Summary Sheet - Hybridization And Bonding

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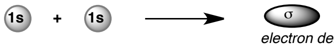
What is bonding and why does it occur?

In a chemical bond, electrons are shared between atoms.

This is energetically favorable (more stable) because of Coulomb's law (opposite charges attract; negatively charged electrons held between two postitively charged nuclei)

Constructive end-on-end overlap between atomic orbitals results in a σ ("sigma") molecular orbital

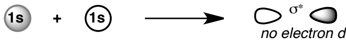


constructive overlap

electron density shared between both nuclei (stabilizing)

What is antibonding?

Destructive overlap between atomic orbitals gives an antibonding molecular orbital. This means that two positively charged nuclei are held closely together without any electrons between them to "glue" them together; repulsion between nuclei makes this a very unstable situation



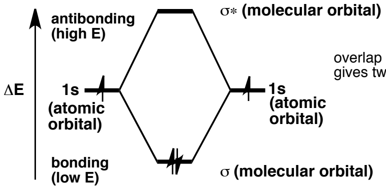
destructive overlap

no electron density between nuclei; destabilizing

Can't we just have bonding without antibonding?
No. When atomic orbitals come together, the number of molecular orbitals has to equal the number of atomic orbitals. Bringing together two atomic orbitals will always result in two new molecular orbitals, one bonding ("constructive overlap") and one antibonding ("destructive overlap")

Sigma bonds are formed through end-on overlap of two atomic orbitals, as distinguished from **pi bonds** (see later section).

Molecular Orbital Diagram for H_2



This is the lowest unoccupied molecular orbital (LUMO)

overlap of two atomic orbitals gives two new molecular orbitals

Note that this is the highest occupied molecular orbital (HOMO)

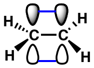
Why care about antibonding if it's usually empty?

- In the diagram above for H_2, if we added a third electron, it would have to go to the antibonding orbital because there's nowhere else to put it.
- Antibonding orbitals can be filled when electrons absorb energy of a certain frequency (promoting a bonding electron to antibonding) or if an extra electron is added to a molecule where all orbitals are already full.

What is Pi (π) bonding?

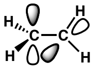
Pi bonding occurs when orbitals overlap in a "side-on" fashion.
This is possible when neighboring atoms have electrons in unhybridized p orbitals (like alkenes and alkynes)

Pi bonding occurs when orbitals overlap in a "side-on" fashion.



Electron density is shared between neighboring p orbitals, resulting in a π bond.

Atoms involved in pi bonding cannot be rotated, since this would destroy overlap.

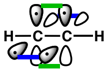


Pi bonding not possible here because these p orbitals are at 90° to each other

There are also π* orbitals (not shown)

It is possible for two pi bonds to be present; this involves the side-on overlap of two p orbitals, each at 90° to each other

H—C≡C—H



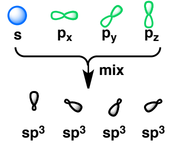
Hybridization

Type	s	hybridized p	leftover (unhybridized) p	orbital geometry
sp^3	1	3	0	tetrahedral
sp^2	1	2	1	trigonal planar
sp	1	1	2	linear

molecules adopt a geometry that maximizes the distance between electron pairs

sp^3 Hybridization

The bond angles in CH_4 are 109.5° .
The orbitals containing each pair of electrons are neither "pure p" or "pure s". They are a hybrid between p and s. Since we are hybridizing one s orbital and three p orbitals, we call this "sp^3" hybridization

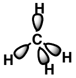


4 orbitals

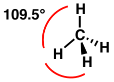
4 hybrid orbitals

(Each 109.5° apart - "tetrahedral" orbital geometry)

In CH_4 the hydrogens are arranged in a tetrahedral fashion around the central carbon atom. We say CH_4 has "tetrahedral" molecular geometry

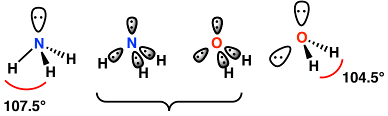


Tetrahedral orbital geometry



Tetrahedral molecular geometry

Molecules such as NH_3 and H_2O also have four electron pair domains that are arranged tetrahedrally around the central atom; some of these are "lone pairs" that are not bonded to an atom. The lone pairs take up slightly more space than bonding pairs, which compresses the bond angles



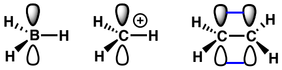
"Trigonal pyramidal" molecular geometry

Tetrahedral orbital geometry

"Bent" molecular geometry

sp^2 Hybridization

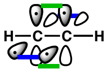
If one s orbital is hybridized with two p orbitals we obtain three hybrid orbitals that will be 120° apart. We will have one "leftover" unhybridized p orbital. This is the geometry of the central atom in trivalent boron compounds, carbocations, and atoms with a single pi bond

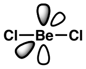


Trigonal planar

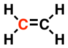
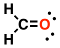
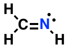
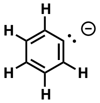
sp Hybridization

If one s orbital is hybridized with one p orbital we obtain two hybrid orbitals 180° apart. We have two "leftover" unhybridized p orbitals. This is the geometry of the central atom in beryllium compounds (e.g. $BeCl_2$) as well as that of atoms with triple bonds





Some examples

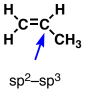
Example	Hybridization	Orbital Geometry	Molecular geometry
CH_4	sp^3	tetrahedral	tetrahedral
NH_3	sp^3	tetrahedral	trigonal pyramidal
H_2O	sp^3	tetrahedral	bent
$^{\ominus}NH_2$	sp^3	tetrahedral	bent
$^{\ominus}:CH_3$	sp^3	tetrahedral	trigonal pyramidal
BH_3	sp^2	trigonal planar	trigonal planar
$^{\oplus}CH_3$	sp^2	trigonal planar	trigonal planar
$BeCl_2$	sp	linear	linear
	sp^2	trigonal planar	
	sp^2	trigonal planar	
	sp^2	trigonal planar	
	sp^2	trigonal planar	

How does hybridization affect bond strength?

s orbitals are closer to the nucleus and more tightly held
The more "s-character" a bond has, the stronger (and shorter) it will be

$H_3C–CH_3$

$sp^3–sp^3$
weaker
(less s-character)



$H–C≡C–CH_3$

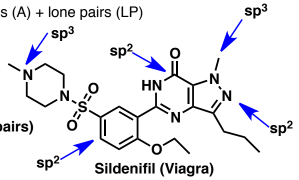
$sp–sp^3$
stronger
(more s-character)

The Shortcut For Finding The Hybridization Of Any Atom

Count the number of surrounding atoms (A) + lone pairs (LP)

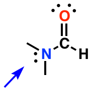
If A+LP = 4 hybridization is sp^3
If A+LP = 3 hybridization is sp^2
If A+LP = 2 hybridization is sp

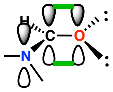
Try it with Viagra!
(don't forget the "hidden" lone pairs)



Sildenifil (Viagra)

Exception - not always covered - if atom with lone pair next to pi bond, rehybridization occurs to put that lone pair in a p orbital. So it's actually sp^2 not sp^3





rehybridization to sp^2 allows lone pair to be in conjugation with p orbitals of pi bond (allows for resonance)

atom with lone pair adjacent to sp^2 hybridized atom; lone pair will be in p orbital, not sp^3 orbital.
Nitrogen is **sp^2 not sp^3**

Omissions, Mistakes, Suggestions?

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Formal Charge, Dipoles, Boiling Points, and Curved Arrows

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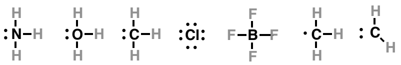
How To Calculate Formal Charge Of An Atom

1. Start with the number of valence electrons, "V"

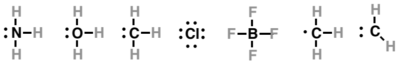
e.g.	B	C	N	O	F
"V"	3	4	5	6	7

2. Count the number of non-bonded electrons, "N"



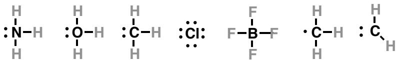
"N" 2 2 2 8 0 1 2

3. Count the number of bonding electrons, "BE" [2 electrons per bond]



"BE" 6 6 6 0 8 6 4

$$\text{Formal charge} = V - [N + \tfrac{1}{2}BE]$$



Charge 0 +1 −1 −1 −1 0 0

Alternative: instead of multiplying the # of bonding electrons "BE" by 1/2, count the number of bonds, "B" around the atom instead

Formal charge = V − [N + B]

Dipoles

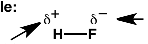
Atomic nuclei differ in their ability to pull electrons toward themselves. This property is called "electronegativity", and is measured on a scale from roughly 1.0 (low) to 4.0 (high). The higher the electronegativity, the "greedier" that atom is for electrons.

B	H	P	S	C	I	Br	N	Cl	O	F
2.0	2.2	2.2	2.6	2.6	2.7	3.0	3.0	3.2	3.4	4.0

A consequence of electronegativity is that electrons in bonds between atoms with different electronegativities are not equally shared. The more electronegative atom will have a greater "share" of the bonding electrons, giving it a partial negative charge, and the less electronegative atom will have a lesser "share" of the bonding electrons, giving it a partial positive charge.

This is what is known as a **dipole**

example:

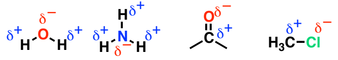


the δ− means that fluorine bears a partial negative charge

hydrogen bears a partial positive charge

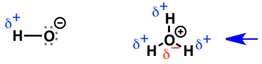
2.2 4.0
electronegativities

Representative examples (with largest dipoles shown)



Understanding dipoles is KEY for comprehending boiling points (this sheet) but also many aspects of reactivity!

One important thing to keep in mind: **dipoles** always give an accurate portrait of electron density, whereas **formal charge** may not



hydrogen is electron-poor, oxygen is electron-rich

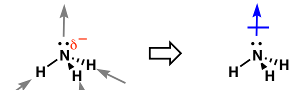
hydrogen is electron-poor, oxygen is (still) electron-rich

even though oxygen bears a **positive** formal charge, it is still more electron-rich than hydrogen due to electronegativity

The hydrogens are still electron-poor ("electrophilic")

Dipole Moments

The dipoles of bonds in a molecule add up (as vectors) to give an overall dipole moment. Example: NH_3

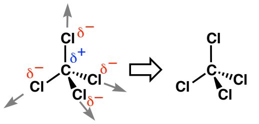


Dipole moment: 1.42 D

individual dipoles shown

add up to overall dipole moment **D** (shown)

Some molecules with dipoles along individual bonds will have no overall dipole moment since the vectors cancel



Dipole moment: 0 D
(i.e. no dipole moment)

A good rule of thumb: the larger the dipole moment, the more polar the molecule

Polar molecules: tend to have larger dipole moments, higher water solubility, lower solubility in non-polar solvents, and relatively higher boiling and melting points than non-polar molecules.

Factors That Affect Boiling Points

Boiling occurs when enough energy is added to a liquid to overcome the attractive forces between molecules.

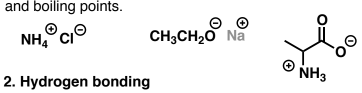
The greater the attractive forces, the higher the boiling point.

As bonds become more polarized, the charges on the atoms become greater, which leads to stronger intermolecular attractions, which leads to higher boiling points

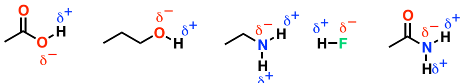
There are four types of attractive forces between molecules. Here they are in order from largest to smallest:

Ionic > Hydrogen Bonding > VDW Dipole-Dipole > VDW Dispersion
(VDW = Van der Waals)

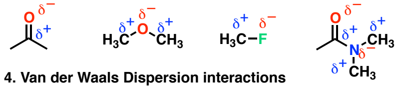
1. Ionic forces
Attraction between point charges. Ionic compounds have the highest melting and boiling points.



2. Hydrogen bonding
The next-strongest intermolecular force. Look for O-H, N-H, or F-H bonds. These are highly polarized and lead to relatively large boiling points.



3. Van der Waals Dipole interactions
Look for bonds between C and highly electronegative elements like O, N, or halogens. Smaller differences in electronegativity than with hydrogen bonding, but still significant



4. Van der Waals Dispersion interactions
Temporary (instantaneous) dipoles; weakest attractive interactions Present in all molecules (even hydrocarbons and noble gases)

Generally will **increase with surface area**

This is why **boiling points increase with increasing chain lengths**

Curved Arrows

Curved Arrows: A way to show the "movement" of electrons.

Electrons move ***from*** the tail ***to*** the head

*Take a pair of electrons from **here** (bond / lone pair)*

*and move them **here** (bond / lone pair)*

- The curved arrow shows "movement" of a pair of electrons... it's an extremely useful accounting system that lets us keep track of changes in **bonding** and **charge**
- The tail ***must*** be at a source of electrons, **either a lone pair or a bond.**
- The head ***must*** be able to accept a pair of electrons without breaking the octet rule

There are only three "moves" possible for a curved arrow

Bond → Lone pair **Lone pair → Bond** **Bond → Bond** ~~Lone pair → Lone pair~~

not possible

Simple example:

Shows bond forming between O and H

[Lone pair → Bond]

Shows bond breaking between H and Cl

[Bond → Lone pair]

Oxygen goes from "owning" a lone pair to "sharing", so its formal charge becomes less negative by 1

Negative charges can stand in for lone pairs. It's OK to draw the tail from a negative charge, so long as the atom has a lone pair of electrons

The pair of electrons in the bond will become a new lone pair on Cl

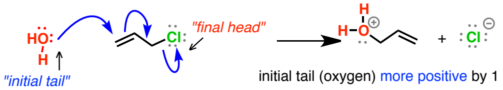
Cl goes from "sharing" this pair to "owning" it so the charge becomes more negative by 1

Note change in formal charge at oxygen:
−1 → 0

Note change in formal charge at chlorine:
0 → −1

Only two charges are changed: the initial tail becomes more positive and the final head becomes more negative

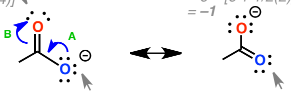
Example with three arrows:



initial tail (oxygen) more positive by 1 0 → +1

final head (chlorine) more negative by 1 0 → −1

Resonance example:



*Formal charge = 6 – [4 + 1/2(4)] = **0***

*Formal charge = 6 – [6 + 1/2(2)] = **–1***

*Formal charge = 6 – [6 + 1/2(2)] = **–1***

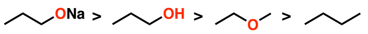
*Formal charge = 6 – [4 + 1/2(4)] = **0***

Bonds formed	Bonds broken
A **O–C (π)**	B **O–C (π)**

Charges

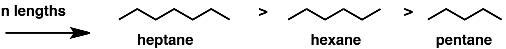
O	−1 → 0
C	0 → 0
O	0 → −1

Examples of how the 4 forces lead to boiling point differences:



b.p. >200 °C		**b.p. 97 °C**		**b.p. 7°C**		**b.p. –1°C**
[Ionic]		**[H-bonding]**		**[Dipole-dipole]**		**[Dispersion]**

Boiling point also increases with chain length



heptane	>	**hexane**	>	**pentane**
b.p. 98°C		**b.p. 68°C**		**b.p. 36°**

Omissions, Mistakes, Suggestions?

