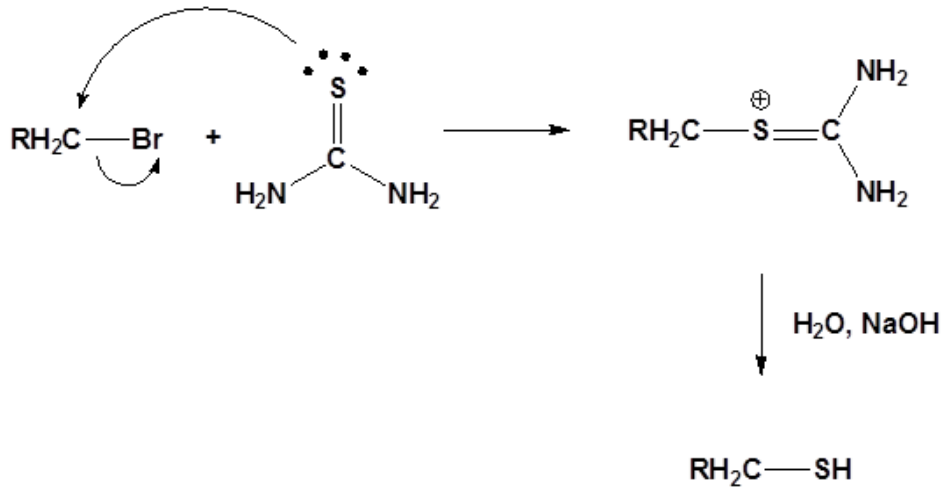
Propanethiol **Cyclopentanethiol** **o-Mercaptobenzoic acid**

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a neucleophile in an S_N2 reaction with alkyl halides.



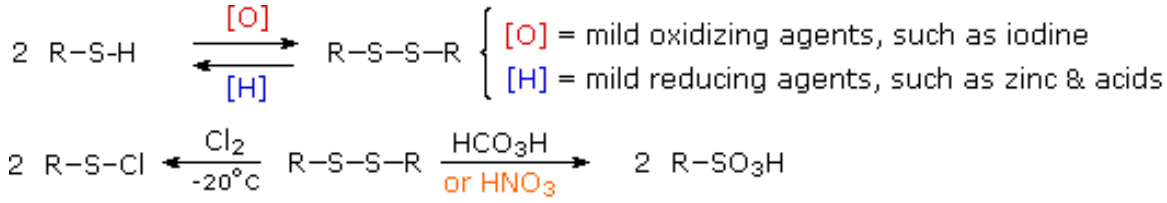
On problem with this reaction is that the thiol product can undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C=S$, as

the nucleophile. The reaction first produces an alkyl isothiourea salt and an intermediate. This salt is then hydrolyzed by a reaction with aqueous base.



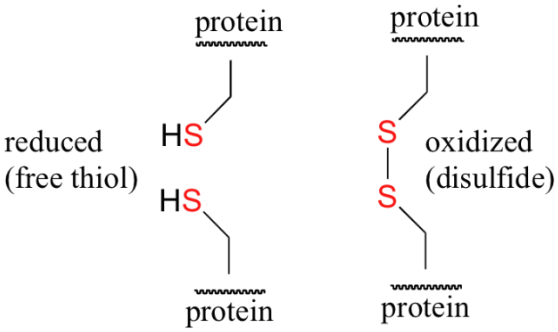
Disulfides

Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disufides. An equivalent oxidation of alcohols to peroxides is not normally observed. The reasons for this different behavior are not hard to identify. The S–S single bond is nearly twice as strong as the O–O bond in peroxides, and the O–H bond is more than 25 kcal/mole stronger than an S–H bond. Thus, thermodynamics favors disulfide formation over peroxide.



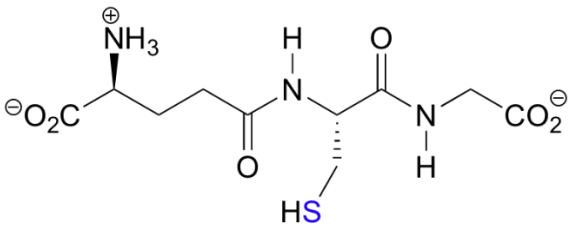
Disulfide Bridges in Proteins

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.



Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox

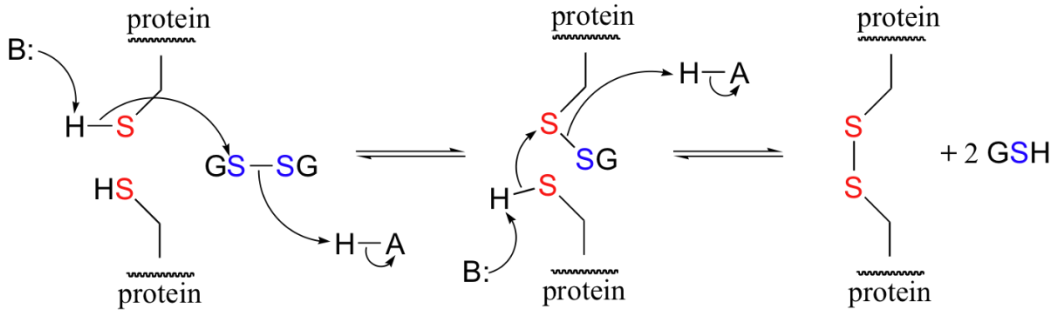
agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme that we have met before in a different context. Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'.

A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSH, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.

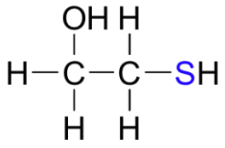


In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

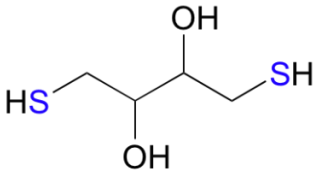
Disulfide bridges exist for the most part only in proteins that are located outside the cell. Inside the cell, cysteines are kept in their reduced (free thiol) state by a high intracellular concentration of GSH, which in turn is kept in a reduced state (ie. GSH rather than GSSG) by a flavin-dependent enzyme called glutathione reductase.

Disulfide bridges in proteins can also be directly reduced by another flavin-dependent enzyme called 'thioredoxin'. In both cases, NADPH is the ultimate electron donor, reducing FAD back to FADH2 in each catalytic cycle.

In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of b-mercaptoethanol (BME) or dithiothreitol (DTT). These reducing agents function in a manner similar to that of GSH, except that DTT, because it has two thiol groups, forms an intramolecular disulfide in its oxidized form.



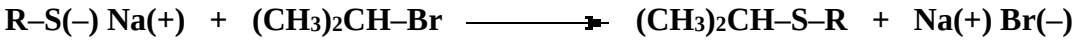
β-mercaptoethanol
(BME)



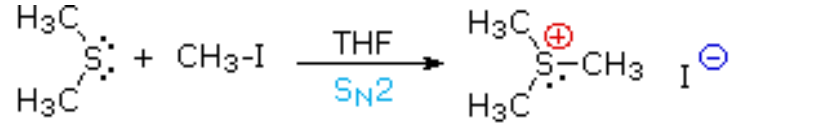
dithiothreitol
(DTT)

Sulfides

Sulfur analogs of ethers are called **sulfides**. The chemical behavior of sulfides contrasts with that of ethers in some important ways. Since hydrogen sulfide (H_2S) is a much stronger acid than water (by more than ten million-fold), we expect, and find, thiols to be stronger acids than equivalent alcohols and phenols. Thiolate conjugate bases are easily formed, and have proven to be excellent nucleophiles in S_N2 reactions of alkyl halides and tosylates.

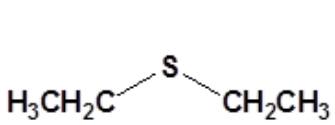


Although the basicity of ethers is roughly a hundred times greater than that of equivalent sulfides, the nucleophilicity of sulfur is much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. Sulfides, for example, react with alkyl halides to give ternary sulfonium salts (the equation below) in the same manner that 3º-amines are alkylated to quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

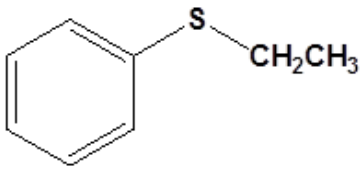


dimethyl sulfide — trimethylsulfonium iodide

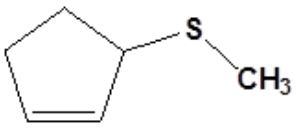
Sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substance alkylthio is used instead of alkoxy.