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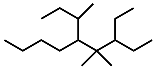
Introduction to Alkane Nomenclature

http://masterorganicchemistry.com

What's in a name?



3-ethyl-5-(1-methylpropyl)-4,4-dimethylnonane ← **suffix**

the NUMBERS are called "locants" (sometimes "locators")
items in BLUE are called "**substituents**".
the name in **RED** at the end is called the **suffix.**

The purpose of this sheet is to demonstrate the rules by which alkanes are named.

ORDER OF BUSINESS

A. Determine the priority of functional groups (not covered here since we're dealing with alkanes only)
B. Find the longest linear chain of your molecule, or the largest ring (whichever is greatest). This is the **Chain length rule** which defines both the "main chain" and also the suffix.
tiebreaker: where more than one "path" along the molecule leads to the longest chain, **the main chain is the one that contains the most substituents.**
C. Identify the substituents along your main chain. Substituents are classified according to length of carbon chain and the suffix "yl" is attached.
D. Number your chain from one of the ends. The **LOWEST LOCATOR RULE** determines which end is chosen as carbon #1: **"Number the chain such as to provide the lowest possible locators for the chain."**
tiebreaker for lowest-locator rule: **alphabetization**
E. Multiple instances of substituents are given the prefixes di, tri, tetra, etc.
***note:* must have locator for all substituents. Example:** 2,2-dimethyl is correct. 2-dimethyl is incorrect.
F. Branched substituents are numbered and named seperately from the main chain, and put in brackets.
G. The FINAL name is assembled such as to arrange the substituents in alphabetical order.
-"di", "tri", "tetra" are ignored for alphabetization purposes.
-prefixes like "n", "tert", "i" and "sec" are ignored for alphabetization purposes.
THE EXCEPTION is "isopropyl" and "isobutyl". For some reason these count as "i"
- not covered here, but this is also where one puts in descriptors like "cis", "trans", *(R), (S) (E), (Z)* and so on.

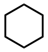
Names for Hydrocarbon Chains and Rings

1	methane
2	ethane
3	propane
4	butane
5	pentane
6	hexane
7	heptane
8	octane
9	nonane
10	decane
11	undecane
12	dodecane
20	eicosane

3 cyclopropane

4 cyclobutane

5 cyclopentane



6 cyclohexane

7 and higher follow the same pattern.

butane

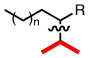
heptane

Sometimes you will see "n" in front to indicate that it is a straight-chain alkane

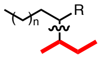
n-hexane

n-pentane

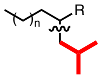
Trivial names for substituents



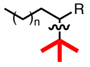
isopropyl



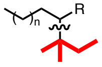
sec-butyl



isobutyl



tert-butyl

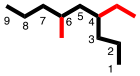


tert-pentyl

A. Determining the Priority of Functional Groups.

Too big a subject to cover on one sheet! This paper will focus on alkanes. Determining functional group priority will be the subject of a subsequent sheet.

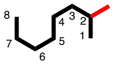
B. Applying the Chain Length Rule



4-ethyl-6-methyl**nonane**

Longest chain is 9 carbons - suffix will be **nonane**

Watch out! Longest chain might not be drawn as a "straight chain"



2-methyl**octane**

*Longest chain is 8 carbons - suffix will be **octane***

Chains vs. rings

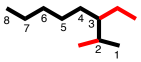
Rings take priority over chains, assuming there are only alkyl groups in the chain. ***see note below

propyl**cyclobutane**

butyl**cyclopropane**

Tiebreaker: Alphabetization

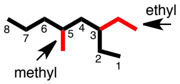
Where more than one "longest chain" exists, the more substituted chain is chosen as the "longest chain"



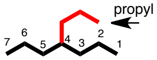
3-ethyl-2-methyloctane
(*NOT* - 3-isopropyloctane)

C. Identifying Substituents

Substituents are carbon fragments branching off the main chain. They are named according to the number of carbons like the main chain would be, except the "ane" is dropped and replaced with "yl"



3-ethyl-5-methyloctane

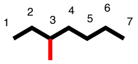


4-propylheptane

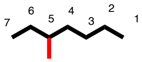
*** IUPAC 61.2 says, "Choice between these methods [either choosing rings or chains as the root] is made according to the more appropriate of the following principles: (a) the maximum number of substitutions into a single unit of structure; (b) treatment of a smaller of structure as a substituent into a larger."

D. Applying the Lowest Locator Rule

Number the chain from one end so as to provide the lowest locator possible for the first substituent.

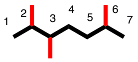


3-methyl heptane

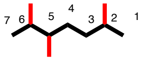


NOT *5-methyl heptane*

This also applies for *subsequent* substituents, if either direction would give the same number.

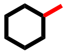


2,3,6-trimethylheptane

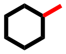


NOT *2,5,6-trimethylheptane*

For rings with one substituent, the locator "1" can be dropped. Why? Imagine a street that had only one house on it. Would the house really need a number?

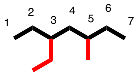


methylcyclohexane *the same as* **1-methylcyclohexane**

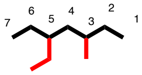


Tiebreaker: Alphabetization

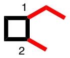
If the same locators are obtained from either direction of the chain, the chain is numbered according to alphabetical order of the substituents.



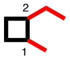
3-ethyl-5-methylheptane



NOT 3-methyl-5-ethylheptane



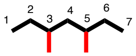
1-ethyl-2-methylcyclobutane



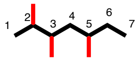
NOT
1-methyl-2-ethylcyclobutane

E. Multiples of the Same Substituent

Multiples of the same substituent are given the prefixes "di", "tri", "tetra", etc. The lowest locator rule still applies.

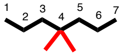


3,5-dimethylheptane



2,3,5-trimethylheptane

Also applies to substituents on the same carbon:



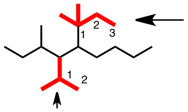
4,4-dimethylheptane

NOT 4-dimethylheptane
NOT 4,4-methylheptane

Extremely common mistakes!

F. Dealing With Branched Substituents (the IUPAC Way)

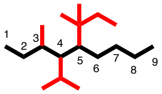
Treat each branched substituent as its own naming problem.
Carbon #1 of the branched substituent will be where it meets the main chain.



- •Longest chain is propyl
- •Methyl substituents are on carbon #1
- •Name of substituent is (**1,1-dimethylpropyl**)

- •Longest chain is ethyl
- •Methyl substituent is on carbon #1
- •Name of substituent is (**1-methylethyl**)

We put the name in brackets to avoid confusing the numbers of the branched substituent with the numbers of the main chain.



3-methyl 4-(1-methylethyl) 5-(1,1-dimethylpropyl) nonane

In certain instances, you may see the trivial names isopropyl, isobutyl, tert-butyl, tert-pentyl used.

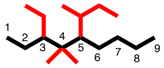
e.g. 4-isopropyl-3-methyl-5-tert-pentylnonane.

The official IUPAC nomenclature system will never let you down. It would probably be best to just go with that.

G. Putting the Name Together.

1. Put your substituents together in **alphabetical order.**
   For alphabetization purposes:
   IGNORE •"di", "tri", "tet", etc.
   • *sec-, tert-, n-,*
   •cyclo-

   DO NOT IGNORE
   • **"iso". For some reason "isopropyl" is alphabetized under "i" and not "p".**
2. Affix the **locators.**
3. Make sure any **branched substituents** are in brackets.
4. Attach the **suffix** at the end.



3-ethyl-4,4-dimethyl-5-(1-methylpropyl)-nonane

Errors/omissions/suggestions?
james@masterorganicchemistry.com

For more comoplete resources on nomenclature consult:

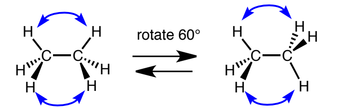
1) "Organic Chemistry Online" by William Reusch:
http://www2.chemistry.msu.edu:80/faculty/reusch/VirtTxtJml/intro1.htm
2) IUPAC "Blue Book"
http://www.acdlabs.com/iupac/nomenclature/

Introduction to Conformations

"Master Organic Chemistry"
masterorganicchemistry.com

What are conformations?

- Sigma bonds (single bonds) are free to rotate.
- Through the rotation of bonds, molecules can adopt different 3-dimensional shapes. These are called **conformations**. Two identical molecules with different 3-D shapes are called **conformational isomers**.
- Not all conformations are equal in energy Because electron clouds repel, conformations which maximize the distance between atoms are generally favored (i.e. lower in energy).



bonds are lined up next to each other: "eclipsed"

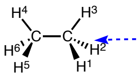
less stable

bonds are offset from each other: "staggered"

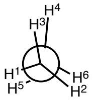
more stable

difference: 2.4 kcal/mol (10 kJ/mol)

Key Tool: The Newman projection

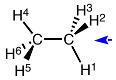


Take this molecule, and look at it from the side...
...and you get this →

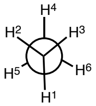


"eclipsed"

Note how the hydrogens from the front carbon are directly in front of the hydrogens from the back carbon, hence "eclipsed"



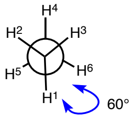
Take this molecule, and look at it from the side...
...and you get this→



"staggered"

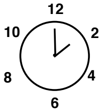
Note how the hydrogens are "spaced" out from each other, hence "staggered"

Key Concept: The "Dihedral Angle"

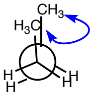


The dihedral angle is the angle between groups on the front and the back carbons.

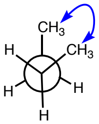
Analogy: think of the hands of a clock



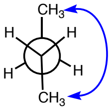
Each 2 hour increment represents 60 degrees.



0° : "syn"



60° : "gauche"
French for "awkward"



180° : "anti"

These repulsions between groups are called **"steric interactions"**. The larger the group involved, the greater the steric interactions, or "cost".

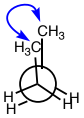
$C(CH_3)_3 > CH(CH_3)_2 > CH_3 > Cl, OH > H$

largest **smallest**

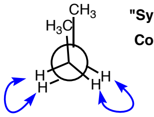
interestingly, CH_3 is larger than Cl or OH, since it "sweeps out" a larger area

Repulsions between groups cause **strain**, which can be relieved through bond rotation; this is often called *"torsional strain"*.

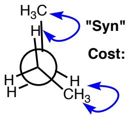
Example of a Price List: 4 interactions with different "costs"



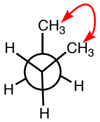
"Syn" (eclipsed) CH_3 CH_3
Cost: 2.9 kcal/mol
(12.1 kJ/mol)



"Syn" (eclipsed) H H
Cost: 1.0 kcal/mol (each)
(4.18 kJ/mol each)
= 2.0 kcal/mol (total)



"Syn" (eclipsed) CH_3 H
Cost: 1.4 kcal/mol (each)
(5.86 kJ/mol (each)
= 2.8 kcal/mol (total)



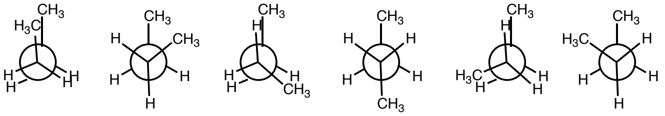
Gauche ("awkward") CH_3 CH_3
Cost: 0.9 kcal/mol
(3.8 kJ/mol)

Example: how to figure out the rotational energies for butane ($CH_3CH_2CH_2CH_3$) ?

Step 1: like a clock, pick one group as the "hour hand" and one as the "minute hand". Then rotate that "hand" through 360°, in 60° (2h) increments. In this example, it's best to pick the two methyl groups as your "hands" since there is only one on each carbon.

Step 2: Calculate the "costs" for each of the six conformations

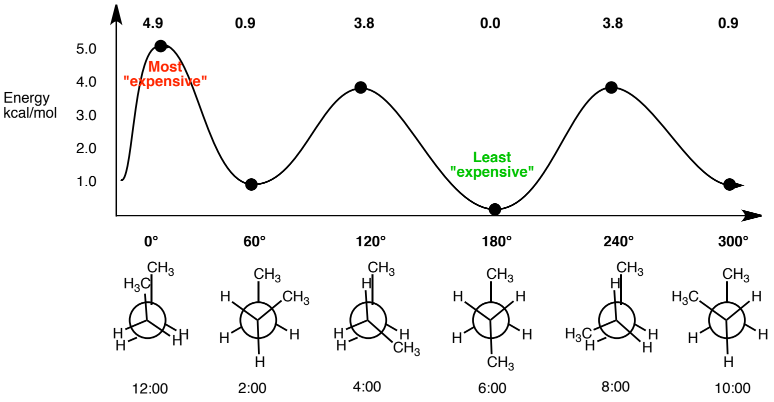
Example: Adding up the "costs" of each conformation for butane



"Time"	12:00	2:00	4:00	6:00	8:00	10:00
Dihedral angle	0°	60°	120°	180°	240°	300°
Eclipsed CH_3 CH_3	2.9	–	–	–	–	–
Eclipsed CH_3 H	–	–	2 x 1.4	–	2 x 1.4	–
Eclipsed H – H	2 x 1.0	–	1.0	–	1.0	–
Gauche CH_3 CH_3	–	0.9	–	–	–	0.9
Total Cost (kcal/mol)	**4.9** **Most "expensive"**	**0.9**	**3.8**	**0.0** **Least "expensive"**	**3.8**	**0.9**

Step 3: Make a graph

The Graph: Energy versus angle (in 60 degree increments)



Omissions, Mistakes, Suggestions?

james@masterorganicchemistry.com

Introduction to Cycloalkanes

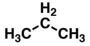
"Master Organic Chemistry"
masterorganicchemistry.com
Mar 2015. Version 1.2

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

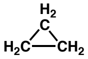
Cyclic molecules

Molecules in organic chemistry don't just exist as chains - they can also exist as **rings**. Compare propane and cyclopropane:

Propane
C_3H_8



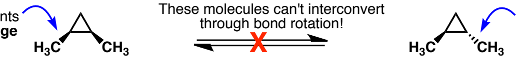
Cyclopropane
C_3H_6



note how there are two fewer hydrogens in the molecular formula of cyclopropane than for propane

Stereochemistry

When groups are on a ring, they are constrained - they can't rotate in the same way that linear molecules can. This can give rise to "cis" and "trans" isomers - stereoisomers.



"wedge" group points **out of page**

These molecules can't interconvert through bond rotation!

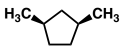
"dash" group points **behind page**

cis-1,2-dimethylcyclopropane

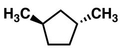
trans-1,2-dimethylcyclopropane

stereoisomers: *same molecular formula, different boiling points/melting points*

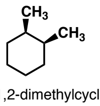
Other examples:



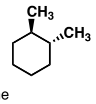
cis-1,3-dimethylcyclopentane



trans-1,3-dimethylcyclopentane



cis-1,2-dimethylcyclohexane



trans-1,2-dimethylcyclohexane

Ring Strain

In contrast to chains, where sp^3 hybridized carbons can adopt their ideal geometry of 109.5°, the geometry of carbons in some cycloalkanes can be far from ideal, leading to **ring strain**

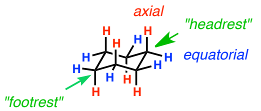
Name:	Cyclopropane	Cyclobutane	Cyclopentane	Cyclohexane
Interior angle:	60°	90°	108°	* see below
Ring strain (kcal/mol)	27.6 kcal/mol	26.4 kcal/mol	6.5 kcal/mol	0
(kJ/mol)	115.5 kJ/mol	110.4 kJ/mol	27.2 kJ/mol	0

Ring strain is a combination of **angle strain** (where geometry of the carbon deviates from the ideal) and torsional strain (arising from eclipsing interactions)

The Chair Conformation of Cyclohexane

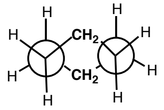
The cyclohexane ring is not a flat hexagon. Why not? Two reasons: 1) the bond angles would be 120° (creating angle strain) and 2) the neighboring hydrogen atoms would be eclipsed with each other. Instead cyclohexane adopts a *chair* conformation where all bond angles are close to 109 degrees and all neighboring groups are staggered.

Groups that point "straight" up and down are said to be "axial" - ***in red***



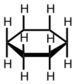
Groups that point "somewhat" up or down are said to be "equatorial" - ***in blue***

Newman projection of chair

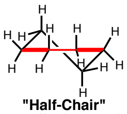


In the chair form, all substituents are staggered along every C–C bond

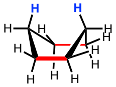
Other conformations of cyclohexane (higher in energy than the chair)



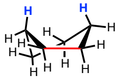
Planar
angle strain (120°)
eclipsing strain
(two hydrogens omitted for clarity)



"Half-Chair"
eclipsing strain
steric crowding
10.7 kcal/mol less stable than chair

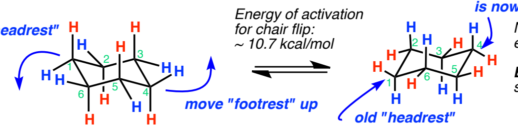


"Boat"
eclipsing strain
steric crowding
6.9 kcal/mol less stable than chair



"Twist boat"
eclipsing strain
steric crowding
5.3 kcal/mol less stable than chair

Cyclohexane rings can be drawn as two different "chair" forms



move "headrest" down

move "footrest" up

Energy of activation for chair flip: ~ 10.7 kcal/mol

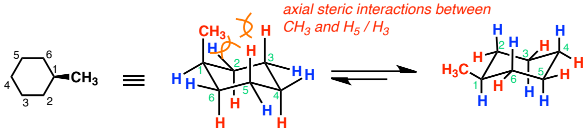
old "footrest" is now "headrest"

old "headrest" is now "footrest"

Note how all axial groups became equatorial and all equatorial groups became axial....

BUT *all "up" groups are still "up", and all "down" groups are still "down" !!!*

For substituted cyclohexanes, these two forms are not generally equal in energy



axial steric interactions between CH_3 and H_5 / H_3

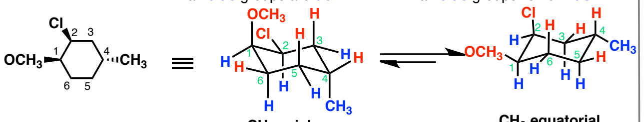
CH_3 axial (less stable by 1.8 kcal/mol)

CH_3 equatorial

Another example: note the positions of axial and equatorial groups

all **red** groups are **up**
all **blue** groups are **down**

all **red** groups **remain up**
all **blue** groups **remain down**

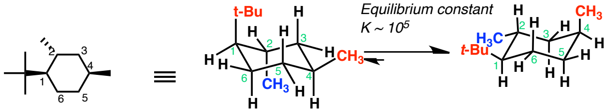


CH_3 axial
OCH_3 axial
Cl equatorial

CH_3 equatorial
OCH_3 equatorial
Cl axial

Important: the *t*-butyl group is conformationally "locked" in the equatorial position

The *t*-butyl group is so bulky that the axial position is extremely disfavored. Equilibrium favors the equatorial position to such an extent that one can consider the chair to be "locked" in the conformation with *t*-Bu equatorial



Equilibrium constant $K \sim 10^5$

***t*-Bu axial (strongly disfavored)**
CH_3 axial
CH_3 equatorial

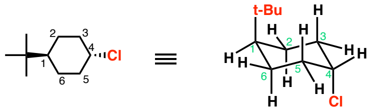
***t*-Bu equatorial**
CH_3 equatorial
CH_3 axial

Application in substitution and elimination reactions (S_N2 and E2)

Understanding the proportions of different chair forms is important because S_N2 and E2 reactions will only occur when the leaving group is in the **axial** position.

only this conformation will undergo S_N2 or E_2 reactions (leaving group axial)

t-Bu is equatorial (favored)



only this conformation will undergo S_N2 or E_2 reactions (leaving group axial)

t-Bu is axial (disfavored)

Substitution and elimination reactions will be extremely slow for this molecule

The axial position is less favored for substitutents since it can undergo unfavorable steric interactions with other axial substitutents. These are avoided in the equatorial position.

(Technically these are "gauche" interactions)

Each interaction between axial CH_3 and axial H "costs" ~0.9 kcal/mol, for a total of about 1.75 kcal/mol.

Using this value we can calcuate the % of 1-methylcyclohexane that is present in the axial form at equilibrium:

$\Delta G = -RT \ln K \qquad K = e^{-\Delta G/RT}$

At 1.75 kcal/mol this gives us K = 0.052, or approximately 95:5 ratio in favor of the equatorial CH_3

This value: 1.75 kcal/mol is sometimes referred to as the "A" value of CH_3

The size of the A value is related to the magnitude of the steric interactions between axial substitutents

Group	**A Value**	**Group**	**A Value**
CH_3	**1.74**	**Cl**	**0.43**
CH_2CH_3	**1.75**	**OH**	**0.87**
***i*-Pr**	**2.15**	**OCH_3**	**0.6**
***t*-Bu**	**4.7**	**NH_2**	**1.6**

This table gives an idea of the preference of the substituent for the equatorial position. For example *t*-Bu is the bulkiest of these groups, whereas Cl is the least bulky.

Using the Gibbs equation it's possible to calculate the position of the equilibrium for each substituent.

For example	**A value**	**% equatorial** (at 25°C)
	0	50%
	0.5	70%
	1	84%
	1.5	93%
	2	97%
	2.5	98.5%
	3	99.4%
	3.5	99.7%
	4.0	99.9%
	4.5	99.95%
	5	99.98%

Omissions, Mistakes, Suggestions?

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Introduction to Resonance

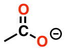
"Master Organic Chemistry"
masterorganicchemistry.com

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

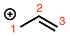
1. What is Resonance?

The true distribution of electrons in a molecule cannot always be accurately depicted through a single Lewis structure. Resonance is a tool to show this.

So what about applying this concept to these molecules?



The Lewis structure of this molecule **appears** to tell us that one oxygen is more negative than the other (bears a greater electron density). Our model based on pure electronegativity would suggest that it should be more reactive than the neutral oxygen.



Similarly, the Lewis structure of this molecule appears to tell us that one carbon bears the positive charge and the others are neutral

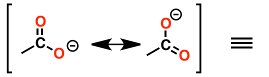
In reality, the charge in both of these molecules is distributed equally between the different ends

Important: this is **not** an equilibrium!

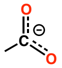
Acetate ion

numbering is for placeholding, not IUPAC

Instead, the "true" structure of the molecule is a **hybrid** of these two forms.

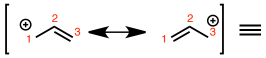


Acetate ion resonance forms



Resonance hybrid

*The "double-headed" arrow denotes that two molecules are resonance isomers (**NOT** in equilibrium)*



Allyl carbocation resonance forms

Resonance hybrid

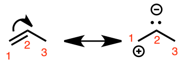
The true bond order is an average of the bond order in each resonance hybrid, weighted by the importance of the hybrid to the overall structure

Here it would be 1.5

2. How to Use Curved Arrows

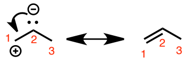
There are only **three** legal "moves" we can do with curved arrows to show resonance.

π Bond → Lone pair



Tail is at π bond between C1 and C2
Head is at C2
Arrow shows movement of electrons
from the C1-C2 π bond
to become a lone pair on carbon 2.

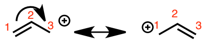
Lone pair→ π Bond



*only possible if an sp^2 or sp hybridized carbon is next door (i.e. don't break the octet rule)

Tail is on lone pair of C2
Head is between C1 and C2.
Arrow shows movement of electrons
from the lone pair on C2
to become a π bond between C1 and C2

π Bond → π Bond



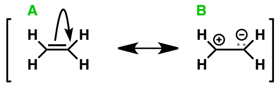
*only possible if an sp^2 or sp hybridized carbon is next door (i.e. don't break the octet rule)

Tail is at π bond between C1 and C2
Head is at π bond between C2 and C3
Arrow shows movement of electrons from the C1-C2 π bond (which breaks) to the C2-C3 π bond (which forms).

3. When Resonance Forms are Not Equal: How to tell which are most significant?

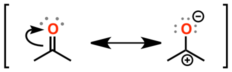
Rule #1 - The Fewer Charges, the Better

Resonance forms decrease in importance as their charges increase



0 charges
more significant
this contributes more to the resonance hybrid

2 charges
less significant

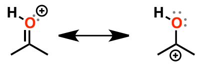


0 charges
more significant
this contributes more to the resonance hybrid

2 charges
less significant

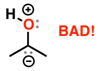
Rule #2 - Full Octets Are Preferred

A resonance form in which all atoms have a full octet is more significant than one where at least one atom lacks a full octet.



full octets
More significant

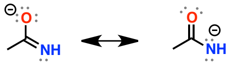
carbon lacks a full octet
Less significant



Note: **never** have less than a full octet on oxygen or nitrogen.

Rule #3 - Place a negative charge on the least basic atom

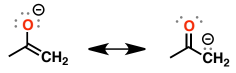
"Amide anions"



Best
negative charge is on least basic atom (O)

Second-best
negative charge is on most basic atom (N)

"Enolates"



Best
negative charge is on least basic atom (O)

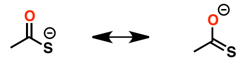
Second-best
negative charge is on most basic atom (C)

If given a choice, the best place to put a negative charge on a resonance form is on the least basic atom

Use acidity trends to determine the "best" resonance form in these cases

- *Electronegativity*
- *Polarizability*
- *Induction*

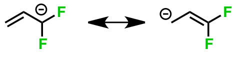
Polarizabilty



Best
negative charge is on least basic atom (S)

Second-best
negative charge is on most basic atom (O)

Electron withdrawing groups



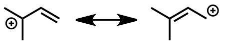
Best
negative charge is on least basic atom

Second-best
negative charge is on most basic atom

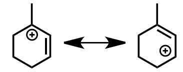
Rule #4 Stabilizing positive charge

If the resonance form has a positive charge, try and find a resonance form in which all octets are full (Rule #2)

If all octets are **not** full, place positive charge on the atom best able to support a carbocation (i.e. **the most substituted carbon**)



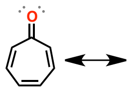
Best **2nd-best**



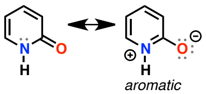
Best **2nd-best**

Rule #5 - Aromaticity (Org 2 Topic)

A resonance form that is aromatic will have a disproportionate contribution to the resonance hybrid



aromatic



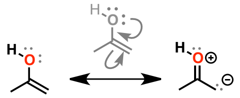
aromatic

4. Applications of Resonance

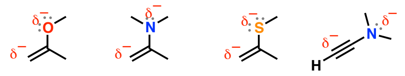
1) π–donation

Alkenes attached to an atom with a lone pair such as O, N, S, etc. (often called "heteroatoms") **have an important resonance form with a negative charge adjacent to the carbon-atom bond.**

Example:



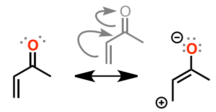
This effect makes these alkenes more nucleophilic (electron-rich).



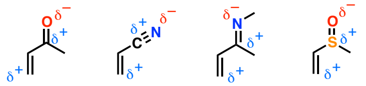
2) π–accepting

When double bonds are connected to a *polarized* π bond, the molecule will have a significant resonance form where there is positive charge on the adjacent carbon.

Polarized π-bond (C=O)



This effect makes these alkenes more electrophilic (electron-poor)



Omissions, Mistakes, Suggestions?

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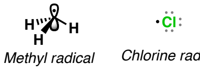
Summary Sheet - Free Radicals

"Master Organic Chemistry"
masterorganicchemistry.com

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

Free radicals contain an unpaired electron in their valence shell



Methyl radical *Chlorine radical*

As free radicals contain less than a full octet of electrons, they are electron-deficient and therefore are highly reactive

Properties: **Neutral (formal charge of zero)**

geometry of methyl radical is a "shallow" trigonal pyramid

What Factors Stabilize Free Radicals?

The same factors which stabilize carbocations. Keep these two general principles in mind: 1) electron-poor species (like radicals) are stabilized by electron-rich neighbors, or 2) by being able to spread electron density out over a greater volume.

1. Substitution

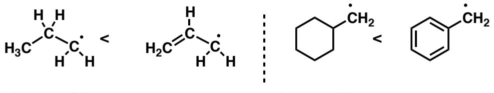
Stability increases with the number of attached carbons. Neighboring alkyl groups can donate electron density to the electron-poor radical

Methyl radical **Primary radical** **Secondary radical** **Tertiary radical**

Least stable Most stable

2. Free Radicals Are Stabilized By Resonance

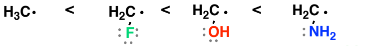
Radicals are stabilized if they can be delocalized over several atoms (as in resonance)



Less stable More stable Less stable More stable

3. (Advanced) Atoms With Adjacent Lone Pairs

Adjacent lone pairs stabilize free radicals through "hyperconjugation"



least stable *most stable*

Stability increases with increasing donor ability of adjacent atom with lone pairs

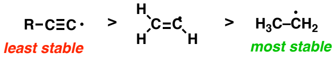
Other Factors Affecting Free Radical Stability

Polarizability: Stability increases with increasing distance of the half-filled orbital from the nucleus; in other words, with increasing size of the atom (stability increases going down the periodic table)

:F• > :Cl• > :Br• > :I•

least stable *most stable*

Hybridization: Stability increases with decreasing s-character, which moves the free radical farther from the nucleus



least stable *most stable*

sp sp^2 sp^3

Electron-Withdrawing Groups: Groups which withdraw electron density from the free radical (without being able to donate a lone pair) destabiize radicals

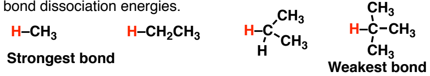
$F_3C–\dot{C}H_2$ > $H_3C–\dot{C}H_2$

less stable *most stable*

Bond strengths are a useful guide to free radical stability

Since bond dissociation energies measure homolytic cleavage

It's possible to discern trends in free radical stability by examining bond dissociation energies.