Diethyl sulfide



Ethyl phenyl sulfide



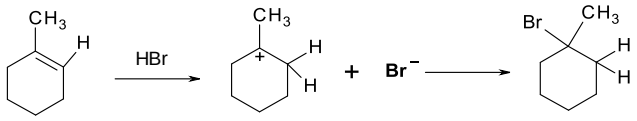
3-(Methylthio)cyclopentene

End Review: The Big Picture

Mechanisms

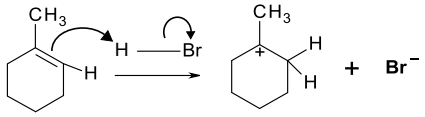
We have learned quite a number of mechanisms. Mechanisms tell us how compounds react with each other, how old bonds are broken and new bonds are formed, or more fundamentally, how electrons flow. Thus the most important and useful tool in learning mechanisms is the ability to draw the curved arrows properly.

Example 1: For the following reactions, provide a mechanism for each step with curved arrows.

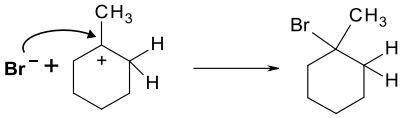


Strategy:

First we need to see which bonds are broken and which bonds are formed. In the first step, the products tell us that, in the alkene reactant, the π bond in the double bond is broken and a C-H bond is formed. At the same time, the H—Br bond is broken and the Br atom gained a pair of electrons to become Br^-. This shows that we need two curved arrows and the electrons are flowing from the π bond to the Br atom. Thus the mechanism for the first step would be:



In the second step, only one new C—Br bond is formed. No bonds are broken. So we only need one curved arrow showing that the lone pair from the bromide ion is used to form the new C—Br bond. The mechanism is:

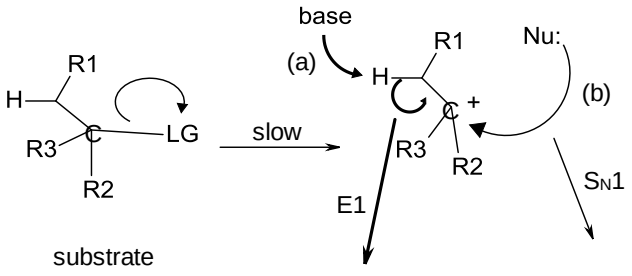


Remember: the curved arrows show where electrons go, not where atoms go.

Which Mechanism Predominates?

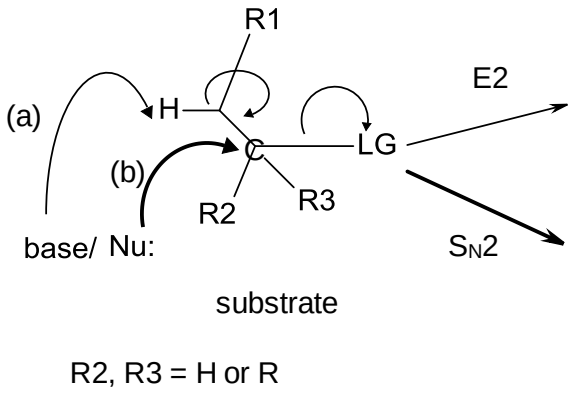
Of all the mechanisms we have learned so far, S_N1, S_N2, E1 and E2 seem to be the most confusing. This situation is not at all uncommon considering that (1) these are the very first mechanisms you ever encounter; (2) they all involve compounds that can function as both nucleophiles and bases, and (3) they are constantly competing with each other. Now that we have learned all four of them, the time has come to do some sorting out. It is possible to decide on the predominant mechanism via which a given reaction will proceed, so long as we keep a clear mind and take all factors into account. As the following schemes indicate, the key factors that are at work are, namely, substrate, nucleophile/base, and leaving group (LG). Fortunately, knowing the mechanism of each reaction greatly simplifies the situations.

Let's look at scheme I, where we consider a tertiary substrate. If kinetic studies show that this is a first-order reaction then the rate-determining step is the formation of the carbocation intermediate. The next step could be (a) a base grabs β-H which leads to the formation of a double bond (E1 mechanism) or, (b) a nucleophile donates a pair of electrons to the carbocation which leads to a substitution product (S_N1 mechanism).



Scheme I

Now let's look at scheme II, where we consider a substrate with the reactive center being primary, seconday or tertiary. If kinetic studies indicate that the reaction is a one-step second-order reaction, then the mechanism could be (a) a base grabs β-H which leads to the formation of a double bond and the kicking-out of the leaving group (E2 mechanism) or, (b) a nucleophile attacks the carbon and kicks out the leaving group which leads to a substitution product (S_N2 mechanism).