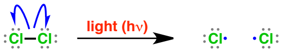


Strongest bond **Weakest bond**

104 kcal/mol **98 kcal/mol** **96 kcal/mol** **93 kcal/mol**

Electron movement is shown with "single-barbed" arrows

Example #1 - homolytic cleavage



Each barbed arrow shows the movement of one electron

Example #2 - showing interconversion of resonance forms

resonance forms

Key Reaction: Halogenation of Alkanes With Cl_2 or Br_2

$$R–H \xrightarrow[h\gamma \text{ or } \Delta]{Cl_2} R–Cl \quad + H–Cl$$

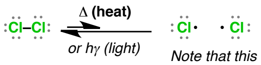
$$R–H \xrightarrow[h\gamma \text{ or } \Delta]{Br_2} R–Br \quad + H–Br$$

Iodination doesn't work well (thermodynamically unfavorable) and fluorination is difficult to control

The Three Key Mechanistic Steps In Free-Radical Halogenation Are Initiation, Propagation, and Termination

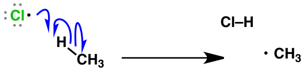
- Initiation steps have a net increase in the number of free radicals
- Propagation steps have no net change in the number of free radicals
- ª Termination steps have a net decrease in the number of free radicals

Initiation



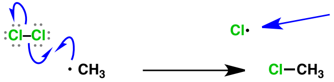
Note that this is an equilibrium!
Not all the Cl_2 is consumed!

Propagation (Step 1)



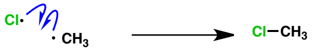
Note that each side of the equation has one free radical (no change in #)

Propagation (Step 2)



This chlorine radical can then participate in Propagation Step 1 with a new molecule of alkane; therefore, this is a chain reaction!

Termination



Note that the product side of the equation has no free radicals

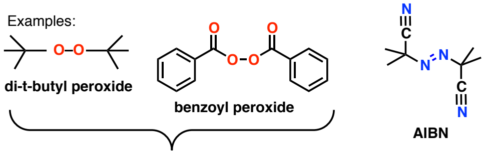
other termination reactions also possible

Avoid the common mistake of writing this step as Propagation Step 2!
Note how the number of free radicals decreases from 2 to to zero; therefore it is a termination step

Free Radical Initiators

Free radical "initators" generate free radicals when heated. They generally have a weak bond (such as O–O) that readily undergoes homolytic cleavage.

Examples:

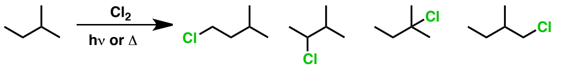


di-t-butyl peroxide **benzoyl peroxide** **AIBN**

Often just abbreviated as "RO–OR" or "peroxides"

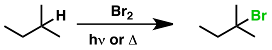
Chlorination Reactions Are Less Selective Than Bromination Reactions

Example: Chlorination can lead to substitution at primary, secondary, and tertiary positions



4 possible products formed here; chlorination occurs at primary, secondary and tertiary positions

Bromination tends to be very selective for substitution at tertiary C–H



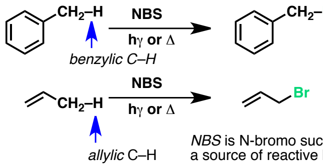
Major product

How much more selective is Br• than Cl• ?

Selectivity of Radicals Towards Alkyl Hydrogens

Radical	CH_3–H (methyl)	CH_3CH_2–H (primary)	$(CH_3)_2CH$–H (secondary)	$(CH_3)_3C$–H (tertiary)
Br •	0.007	1	220	19,400
Cl •	0.004	1	4.3	6.0

Allylic And Benzylic Bromination



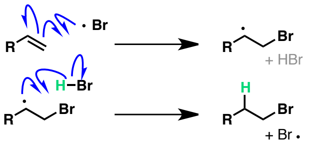
Allylic and benzylic C–H bonds are relatively weak, since removal will result in a resonance-stabilized free radical

NBS is N-bromo succinimide, a source of reactive bromine

Free-Radical Addition of H-Br To Alkenes

Note that Br adds to least substituted end of double bond. Why?

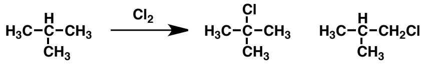
After initiation forms peroxide radical, and peroxide radical removes H from H–Br to give Br• , this key step occurs:



Br• adds to the end of the alkene such that the more stable secondary radical is formed

In the second propagation step, the alkyl radical removes a hydrogen from H–Br, regenerating Br•

How To Calculate Selectivity? An Example



43% 57%

Here there are two types of C-H bonds; a tertiary C-H and a primary C-H
How selective is the reaction for tertiary C-H ?

We can't compare by the yields directly [43% and 57%] because there is one tertiary C-H and 9 primary C-H . To adjust for this statistical factor we divide 57 by 9.

This gives us 6.3 .
Now we divide 43 by 6.3, which gives us 6.8 .

Therefore the reaction is 6.8 times more selective for tertiary C-H than primary C-H

Omissions, Mistakes, Suggestions?

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Introduction to Acids and Bases

"Master Organic Chemistry"
masterorganicchemistry.com

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

1. Introduction

Two definitions of acids:

Brønsted definition: An acid donates a proton (H+)
Lewis definition: An acid accepts a lone pair of electrons

Two definitions of bases:

Brønsted definition: A base accepts a proton (H+)
Lewis definition: A base donates a lone pair of electrons

Simple example of an acid-base reaction

$$\underset{\text{Acid}}{H{-}Cl{:}} + \underset{\text{Base}}{Na^{\oplus}{:}OH^{\ominus}} \longrightarrow \underset{\text{Conjugate acid}}{H{-}OH} + \underset{\text{Conjugate base}}{Na^{\oplus}\ {:}Cl{:}^{\ominus}}$$

Form	Break
H–OH	H–Cl

Every acid base reaction will involve the formation and breakage of a bond to hydrogen

The four actors:

Acid: donates a proton (**or** - accepts a lone pair)
Base: accepts a proton (**or** - donates a lone pair)
"**Conjugate base**": is what remains of the acid after it donates H+
"**Conjugate acid**" is the species formed when the base accepts H+

2. How Do We Define and Measure Acidity?

Acidity is defined as the position of the equilibrium between an acid and its conjugate base. We obtain this number through **experimental measurement**.

For a generic acid-base reaction:

$$\underset{\text{acid}}{H{-}A} \rightleftharpoons H^{\oplus} + \underset{\text{conjugate base}}{{:}A{:}^{\ominus}}$$

The acidity constant, K_a is:

$$K_a = \frac{[A^{\ominus}][H^{\oplus}]\ \cancel{[solv]}}{[H{-}A]\ \cancel{[solv]}}$$

solvent is technically a part of the acid-base equation, but we can ignore this because all K_a's are expressed in the same solvent

These values can differ by an extremely large amount (10^{60}) so it is convenient to work with the logarithm of this number, defined as the pKa:

$$pK_a = -\log K_a$$

3 concrete examples:

	experimental measurement	pKa ($-\log K_a$)	
$\underset{\text{acid}}{H{-}I} \rightleftharpoons H^{\oplus} + \underset{\text{conjugate base}}{{:}I{:}^{\ominus}}$	$K_a = 1 \times 10^{10}$	–10	***Strong acid!***
$\underset{\text{acid}}{H{-}OH} \rightleftharpoons H^{\oplus} + \underset{\text{conjugate base}}{{:}OH^{\ominus}}$	$K_a \sim 1 \times 10^{-15}$	15.7	***Weak acid***
$\underset{\text{acid}}{H{-}CH_3} \rightleftharpoons H^{\oplus} + \underset{\text{conjugate base}}{{:}CH_3^{\ominus}}$	$K_a = 1 \times 10^{-50}$	50	***Extremely weak acid!***

3. What factors make an acid strong or weak?

Generally, the strength of an acid is related to the **stability** of the conjugate base.

The greater the stability of the conjugate base, the stronger the acid.
The lower the stability of the conjugate base, the weaker the acid.

A different way to put it: **stability is inversely related to basicity.**

Stable conjugate base = a "weak" base
Unstable conjugate base = a "strong" base

The stronger the acid, the weaker the conjugate base
The weaker the acid, the stronger the conjugate base.

The best way to understand acidity/basicity is to understand the factors that stabilize negative charge (i.e. high electron density)

There are seven important factors (placed here in roughly decreasing order of importance).

Factor #1: The less charge, the better

$$O^{2\ominus} < {}^{\ominus}O{-}H < H{-}O{-}H$$

least stable (i.e. most basic) … *most stable (least basic)*

$$H{-}O^{\ominus} < H{-}OH < H{-}OH_2^{\oplus}$$

weakest acid … *strongest acid*

Factor #2: Going across the periodic table, greater electronegativity stabilizes negative charge.

$${:}CH_3^{\ominus} < {:}NH_2^{\ominus} < {:}OH^{\ominus} < {:}F{:}^{\ominus}$$

least electronegative (least stable) (most basic) … *most electronegative (most stable) (least basic)*

$$H{-}CH_3 < H{-}NH_2 < H{-}OH < H{-}F$$

Weakest acid … *strongest acid*

Factor #3: Going down the periodic table, greater polarizability stabilizes negative charge.

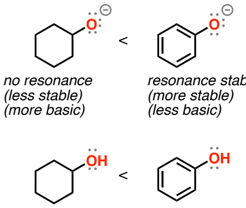
$${:}F{:}^{\ominus} < {:}Cl{:}^{\ominus} < {:}Br{:}^{\ominus} < {:}I{:}^{\ominus}$$

least polarizable (least stable) (most basic) … *most polarizable (most stable) (least basic)*

$$H{-}F < H{-}Cl < H{-}Br < H{-}I$$

Weakest acid … *strongest acid*

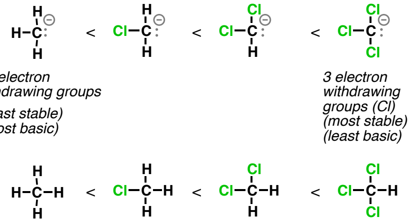
Factor #4: Negative charge is stabilized by resonance, which delocalizes electron density



no resonance (less stable) (more basic) … *resonance stabilization (more stable) (less basic)*

Weaker acid … *Stronger acid*

Factor #5: Negative charge is stabilized by adjacent electron withdrawing groups (inductive effects)



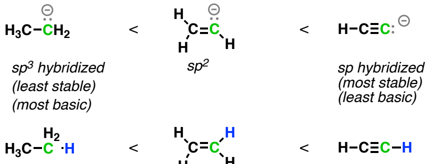
$$H{-}\overset{H}{\underset{H}{C}}{:}^{\ominus} < Cl{-}\overset{H}{\underset{H}{C}}{:}^{\ominus} < Cl{-}\overset{Cl}{\underset{H}{C}}{:}^{\ominus} < Cl{-}\overset{Cl}{\underset{Cl}{C}}{:}^{\ominus}$$

No electron withdrawing groups (least stable) (most basic) … *3 electron withdrawing groups (Cl) (most stable) (least basic)*

$$H{-}\overset{H}{\underset{H}{C}}{-}H < Cl{-}\overset{H}{\underset{H}{C}}{-}H < Cl{-}\overset{Cl}{\underset{H}{C}}{-}H < Cl{-}\overset{Cl}{\underset{Cl}{C}}{-}H$$

Weakest acid … *Strongest acid*

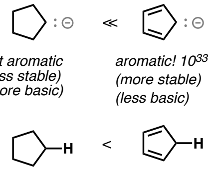
Factor #6: Negative charge is stabilized as the hybridization includes greater s character



sp³ hybridized (least stable) (most basic) … *sp²* … *sp hybridized (most stable) (least basic)*

Weakest acid … *Strongest acid*

Factor #7: A Special case - negative charge is especially stable if the electrons are part of an aromatic π-system



not aromatic (less stable) (more basic) … *aromatic! 10^{33} more stable than the molecule on the left! (more stable) (less basic)*

Weaker acid … *Stronger acid*

4. What makes an acid-base reaction favorable (or not?)

Key principle: In **favorable** acid-base reactions, a stronger acid adds to a stronger base to give a weaker acid and a weaker base

Key questions to ask: Is the "acid" stronger than the "conjugate acid" ?
Is the "base" stronger than the "conjugate base" ?
If so, the acid-base reaction will be favorable.

How do you tell which acid is stronger or weaker?
A **pKa table** collates **experimental measurements** of acidity, and thus incorporates all the factors mentioned above.

Strong acids have **low** pKa values. Weak acids have **high** pKa values.

A very abridged pKa table:

	Acid	pKa	Conjugate Base	
strongest acid	$H{-}Cl$	–8	${}^{\ominus}Cl$	*weakest base*
↑	$H{-}\overset{\oplus}{O}H_2$	–1.7	H_2O	↓
	$H{-}\overset{H}{O}{-}\overset{O}{\overset{\|}{C}}CH_3$	4.5	${}^{\ominus}O{-}\overset{O}{\overset{\|}{C}}CH_3$	
	$H{-}\overset{\oplus}{N}H_3$	10	${:}NH_3$	
	$H{-}OH$	15.7	${}^{\ominus}OH$	
	$H{-}OCH_2CH_3$	16	${}^{\ominus}OCH_2CH_3$	
	$H{-}C{\equiv}C{-}H$	25	${}^{\ominus}{:}C{\equiv}C{-}H$	
	$H{-}NH_2$	38	${}^{\ominus}NH_2$	
weakest acid	$H{-}CH_3$	~50	${}^{\ominus}{:}CH_3$	*strongest base*

Example of a favorable acid-base reaction:

$$H{-}Cl{:} + Na^{\oplus}{:}OH^{\ominus} \longrightarrow H{-}OH + {:}Cl{:}^{\ominus}$$

pKa –8 … pKa ~15

Here, we're going from a stronger acid (HCl, pKa –8) to a weaker acid (H_2O, pKa 15) so this acid-base reaction is favorable.

Omissions, Mistakes, Suggestions?

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Summary of Functional Groups (1)

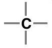
"Master Organic Chemistry"
masterorganicchemistry.com
2015 Version

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

What Are Functional Groups?