R2, R3 = H or R

Scheme II

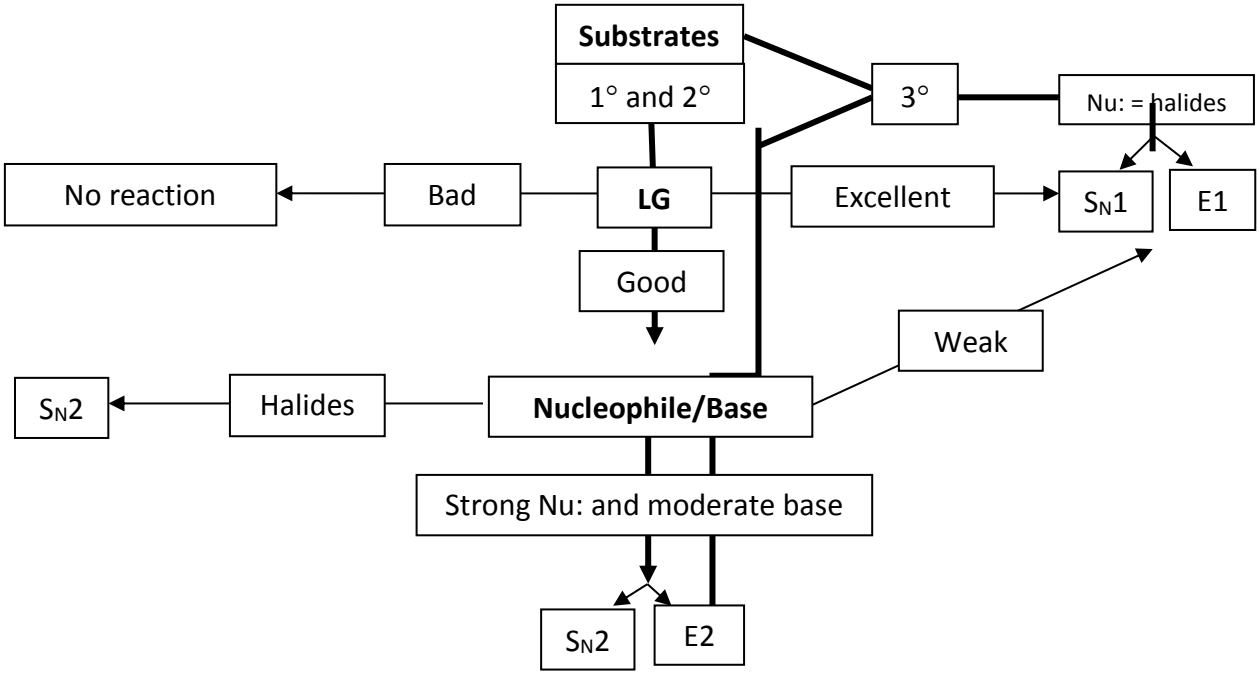
From the substrate point of view, for S_N2 reactions we can safely exclude tertiary substrates from consideration because the carbon center would be too crowded to be approached by the nucleophile. However for E2 reactions we cannot do so because the base is approaching a β-H. The rule of thumb could be:

Primary and secondary substrates most likely react via S_N2 and/or E2 Tertiary substrates might react via S_N1, E1, and E2

To choose between substitution and elimination, we need to consider the "other factors", that is, the incoming groups and the out-going groups. We consider three general types. They are all listed under "other factors" in the table below as they can be the same reagent but plays different roles in different reactions. An incoming group is acting as a nucleophile if it attacks the carbon center—where the action takes place. The same group would be acting as a base if it is pulling off an "H" from a neighboring carbon. It could also be the leaving group if it is the one being kicked out.

Other Factors		
Groups with a negative charge and less stable are:	Groups with a negative charge and are very stable are:	Neutral molecules are:
• Strong nucleophiles	• Moderate nucleopohiles	• Weak nucleophiles
• Strong bases	• Moderate bases	• Weak bases
• Bad leaving groups	• Good leaving groups	• Excellent leaving groups
e.g. OH^-, NH_2^-, RO^-	e.g. Halides, $RCOO^-$	e.g. H_2O, NH_3, ROH

Now we are ready to work through the following flow chart.