Functional groups are collections of atoms that have a common pattern of chemical reactivity

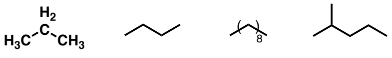
Alkane



a hydrocarbon with no multiple bonds is an alkane

Suffix: "-ane". As a substituent: "alkyl"

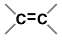
Examples:



Propane | Butane | Decane | 2-methylpentane

Characteristics: nonpolar
Geometry: tetrahedral (*sp^3 hybridized*)
Reactivity: ***free radical reactions*** *(e.g. free radical chlorination or bromination)*

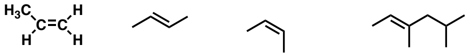
Alkene



a hydrocarbon with at least one C–C double bond (π bond) is an alkene

Suffix: "-ene". As a substituent: "alkenyl"

Examples:



Propene | *trans*-2-butene [or (*E*)-2-butene] | *cis*-2-butene [or (*Z*)-2-butene] | (*E*)-3,5-dimethylhex-2-ene

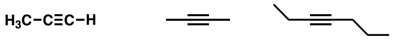
Characteristics: nonpolar. Molecule cannot rotate along double bond.
Geometry: trigonal planar (*sp^2* hybridized)
Reactivity: *undergo* ***addition*** *reactions, as well as* ***oxidative cleavage***
Stability increases with increasing # of carbons attached

Alkyne $-C\equiv C-$

a hydrocarbon with at least one C–C triple bond (π bond) is an alkyne

Suffix: "-yne". As a substituent: "alkynyl"

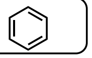
Examples:



Propyne a *terminal* alkyne | 2-butyne | 3-heptyne
internal alkynes

Alkynes with a C–H bond are called "terminal" alkynes
Geometry: linear (*sp* hybridized)
Characteristics: non polar
Reactivity: ***addition*** *reactions*
oxidative cleavage *reactions*
acid-base *reactions (terminal alkynes are unusually acidic)*

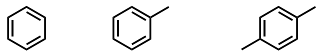
Benzene ring



A six-membered ring containing 3 alternating double bonds is a benzene ring

Suffix: "benzene". As a substituent: "phenyl"

Examples:



Benzene | Methylbenzene (toluene) | 1,4-dimethylbenzene (*para*-dimethylbenzene)

Reactivity: ***substitution*** *reactions (e.g. electrophilic aromatic substitution or nucleophilic aromatic substitution)*
Less reactive than normal alkenes due to aromatic stability

Alcohol $R-\overset{\delta-}{O}-\overset{\delta+}{H}$

"OH" attached to an alkyl group is referred to as an alcohol. OH attached to a benzene ring is a "phenol" (not shown).

Suffix: "-ol". As a substituent: "hydroxy"

Examples:

Methanol | Ethanol a *primary* alcohol | 2-propanol ("Isopropanol") a *secondary* alcohol | 2-methyl-2-propanol (*t*-butanol) a *tertiary* alcohol

Characteristics: polar (O-H group participates in hydrogen bonding)
Reactivity: ***acid-base*** *reactions (can act as acids or bases)*
substitution *reactions (can act as nucleophiles)*
oxidation *reactions (primary and secondary alcohols (and methanol) can be oxidized to aldehydes, ketones, or carboxylic acids, depending on structure and reagent used)*

Ether $R-\overset{\delta-}{O}-\overset{\delta+}{R}$

An oxygen flanked by two carbons is an ether

As a substituent: "alkoxy"

Examples:

Dimethyl ether | Ethyl methyl ether (or "methoxyethane") | Methyl phenyl ether (or "methoxybenzene", or "anisole") | Tetrahydrofuran (THF) a cyclic ether

Characteristics: borderline between nonpolar and polar (due to dipole-dipole)
Reactivity: ***acid-base*** *reactions (oxygen can act as a very weak base)*

Alkyl halide $\overset{\delta+}{R}-\overset{\delta-}{F}{:}$ $\overset{\delta+}{R}-\overset{\delta-}{Cl}{:}$ $\overset{\delta+}{R}-\overset{\delta-}{Br}{:}$ $\overset{\delta+}{R}-\overset{\delta-}{I}{:}$

An alkyl group attached to a halogen is an alkyl halide

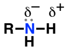
Suffix: "-ane". As a substituent: "haloalkyl"

Examples:

Iodomethane (methyl iodide) | Fluoroethane (ethyl fluoride) a *primary* alkyl halide | 2-chloropropane (isopropyl chloride) a *secondary* alkyl halide | 2-methyl-2-bromopropane (*t*-butyl bromide) a *tertiary* alkyl halide

Characteristics: generally considered non polar (but more polar than alkanes)
Reactivity: ***substitution*** *reactions (Cl, Br, I can be good leaving groups)*
elimination *reactions (Cl, Br, I can be good leaving groups)*

Amine

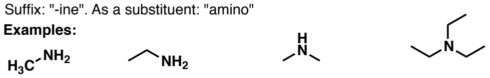


$R-\underset{H}{\overset{\delta-}{N}}-\overset{\delta+}{H}$

A nitrogen attached to simple carbon or hydrogen atoms is an amine

Suffix: "-ine". As a substituent: "amino"

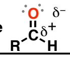
Examples:



Methylamine | Ethylamine a *primary* amine | Dimethylamine a *secondary* amine | Triethylamine a *tertiary* amine

Characteristics: polar (N-H group participates in hydrogen bonding, although not as much as a hydroxy group
Reactivity: ***acid-base*** *reactions (tend to act as bases)*
substitution *reactions (can act as nucleophiles)*

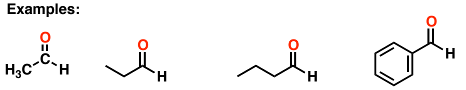
Aldehyde



A carbonyl (C=O) attached to a hydrogen and another carbon is an aldehyde

Suffix: "-al" (if attached to ring: carbaldehyde) As a substituent: "oxo"

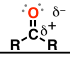
Examples:



Ethanal | Propanal | Butanal | Benzaldehyde

Characteristics: the C=O bond is somewhat polar
Reactivity: ***addition*** *reactions (the carbonyl carbon reacts easily with nucleophiles)*

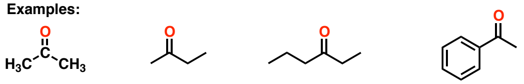
Ketone



A carbonyl (C=O) flanked by two carbons is a ketone

Suffix: "-one". As a substituent: "oxo"

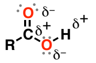
Examples:



2-propanone ("acetone") | 2-butanone ("methyl ethyl ketone") | 3-hexanone | phenyl methyl ketone ("acetophenone")

Characteristics: the C=O bond is somewhat polar (less so than O-H however)
Reactivity: ***addition*** *reactions (the carbonyl carbon reacts easily with nucleophiles)*
acid-base *reactions (carbons adjacent to the ketone can be deprotonated to give enolates)*

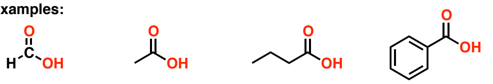
Carboxylic acid



A carbonyl (C=O) adjacent to a hydroxyl (OH) and an R group is a carboxylic acid

Suffix: "-oic acid"

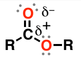
Examples:



Methanoic acid ("formic acid") | Ethanoic acid ("acetic acid") | Butanoic acid | benzoic acid

Reactivity: ***acid-base*** *reactions (the O–H is acidic)*
acyl substitution *reactions (can replace OH with other groups under acidic conditions)*

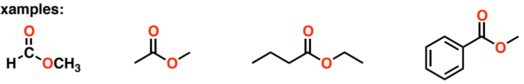
Ester



A carbonyl (C=O) adjacent to an alkoxy (OR) and an R group is an ester

Suffix: "-oate"

Examples:



Methyl methanoate | Methyl ethanoate | Ethyl butanoate | Methyl benzoate

Reactivity: ***acyl substitution*** *reactions (can replace OR with other functional groups under acidic conditions)*
addition *reactions (the carbonyl carbon reacts easily with nucleophiles)*

Omissions, Mistakes, Suggestions?

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Summary of Functional Groups (2)

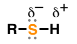
"Master Organic Chemistry"
masterorganicchemistry.com
2015 Version

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

What Are Functional Groups?

Functional groups are collections of atoms that have a common pattern of chemical reactivity

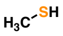
Thiol

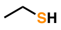


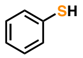
Thiols are the sulfur-containing analogs of alcohols

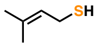
Suffix: "-thiol". As a substituent: "mercapto"

Examples:


Methanethiol

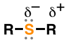

Ethanethiol


Thiophenol


Isoprenyl mercaptan
"eau de skunk"

Reactivity: ***acid-base*** *reactions (thiols can act as weak acids)*
substitution *reactions (thiols are good nucleophiles)*

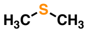
Sulfide (Thioether)

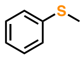


A sulfur flanked by two carbon atoms is a sulfide

Suffix: "-sulfide".

Examples:

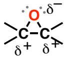

Dimethylsulfide


Phenyl methyl sulfide


tetrahydrothiophene

Reactivity: ***reduction*** *reactions (will reduce the intermediate of ozonolysis reactions); sulfide is oxidized to "sulfoxide"*

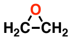
Epoxide

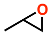


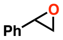
Epoxides are cyclic ethers consisting of a 3-membered ring containing an oxygen and two carbons.

Suffix: "-oxide"

Examples:

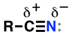

Ethylene oxide


Propylene oxide


Styrene oxide

Reactivity: *epoxides have considerable ring strain, and will undergo* ***ring opening*** *when treated with various types of nucleophiles (e.g. Grignard reagents, organolithium reagents)*

Nitrile

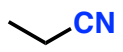


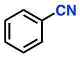
A molecule containing the CN group is a nitrile

Suffix: "-nitrile"

Examples:

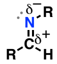
$H_3C{-}CN$
Acetonitrile


Propionitrile


Benzonitrile

Reactivity: ***reduction*** *reactions (nitriles can be reduced to amines with strong reductants such as* $LiAlH_4$*)*
hydrolysis *reactions (nitriles can be converted to carboxylic acids with aqueous acid)*

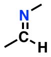
Imine



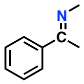
Imines are the nitrogen-containing analogues of ketones and aldehydes

Suffix: "-imine".

Examples:


an *aldimine*


a *ketimine*

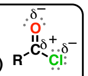


- *Imines formed from aldehydes are sometimes called "aldimines"*
- *Imines formed from ketones are sometimes called "ketimines"*

Imines are also sometimes called "Schiff bases"

Reactivity: ***reduction*** *reactions (imines can be reduced to amines)*
hydrolysis *reactions (imines can be hydrolyzed to give back aldehydes or ketones)*

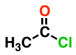
Acyl halide ("Acid halide")

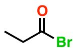


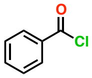
Acyl halides are carboxylic acid derivatives where -OH has been replaced by a halogen

Suffix: "-oyl halide"

Examples:

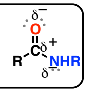

Ethanoyl chloride ("Acetyl chloride")


Propanoyl bromide


Benzoyl chloride

Reactivity: ***acyl substitution*** *reactions (halides are good leaving groups and can be replaced by good nucleophiles)*

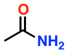
Amide

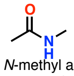


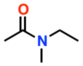
Amides are the nitrogen containing analogues of esters

Suffix: "-amide"

Examples:

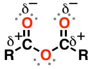

acetamide
a primary amide


N-methyl acetamide
a secondary amide


N-ethyl *N*-methyl acetamide
a tertiary amide

Reactivity: ***reduction*** *reactions (amides can be reduced to amines with strong reductants such as* $LiAlH_4$
hydrolysis *reactions (amides can be hydrolyzed to carboxylic acids with aqueous acid)*

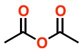
Anhydride

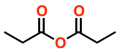


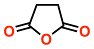
Anhydrides are oxygen atoms flanked by two acyl groups

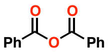
Suffix: "-anhydride"

Examples:


Acetic anhydride
(Ethanoic anhydride)

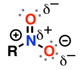

Propionic anhydride


Succinic anhydride


Benzoic anhydride

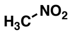
Reactivity: ***acyl substitution*** *reactions (anhydrides can be cleaved with good nucleophiles)*
reduction reactions *(anhydrides can be reduced to aldehydes with various reducing agents)*

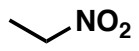
Nitro

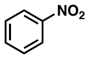


A molecule containing the NO_2 *group is a nitro compound*

Examples:

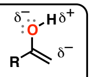

Nitromethane


Nitroethane


Nitrobenzene

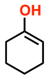
Reactivity: ***reduction*** *reactions (nitro groups can be reduced to amines)*
acid-base *reactions (C-H bonds adjacent to the* NO_2 *group are acidic)*

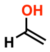
Enol



Enols are alkenes attached to a hydroxyl substitutent. They are obtained from tautomerization of aldehydes/ketones

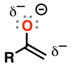
Examples:





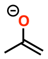
Reactivity: *enols are good* *nucleophiles*. *They will perform* ***addition*** *reactions to aldehydes and ketones, among other reactions.*
Enols will ***tautomerize*** *to aldehydes/ketones*

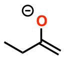
Enolate

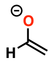


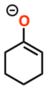
Enolates are the conjugate bases of enols

Examples:



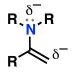






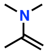
Reactivity: *enolates are excellent* *nucleophiles* *(better than enols) They will perform* ***addition*** *reactions to aldehydes and ketones, as well as* ***substitution*** *reactions with alkyl halides (among others)*

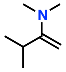
Enamine

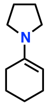


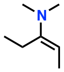
Enamines are alkenes attached to an amino substitutent.

Examples:









Reactivity: *enamines are excellent* *nucleophiles*. *They will perform* ***addition*** *reactions to aldehydes and ketones, as well as* ***substitution*** *reactions with alkyl halides (among others)*

Omissions, Mistakes, Suggestions?

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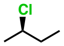
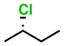
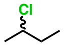
Introduction to Stereochemistry

"Master Organic Chemistry"
masterorganicchemistry.com
2015 Version

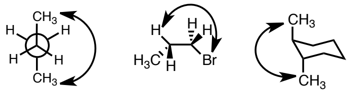
Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

Symbols

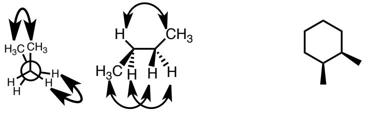
			Example
◀	**"wedge"**	denotes a group pointing "out of the page"	
⋮⋮⋮	**"dash"**	denotes a group pointing "into the page"	
∿	**"squiggle"**	undefined (mixture of stereoisomers) Rarely used.	

Terms

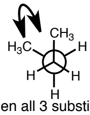
anti two groups on adjacent carbons oriented at 180° to each other



syn two groups on adjacent carbons oriented at 0° to each other

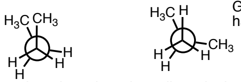


gauche two groups on adjacent carbons oriented at 60° to each other



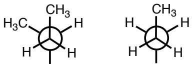
Generally, gauche interactions between bulky groups are intermediate in torsional strain between the anti and syn relations

eclipsed when all 3 substituents overlap completely with all 3 substituents on a neighboring carbon.



Generally, eclipsed conformations have the highest torsional strain

staggered refers to the orientation when all 3 substituents on a carbon are arranged at a 60 deg angle to all 3 substituents on another carbon.

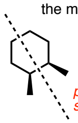


isomers two molecules with the same molecular formula, but different in their structures

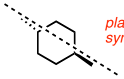
configuration the 3-D arrangement of bonds around a carbon.

racemic mixture a 50:50 mixture of two enantiomers

Meso compound: A molecule with stereocenters, but a plane of symmetry that makes the molecule achiral



plane of symmetry



plane of symmetry

Cis on the same side of a double bond or ring

Trans on opposite sides of a double bond or ring.

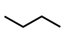
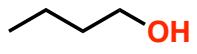
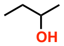
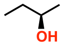
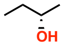
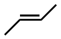
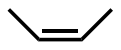
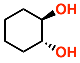
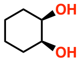
Chiral molecule a molecule with an enantiomer; cannot possess a plane of symmetry

Stereocenter Has 4 different constituents

Torsional Strain Strain that arises from the proximity of bonds (and the electrons in them) - generally eclipsing

Types of isomers

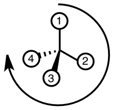
Isomers: same empirical formula, different structural formula.

Type	Connectivity?	Configuration?	3-D Shape?	Physical properties	Example
Conformational isomers	*Same*	*Same*	*Different*	*Identical, as long as they can interconvert through bond rotation*	 staggered  eclipsed
Constitutional isomers	*Different*			*Different boiling points, melting points, and other physical properties*	 1-butanol  2-butanol
Stereoisomers	*Same*	*Different*			
Enantiomers →	*Stereoisomers that are non-superimposable mirror images*			*Identical. Differ in optical rotation*	 (*R*)-2-butanol  (*S*)-2-butanol
Diastereomers →	*Stereoisomers that are* ***NOT*** *non-superimposable mirror images*			*Different boiling points, melting points, etc.*	 *trans*-2-butene  *cis*-2-butene  (trans)-cyclohexane 1,2-diol  (cis)-1,2-cyclohexanediol

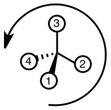
Note: another name for stereoisomers is "configurational isomers": they have the same connectivity, but differ in the configurations of the carbons.

The R,S convention

Rank according to atomic number
Put #4 ranked substituent in back.

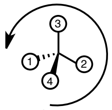


1,2,3 goes CW: R



1,2,3 goes CCW: S

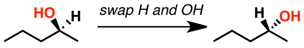
What if #4 is in the front? One approach is to trace 1,2 and 3 as you normally would. Then flip!



1,2, and 3 go counterclockwise.
4 ranked substituent is in front
Therefore, flip: *this is R !*

The single swap rule:

Single swap rule: switching any two groups on a stereocenter will flip (R) to (S) and vice versa.



(S)-2-pentanol (R)-2-pentanol

works for any other two groups as well
(e.g. OH and CH$_3$, H and CH$_3$, OH and CH$_2$CH$_2$CH$_3$, etc.)

Recognizing Enantiomers/Diastereomers Using Only Their Names

Diastereomers: same name, but R/S designations are not exactly opposite

Example:(2S, 3R)-2-bromo-3-chlorobutane and (2S, 3S)-2-bromo-3-chlorobutane
(2S, 3S, 4S, 5R)-2-bromo-3-chloro-4-methyl-5-propyldecane
and (2S, 3R, 4R, 5S)-2-bromo-3-chloro-4-methyl-5-propyldecane

also, diastereomers will have the same name, but differ in E/Z (or cis/trans).

e.g. (Z)-2-butene and (E)-2-butene.
cis-1,2-dimethylcyclohexane and trans-1,2-dimethylcyclohexane

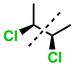
Enantiomers: same name, but have all stereocenters have opposite R/S designations

Example: (R)-2-butanol, (S)-2-butanol

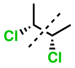
(2S, 3R)-2-bromo-3-chlorobutane and (2R, 3S)-2-bromo-3-chlorobutane
(2S, 3S, 4S, 5R)-2-bromo-3-chloro-4-methyl-5-propyldecane
and (2R, 3R, 4R, 5S)-2-bromo-3-chloro-4-methyl-5-propyldecane

Important exception: If the molecule has a mirror plane, then it is **meso**, and the two "enantiomers" are in fact the same mo**lecule**

Example: (2R,3S)-2,3-dichlorobutane and (2S,3R)-2,3-dichlorobutane are **the same**



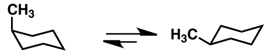
mirror plane



mirror plane

Cyclohexane chair conformations

in the cyclohexane chair conformation: all C–C bonds staggered



CH$_3$ axial (disfavored) *CH$_3$ equatorial (favored)*

Chair flips: all axial groups become equatorial, and all equatorial groups become axial.

BUT all groups that are "up" stay "up" and all groups that are "down" stay "down.

Bulky groups prefer the equatorial position.

The bulkier the group, the greater the energy difference will be.
Bulkiness:
tertiary C (3°) > secondary C (2°) > primary C (1°), methyl (CH$_3$) >> H

The energy difference between two different chair forms (in ΔG) is related to the equilibrium constant by
$K = e^{-(\Delta G/RT)}$

Omissions, Mistakes, Suggestions?

james@masterorganicchemistry.com

Substitution and Elimination - Page 1 of 2

Nucleophilic Substitution Bimolecular (S_N2)

Key points:
- Nucleophilic substitution is swapping of one functional group for another
- Structure of alkyl halide is key: primary > secondary >> tertiary
- Mechanism proceeds through backside attack
- Stereochemistry proceeds with **inversion**
- Rate depends on concentration of **both** nucleophile and alkyl halide
- Reaction occurs faster in **polar aprotic solvents**

Example:

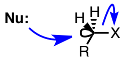
$$Na^{\oplus}\ OH^{\ominus} + CH_3CH_2Br \longrightarrow CH_3CH_2OH + Na^{\oplus}\ Br^{\ominus}$$

substitution of $Br^{\ominus}$ for $HO^{\ominus}$

The S_N2 Reaction is Sensitive to Steric Effects.

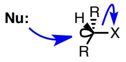
In the S_N2 the electrophile is the antibonding orbital. as you populate the antibonding orbital with electrons you weaken the bond to the leaving group

R groups shield backside from nucleophilic attack



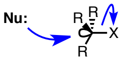
Primary alkyl halide

Fast



Secondary alkyl halide

Intermediate

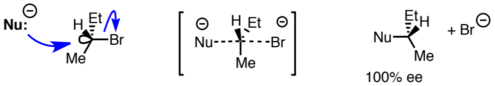


Tertiary alkyl halide.

So slow it doesn't happen.

The S_N2 Mechanism: The Backside Attack Leads to Inversion

The nucleophile (electron pair) attacks the empty antibonding orbital which is on the **backside** of the carbon-leaving group bond



100% ee
(one enantiomer)

100% ee
one enantiomer
inversion of configuration

The Rate Limiting Step of the S_N2 Is Bimolecular

Rate = k [Substrate] [Nucleophile]

Rate	[R–X]	[Nu]
x	1	1
2x	2	1
2x	1	2
4x	2	2

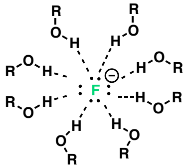
Doubling the concentration of either component will double the rate.

Polar aprotic solvents are the best for the S_N2

Because of the charges involved in the S_N2 mechanism polar solvents are better than nonpolar solvents.

Two types of polar solvents: polar protic (have O-H or N-H bonds)
Polar aprotic (has dipoles but cannot hydrogen bond).

Why? **Polar protic solvents make a "jacket" around nucleophiles through hydrogen bonding, decreasing the reactivity of the nucleophile.**



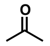
Note that in polar aprotic solvent reactivity of halides **reverses** because there is no hydrogen bonding to solvent

$F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$

Examples of polar protic solvents:
H_2O, CH_3OH, CH_3CH_2OH,
CH_3COOH, *i*-PrOH
$CH_3CH_2CH_2NH_2$

Polar aprotic solvents:

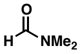
DMSO



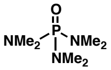
Acetone

Me–C≡N

Acetonitrile



DMF



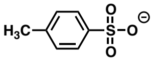
HMPA

What Makes A Good Leaving Group?

One main thing: **Good Leaving Groups are Weak Bases**

Good Leaving Groups

	$I^{\ominus}$	$Br^{\ominus}$	$Cl^{\ominus}$	$TsO^{\ominus}$	H_2O	$AcO^{\ominus}$
pKa of conjugate acid	–9	–8	–7	–3	–1.7	4



TsO = p-methyltoluenesulfonate

Conjugate base of the strong acid tosic acid, similar in strength to H_2SO_4 (sulfuric acid)

Bad Leaving Groups

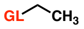
	$F^{\ominus}$	$^{\ominus}OH$	$RO^{\ominus}$	$H_2N^{\ominus}$	$H^{\ominus}$	alkyl, alkenyl
pKa of conjugate acid	1	16	16-18	~38	42	>45

With the exception of $F^{\ominus}$, these are all **strong bases**

Fluorine forms very strong bonds and is thus a very bad leaving group

Note how $HO^{\ominus}$ is not a good leaving group but H_2O is: therefore, HO can be made into a good leaving group by adding a strong acid

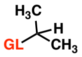
How The Substrate Influences Reactivity



primary alkyl (1°)
(least sterically hindered)
(least stable carbocations)

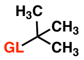
S_N2 (unhindered)
E_2 (provided a proton is on the β carbon)

S_N1/E1: not observed



secondary alkyl (2°)

S_N2 (slower than primary)
E_2 (provided a proton is on the β carbon)
S_N1/E1 : can occur when LG is OH and a strong acid is added
watch out for rearrangements!
Generally poor when LG is a halide.



tertiary alkyl (3°)
(most sterically hindered)
(most stable carbocations)

S_N2: Not observed
E_2 (provided a proton is on the β carbon)

S_N1/E1 : strongly favored
if LG = halide, good reaction
if LG = OH, requires acid

Note that hybridization in all cases here is sp^3

These reactions do not occur for alkenyl and alkynyl halides under normal conditions.

What Factors Influence Nucleophilicity?

1. **Charge:** The conjugate base is always a better nucleophile than the conjugate acid

e.g. $HO^{\ominus} > H_2O$ $HS^{\ominus} > H_2S$ $^{\ominus}CN > HCN$

2. **Electronegativity:** The less tightly held a pair of electrons are, the more readily they can be donated.

Nucleophilicity increases as we go to the LEFT along the periodic table: C: > N: > O: > F:

Nucleophilicity increases as we go DOWN the periodic table:

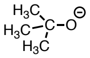
e.g. $HS^{\ominus} > HO^{\ominus}$ $:PH_3 > :NH_3$ $I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$

Another term for how "tightly held" electrons are is **polarizability.**
Nucleophilicity increases with polarizability.

3. **Solvent:** Polar protic solvents will hydrogen bond with nucleophiles (see column on left) which decreases their nucleophilicity.
- More polarizable nucleophiles will be less affected by polar protic solvents, since hydrogen bonding ability is greatest for most electronegative nucleophiles.
- Polar aprotic solvents **will not** hydrogen bond: therefore they are good solvents for the S_N2

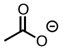
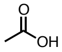
Note that in polar aprotic solvent reactivity of halides **reverses** because there is no hydrogen bonding to solvent

4. **Steric bulk:** If a sterically bulky group surrounds the nucleophilic atom, this will decrease its nucleophilicity.
Example: $CH_3O^{\ominus}$ is more nucleophilic than



$(H_3C)_3C{-}O^{\ominus}$

for this reason

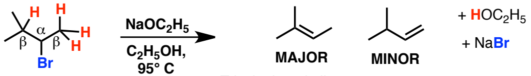
"Good Nucleophiles"	"OK Nucleophiles"	"Weak Nucleophiles"	"Non-Nucleophiles"
$HO^{\ominus}$ $CH_3O^{\ominus}$ $H_2N^{\ominus}$ $N_3^{\ominus}$ $N{\equiv}C^{\ominus}$ $H{-}C{\equiv}C^{\ominus}$ $HS^{\ominus}$ $CH_3S^{\ominus}$	$I^{\ominus}$ $Br^{\ominus}$ $Cl^{\ominus}$ $F^{\ominus}$ 	H_2O CH_3OH 	$HSO_4^{\ominus}$ $H^{\ominus}$ (as NaH)

These are examples only, not comprehensive

Elimination, Bimolecular (E2)

Key points:
- Elimination is the loss of a leaving group from the α-carbon and a hydrogen from the β-carbon resulting in the **formation of a double bond**
- The major product is the more substituted alkene (Zaitsev product) and the bulkiest groups will be trans
- Use of a bulky base will result in formation of more of the less substituted alkene
- Requires strong base
- The leaving group and the hydrogen must be oriented **anti-periplanar**
- Can occur with primary, secondary, tertiary substrates **provided there is a hydrogen on the β-carbon that can orient itself anti to the leaving group**
- Rate determining step is **bimolecular**
- Solvent is generally polar protic
- Reaction is favored with heat

Example: Elimination of HBr



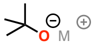
Trisubstituted alkene
"Zaitsev product"
(more C-C bonds on alkene)

Monosubstituted alkene
"Hoffmann product"

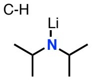
The Major Product Is the Most Substituted Alkene

Why? Because alkenes become more thermodynamically stable as C-H bonds are replaced with C-C bonds

***Exception*: Bulky bases will give less of the Zaitsev product because deprotonation on the less substituted carbon becomes favored.**



M = Na, K



(LDA)

Exception #2 is when the leaving group is bulky (e.g. $NR_3^{\oplus}$)

A Strong Base Is Required

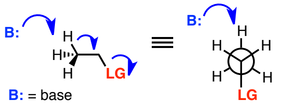
In order for the E2 reaction to occur one must use a good base,

Examples of good bases: $HO^{\ominus}$ $CH_3O^{\ominus}$ $RO^{\ominus}$ $(CH_3)_3C{-}O^{\ominus}$
$H_2N^{\ominus}$ $R_2N^{\ominus}$ $R_3N:$
$H^{\ominus}$ $H_3C^{\ominus}$ $R^{\ominus}$

Basicity increases going to the left along the periodic table: C: > N: > O: > F:

Basicity increases going up the periodic table: $F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$

The H And Leaving Group MUST be Anti-Periplanar

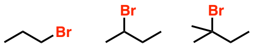


B: = base
LG = leaving group

Why? The lone pair of the C-H bond must be lined up with the σ* (antibonding orbital) of the C-LG bond

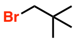
The E2 Can Occur With Primary, Secondary, and Tertiary Substrates

Good Substrates

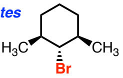


All of these substrates are effective for the E2

Bad Substrates



No H on β-carbon



No H on β–carbon that is **anti** to LG

The Rate Limiting Step of the E2 Is Bimolecular

Rate = k [Substrate] [Base]

Rate	[R–LG]	[B]
x	1	1
2x	2	1
2x	1	2
4x	2	2

Doubling the concentration of either component will double the rate.