It is clear that S_N2 and E2 reactions are most common and are always competing with each other. When all things are equal, we will have to bring in solvent and temperature effects to favor one or the other.

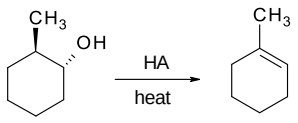
Regiochemistry

When we are adding two different atoms to a double bond or eliminating two different atoms to form a double bond, regioselectivity plays a role in determining what major product(s) will be formed. In other words, regiochemistry is about which atom (out of the two different atoms) goes to or comes off which carbon. The following table summarizes the four scenarios we have seen:

Addition Reactions		Elimination Reactions	
Markovnikov (via most stable carbocation, no peroxides present)	HAH	Zaitsev (E1 and E2)	Forms most substituted alkene
Anti-Markovnikov (Radical mechanism, peroxides present)	Reverse of HAH	Hoffman (Only when a strong and bulky base is used, E2)	Forms least substituted alkene

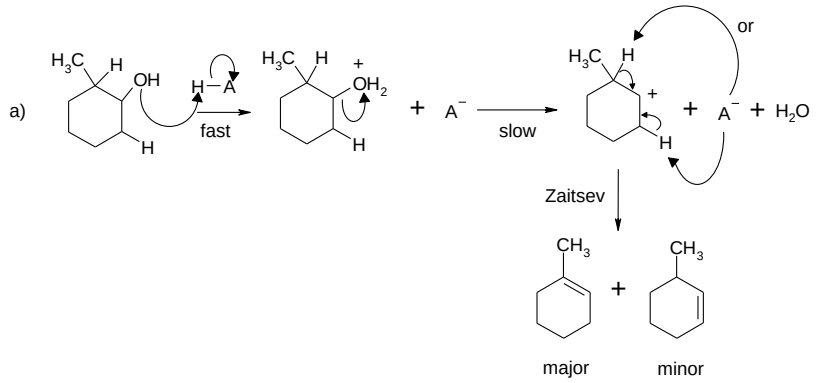
The good news is that in substitution reactions there is only one location of the reaction—where one group is being replaced by another—thus we don't need to consider regioselectivity.

Example 2. Account for the major product formed in this reaction.



major product

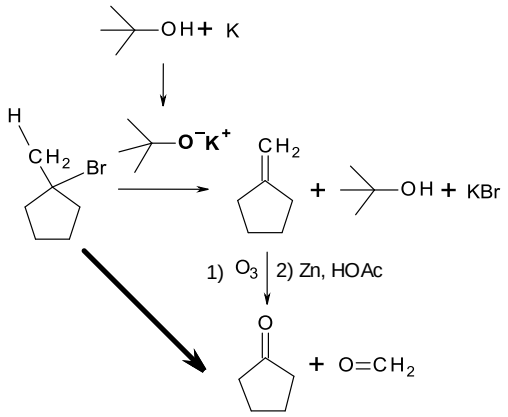
Solution:
Since no strong base is used, the elimination mechanism cannot be E2. Although the "OH" is a very bad leaving group, with the help of an acid (HA) it is possible for the substrate to undergo an E1 acid-catalyzed dehydration via carbocation formation. Following Zaitsev's rule, the more stable alkene is formed as the major product.



Stereochemistry
Stereochemistry comes into play whenever a carbon center changes its geometry during a reaction, especially when new chiral centers are produced. This happens in addition and elimination reactions, as well as in substitution reactions. However, in this course we will just focus on the stereochemistry of S_N1 and S_N2 reactions.

S_N1	S_N2
Racemization (producing a pair of enantiomers)	Inversion of stereo configuration

Example 3. Describe in words each step (the thin arrows) in the following synthetic outline. Name all reagents and major products (IUPAC or common names are both accepted).



Sample Answer:

1-bromo-1-methylcyclopentane undergoes an E2 reaction with the bulky base potassium tert-butoxide which is made from reacting tert-butyl alcohol with potassium metal. The alkene product (called 1-methylenecyclopentane) undergoes ozonolysis to form cyclopentanone and formaldehyde.

Note: How to name the alkene product?
The double bond on the cyclopentane ring is named as a substituent on the ring. The first three commonly seen alkene substituents are:

$=CH_2$	methylene
$—CH=CH_2$	vinyl
$— CH_2—CH=CH_2$	allyl