Solvent is Generally Polar Protic - not in all instances, but polar protic will favor E2 in cases where it competes with the SN2.(see left)

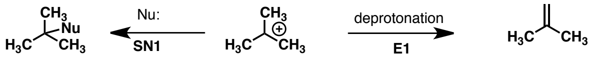
The E2 Is Favored By Heat

- Keep this in mind when considering substrates that could go E2 or SN2
- Heat favors elimination due to higher entropy

Substitution and Elimination - Page 2 of 2

Substitution Nucleophilic Unimolecular (S_N1) and Elimination, Unimolecular (E1)

- These reactions have a **lot** in common and often occur together.
They represent different fates of the same carbocation



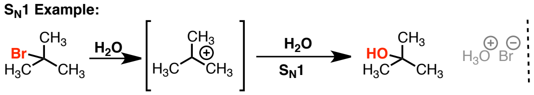
*The SN1 is **nucleophilic attack** at the carbocation*

The E1 is deprotonation of the carbon adjacent to the carbocation

What the S_N1 and E1 Have In Common

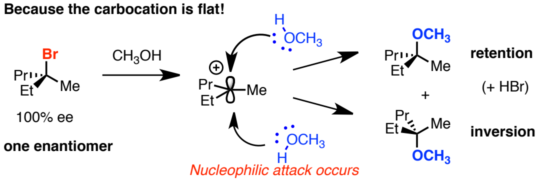
- The rate-limiting step is **formation of a carbocation**
- The rate-limiting step is **unimolecular** and **only** depends on the concentration of the **substrate** (e.g. alkyl halide)
- The rate is also proportional to the **stability of the carbocation** (see column on right)
- Tertiary carbocations > secondary carbocations >> primary carbocations > methyl carbocations
- Carbocations are **ions** (polar) so according to "like dissolves like", polar solvents are favored.In particular, **polar protic solvents** help

S_N1 Example:



The S_N1 involves two steps that occur in sequence:
1) departure of the leaving group 2) attack of the nucleophile at the carbocation
- The reaction proceeds with **weak/moderate nucleophiles** (e.g. H_2O, ROH)
- If the carbon is chiral, the chiral carbon becomes **racemized**
- **The S_N1 is always accompanied by *some* E1** (~95:5)

Why does the S_N1 lead to a mixture of stereoisomers?
Because the carbocation is flat!



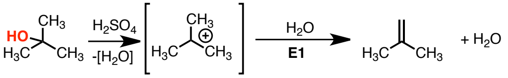
100% ee

one enantiomer

Nucleophilic attack occurs equally from either face

A racemic mixture is obtained

E1 Example:



The E1 also involves two steps that occur in sequence:
1) departure of the leaving group 2) deprotonation of the carbon adjacent to the carbocation

- The proton is removed by a **weak base**
- The **more substituted double bond** is favored (Zaitsev product)
- The major product will have the bulkiest groups *trans* to each other across the double bond
- The reaction is favored by **heat**
- The base can be the solvent, the leaving group, or the counter-ion of the acid (whichever is strongest)

The Rate Limiting Step of the S_N1 and E1 Is Unimolecular

Rate = k [Substrate] [Nucleophile/Base]

Rate	[R–X]	[Nu]
x	1	1
2x	2	1
x	1	2
2x	2	2

Doubling the concentration of the substrate doubles the rate.
Doubling the concentration of the nucleophile/base has no effect

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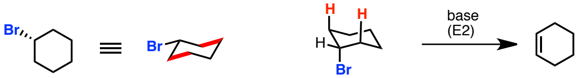
Further Notes on the S_N2 / E_2 (more advanced topics)

The E2 can only occur when the leaving group is axial:



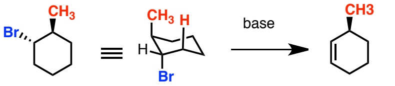
Equatorial

***No** hydrogens anti-periplanar to the Br (only carbons are)*

Axial

***Two** hydrogens are anti-periplanar to the Br. The double bond can form through removal of **either** hydrogen*

If there is no hydrogen *anti* to the leaving group, then the double bond cannot form



only product

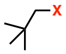
***One** hydrogen are anti-periplanar to the Br*
*Therefore only **one** double bond can form*

The S_N2 can only occur on a cyclohexane when the leaving group is axial

Why?
When the leaving group is equatorial, the antibonding orbital points *into* the center of the ring, making it sterically inaccessible

When the leaving group is **axial,** the antibonding orbital points **above** the ring, where it **can** be attacked by a nucleophile

Relative Rate of S_N2 Reactions where X is a leaving group

CH_3X	30
$H_2CH_2CH_3C-X$	1
H_2CH_3C-X	0.4
	0.025
	1 x 10^{-5}

rate decreases with increasing steric bulk

*note that even though **X** is on a primary carbon, it is adjacent to a quaternary carbon, which results in a very slow reaction*

---

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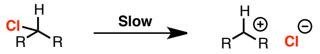
All About Carbocations

- Carbocations are flat (trigonal planar) - the central carbon is sp^2 hybridized
- They are stabilized by 1) increasing substitution at carbon and 2) resonance
- Tertiary carbocations > secondary carbocations >> primary carbocations
- They can be formed in several ways: 1) dissolving a tertary alkyl halide in a polar protic solvent 2) adding acid to a secondary or tertiary alcohol
- They are more stable in polar solvents
- Secondary carbocations can rearrange to tertiary carbocations through hydride or alkyl shifts

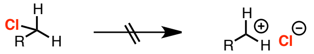
What influences carbocation stability?

1) Carbon substituents stabilize carbocations
Tertiary > secondary >> primary > methyl

Tertiary carbocation: **most stable**



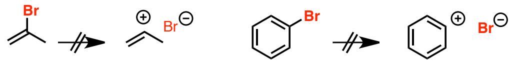
Secondary carbocation



Primary carbocation: **least stable** (methyl carbocations are even more unstable)

2) Resonance stabilizes carbocations

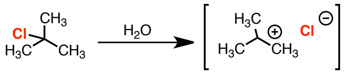
3) Vinyl and aryl carbocations are very unstable



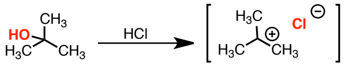
How are Carbocations formed?

Three ways.

1) dissolve a tertiary alkyl halide in a polar protic solvent.

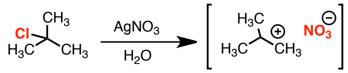


2) Add an acid to a secondary or tertiary alcohol:



Can also be done for secondary alcohols - watch out for rearrangments!

3) (Less common) - addition of silver salts to an alkyl halide



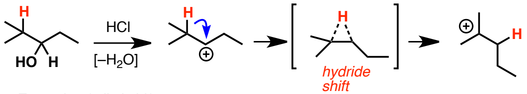
+ AgCl

silver halides form insoluble precipitates, driving reaction forward

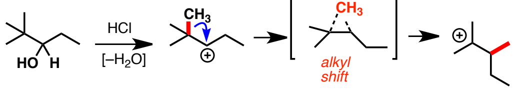
Secondary Carbocations Can Rearrange

Example of hydride shift:

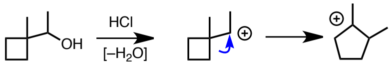
Driving force is formation of more stabilized carbocation



Example of alkyl shift:



This can also lead to ring expansions



Note: applying this framework *mindlessly* without understanding the concepts and variables behind each of the four major reactions is unlikely to lead to success. Usage of this framework assumes you are familiar with the following concepts:

- What makes a good nucleophile
- What makes a good leaving group
- Strength of acids and bases
- Factors that affect carbocation stability

It also goes without saying that it is absolutely necessary to be able to draw the products of each reaction, including stereochemistry

SN1/SN2/E1/E2 Decision Framework

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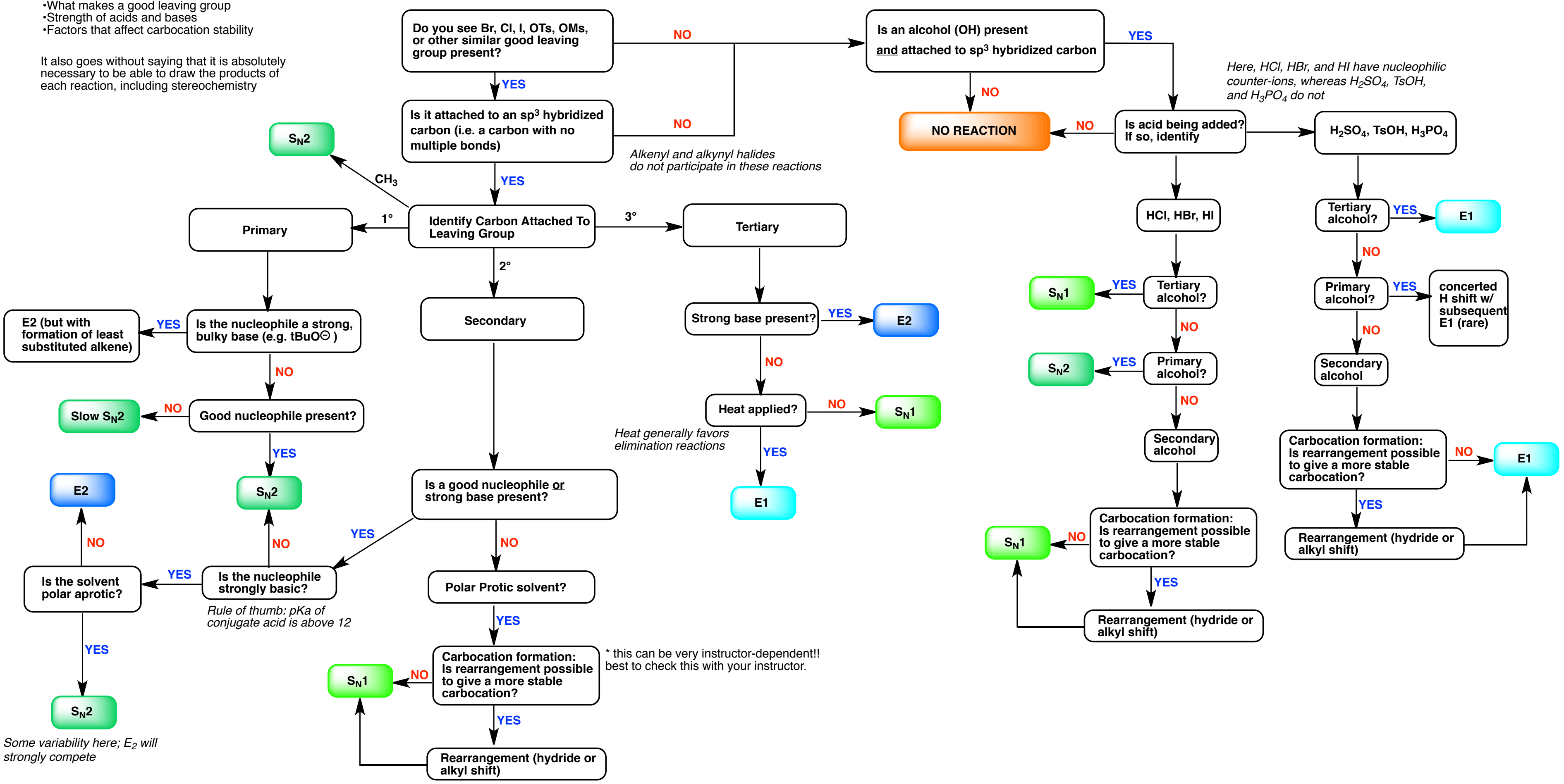
Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.



Do you see Br, Cl, I, OTs, OMs, or other similar good leaving group present?
NO → Is an alcohol (OH) present and attached to sp^3 hybridized carbon
YES → Is it attached to an sp^3 hybridized carbon (i.e. a carbon with no multiple bonds)
NO → Is an alcohol (OH) present and attached to sp^3 hybridized carbon

Alkenyl and alkynyl halides do not participate in these reactions

Is it attached to an sp^3 hybridized carbon (i.e. a carbon with no multiple bonds)
YES → Identify Carbon Attached To Leaving Group

Identify Carbon Attached To Leaving Group
CH_3 → S_N2
1° → Primary
2° → Secondary
3° → Tertiary

Primary → Is the nucleophile a strong, bulky base (e.g. tBuO⊖)
YES → E2 (but with formation of least substituted alkene)
NO → Good nucleophile present?

Good nucleophile present?
YES → S_N2
NO → Slow S_N2

Secondary → Is a good nucleophile or strong base present?
YES → Is the nucleophile strongly basic?
NO → Polar Protic solvent?

Is the nucleophile strongly basic?
Rule of thumb: pKa of conjugate acid is above 12
YES → Is the solvent polar aprotic?
NO → S_N2

Is the solvent polar aprotic?
NO → E2
YES → S_N2

Some variability here; E_2 will strongly compete

Polar Protic solvent?
YES → Carbocation formation: Is rearrangement possible to give a more stable carbocation?

Carbocation formation: Is rearrangement possible to give a more stable carbocation?
NO → S_N1
YES → Rearrangement (hydride or alkyl shift) → S_N1

* this can be very instructor-dependent!! best to check this with your instructor.

Tertiary → Strong base present?
YES → E2
NO → Heat applied?

Heat applied?
NO → S_N1
YES → E1

Heat generally favors elimination reactions

Is an alcohol (OH) present and attached to sp^3 hybridized carbon
NO → NO REACTION
YES → Is acid being added? If so, identify

Is acid being added? If so, identify
NO → NO REACTION
→ HCl, HBr, HI
→ H_2SO_4, TsOH, H_3PO_4

Here, HCl, HBr, and HI have nucleophilic counter-ions, whereas H_2SO_4, TsOH, and H_3PO_4 do not

HCl, HBr, HI → Tertiary alcohol?
YES → S_N1
NO → Primary alcohol?

Primary alcohol?
YES → S_N2
NO → Secondary alcohol → Carbocation formation: Is rearrangement possible to give a more stable carbocation?

Carbocation formation: Is rearrangement possible to give a more stable carbocation?
NO → S_N1
YES → Rearrangement (hydride or alkyl shift) → S_N1

H_2SO_4, TsOH, H_3PO_4 → Tertiary alcohol?
YES → E1
NO → Primary alcohol?

Primary alcohol?
YES → concerted H shift w/ subsequent E1 (rare)
NO → Secondary alcohol → Carbocation formation: Is rearrangement possible to give a more stable carbocation?

Carbocation formation: Is rearrangement possible to give a more stable carbocation?
NO → E1
YES → Rearrangement (hydride or alkyl shift) → E1

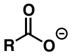
Nucleophilicity

Excellent

$N_3^{\ominus}$ $^{\ominus}CN$ $HS^{\ominus}$ $RS^{\ominus}$ $HO^{\ominus}$ $RO^{\ominus}$ $H\text{-}C\equiv C^{\ominus}$

Good

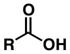
$F^{\ominus}$ $Cl^{\ominus}$ $Br^{\ominus}$ $I^{\ominus}$



R–SH
R_3N R_2NH RNH_2

Poor

H_2O R–OH



$(CH_3)_3CO^{\ominus}$ *due to steric hindrance*

Essentially Non-nucleophilic

$H^{\ominus}$ $HSO_4^{\ominus}$ $TsO^{\ominus}$

Base Strength

Strong Bases

$HO^{\ominus}$ $RO^{\ominus}$ $^{\ominus}NH_2$ $H^{\ominus}$ $R^{\ominus}$
$^{\ominus}NR_2$ $(CH_3)_3CO^{\ominus}$ $H\text{-}C\equiv C^{\ominus}$

For more background see the summary sheet on $S_N1/S_N2/E1/E2$

Leaving Group Ability

Excellent

$I^{\ominus}$ $Br^{\ominus}$ $Cl^{\ominus}$ $TsO^{\ominus}$ $MsO^{\ominus}$ H_2O

Good

R_3N $CH_3COO^{\ominus}$

Poor

$HO^{\ominus}$ $RO^{\ominus}$ $F^{\ominus}$

The weaker the base, the better the leaving group

Non leaving groups

$^{\ominus}NH_2$ $H^{\ominus}$ $R^{\ominus}$

Solvents

Polar Protic	Polar Aprotic			
H_2O	DMSO	(Dimethyl Sulfoxide)	DMF	*N,N-Dimethyl formamide*
CH_3OH (MeOH)	CH_3CN	Acetonitrile	HMPA	
CH_3CH_2OH (EtOH)				
$(CH_3)_3COH$ (*t*-BuOH)	$CH_3\overset{O}{\overset{\|}{C}}CH_3$	Acetone		
CH_3COOH (AcOH)				

In general, solvents with O-H or N-H bonds

Omissions, Mistakes, Suggestions?

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Additions to Alkenes

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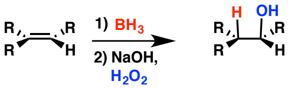
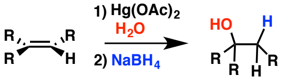
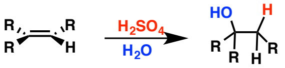
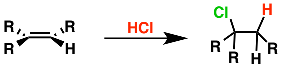
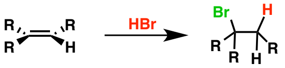
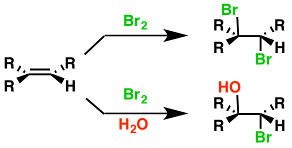
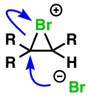
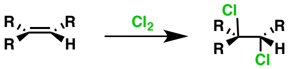
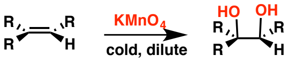
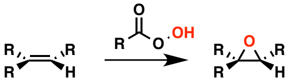
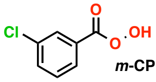
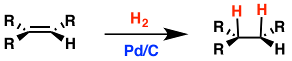
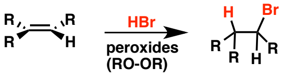
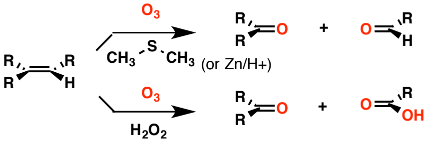
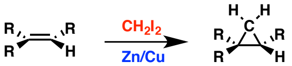
Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

Reaction	*Note: the alkene is drawn in perspective. Imagine it lying flat on a table - the H is coming toward you, that's why it's drawn as a "wedge"*	"Regiochemistry"	"Stereochemistry"	
Hydroboration		Anti-Markovnikoff	syn addition	Sometimes you might see BH_3•THF or B_2H_6 used here: it's the same reagent in a slightly different form. The base (can be NaOH, KOH, identity unimportant) helps make H_2O_2 more reactive. The reaction is *anti* - Markovnikoff because the H–B bond is polarized toward H (electronegativity of H = 2.2, B = 2.0) - the H adds to the carbon best able to stabilize positive charge (i.e. the most substituted one).
Oxymercuration		Markovnikoff	syn + anti	This reaction goes through 3-membered "mercurinium" ion. The $NaBH_4$ step removes the mercury. While the addition is anti, the overall reaction is stereorandom because this step involves a carbon based free radical (usually not discussed). Alternatively, an alcohol used in place of water will produce an ether.
Acid-catalyzed addition of H_2O (hydration)		Markovnikoff	syn + anti	Strong acid protonates the alkene, generating free carbocation. Watch out for possibility of rearrangements when a tertiary carbocation could be generated through a 1,2 shift. HSO_4^- anion is not strongly nucleophilic, hence it does not add. Gives a mixture of syn and anti products due to the free carbocation.
Addition of HX		Markovnikoff	syn + anti	HCl and HBr (as well as HI, not pictured) protonate the alkene to give a free carbocation which can then be trapped by the halide anion. Gives a mixture of syn and anti
Addition of HX		Markovnikoff	syn + anti	
Bromination		N/A	anti addition	 **Bromonium ion mechanism** Br⁻ or H_2O/ROH depending on solvent The key detail in these reactions is solvent: water and alcohol solvents will form the halohydrin products (the ones containing the OH and Br). All other solvents (you might see CCl_4, $CHCl_3$, hexane, etc.) provide the dibromide.
Halohydrin Formation		Markovnikoff	anti addition	
Chlorination		N/A	anti addition	As with bromination, above. Although not depicted, use of water or alcohol as solvent will also lead to formation of the halohydrin product (also anti).
Dihydroxylation		N/A	syn addition	Osmium is a transition metal. The tools won't be given in this course to fully understand how this reaction works. Occasionally a second reagent like $NaHSO_3$, H_2S, or $Na_2S_2O_3$ is also given as a reactant in this reaction - minor detail, it's used to remove the osmium from the hydroxyl groups.
Dihydroxylation		N/A	syn addition	Keywords are "cold, dilute". **NOTE:** If "heat" or "acid" is mentioned in the conditions, the diol will be cleaved to provide carbonyl compounds (same reaction as ozonolysis with **oxidative workup,** below).
Epoxidation		N/A	syn addition	RCO_3H is a peroxyacid. A common peroxy acid for this reaction is m-CPBA (*m*-chloroperoxybenzoic acid). If H_3O^+, heat is written afterwards, this is opening of the epoxide to give the diol (anti-selective)  ***m*-CPBA**
Hydrogenation		N/A	syn addition	The catalyst can vary - you might see Pt or Ni as well. All provide the same product with the same stereochemistry.
Radical addition of HBr		Anti-Markovnikoff	syn + anti	Peroxides generate the Br• radical, which adds to the double bond in the way that will generate the most stable radical (i.e. the radical will go on to the most substituted carbon). This explains the selectivity for the anti-Markovnikoff product. It gives a mixture of syn and anti because it goes through a free radical process.
Ozonolysis (Reductive workup)				**Reductive workup:** Zinc (Zn), or dimethyl sulfide (DMS, Me_2S) is a reducing agent. It reduces excess ozone, allowing for isolation of the aldehyde.
Ozonolysis (Oxidative Workup)				**Oxidative workup:** Hydrogen peroxide is used to obtain the carboxylic acid instead of the aldehyde. **Can also use $KMnO_4$ and acid**
Cyclopropanation		N/A	syn addition	This reaction goes through addition of a *carbene* (actually, "carbenoid") to the double bond. The reaction is stereospecific. Another set of conditions to provide a cyclopropane is **$CHCl_3$ with strong base (NaOH)**, which makes the dichlorocyclopropane.

Omissions, Mistakes, Suggestions?

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Summary of Alkene Reaction Patterns

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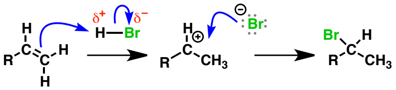
Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

Pattern 1: The Carbocation Pathway

These reactions proceed through attack of an alkene upon an acid, which results in formation of a carbocation. The carbocation is then attacked by a nucleophile, which can occur from either face of the carbocation.

Example: addition of H–Br to alkenes



Regiochemistry: Markovnikoff-Selective. In other words, **hydrogen** ends up bonded to the **less** substituted carbon of the alkene, and (in this case) Br ends up attached to the **most** substituted end of the alkene.

Stereochemistry: Mixture of syn + anti . In other words the H and the other group (e.g. Br) do not add exclusively "syn" or "anti", but provide a mixture of the two

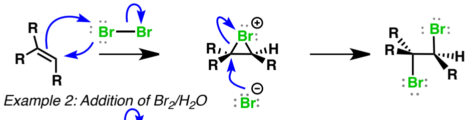
Reactions in this category:
Addition of H–Cl
Addition of H–Br
Addition of H–I
Addition of $H_3O^{\oplus}$
(sometimes written
as H_2O / H_2SO_4)

Note: since this reaction goes through a carbocation, **rearrangements are possible.**

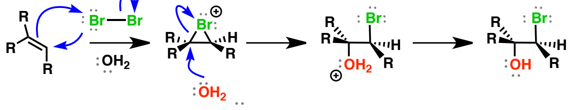
Pattern 2: The 3-Membered Ring Pathway

These reactions proceed through formation of a 3-membered ring cation, which is then attacked from the backside by a nucleophile, on the most substituted carbon.

Example 1: addition of Br_2 to alkenes



Example 2: Addition of Br_2/H_2O



Regiochemistry: Markovnikoff-Selective (where appropriate). For example, with Br_2/H_2O, water adds to the **most** substituted carbon of the alkene.

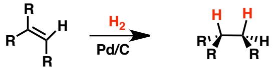
Stereochemistry: Anti. The two groups add to opposite faces of the alkene.

Reactions in this category:
Addition of halogens: Cl–Cl, Br–Br, I–I
Addition of halogens in the presence of nucleophilic solvents: Br_2/H_2O, Br_2/R-OH
Oxymercuration: $Hg(OAc)_2$, H_2O, then $NaBH_4$
Oxymercuration (with an alcohol as solvent) Hg $(OAc)_2$, ROH, then $NaBH_4$
Opening of epoxides under acidic conditions

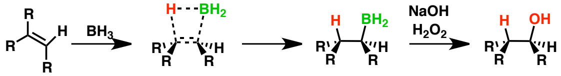
Pattern 3: The "Concerted" Pathway

Although these reactions do not share a common mechanism, they each form two new bonds on the same side of the alkene, a consequence of a "concerted" reaction mechanism.

Example 1 - hydrogenation



Example 2 - hydroboration



Regiochemistry: anti-Markovnikoff-Selective (for BH_3). Note how hydrogen adds to the **most** substituted end of the alkene, and OH ends up on the **least** substituted end.

Stereochemistry: Syn. The two bonds are formed on the same side of the alkene

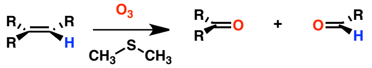
Reactions in this category:
Hydroboration: BH_3, then H_2O_2/NaOH
Hydrogenation: Pd/C, H_2
Epoxidation: RCO_3H (e.g. mCPBA)
Dihydroxylation: OsO_4
Cyclopropanation: CH_2I_2, Zn-Cu
Dichlorocyclopropanation $CHCl_3$, NaOH

Pattern 4: Two miscellaneous reactions

Two reaction patterns of note

Oxidative cleavage: Addition of an oxidant (such as ozone, O_3 leads to cleavage of the carbon-carbon double bond and formation of two new carbon-oxygen double bonds.

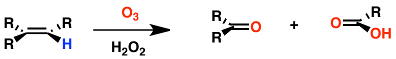
Ozonolysis (Reductive workup)



[or Zn, with H+]

here, the C=C bond is cleaved to give two C=O bonds

Ozonolysis (Oxidative Workup)



alternatively, $KMnO_4$ can be used to give the same products

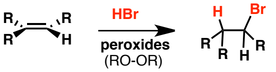
here, the C=C bond is cleaved to give two C=O bonds

and the C-H bond is replaced with a C-OH bond

C–C single bonds are not affected.

Radical addition of HBr

Here, addition of HBr to alkenes in the presence of a radical initiator (peroxides) leads to **anti-Markovnikoff** addition of H-Br to the alkene; the Br adds to the least substituted carbon of the alkene, and the H adds to the most substituted.



Anti-Markovnikoff stereorandom

Regiochemistry: anti-Markovnikoff-Selective. Note that the Br adds to the less substituted end of the alkene.

Stereochemistry: Mixture of syn + anti.
H and Br do not add exclusively "syn" or "anti" across the alkene.

Omissions, Mistakes, Suggestions?

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Introduction to Reactions of Alkynes

"Master Organic Chemistry"
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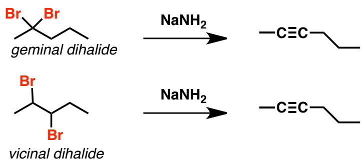
2015 Version

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

Synthesis of Alkynes

Elimination of Hydrogen halides



$NaNH_2$ is a strong base and will lead to elimination of HBr. According to Zaitsev's rule, the most substituted alkyne should form.

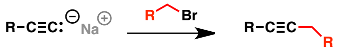
Deprotonation

$R{-}C{\equiv}C{-}H \xrightarrow{NaNH_2} R{-}C{\equiv}C{:}^{\ominus}\ Na^{\oplus}$

Alkynes are relatively acidic [pKa = 25] A strong base like $NaNH_2$ will remove the C-H to provide the acetylide anion. The resulting anion is an excellent nucleophile.

Can also use strong bases like *n*-BuLi, or Grignard reagents (RMgBr, etc.)

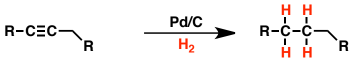
Reaction with Electrophiles



Deprotonated alkynes are excellent, useful nucleophiles and will react with alkyl halides in S_N2 reactions

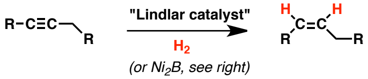
Addition Reactions to Alkynes

Hydrogenation



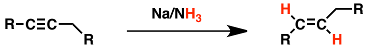
Can also use Pt, Ni, etc. as hydrogenation catalysts. These will also reduce alkynes to alkanes.

Partial Hydrogenation



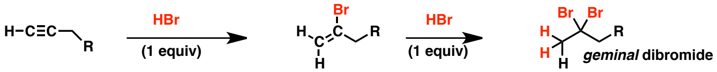
Lindlar catalyst is a "poisoned" palladium catalyst for the partial hydrogenation of alkynes. It contains palladium (Pd), lead (Pb), and quinoline, and is selective for the *cis*-alkene. Sometimes also see "Pd, $CaCO_3$".

Reduction (Dissolving metal reduction)



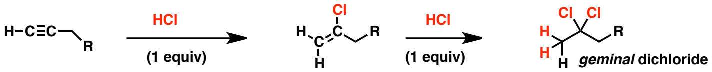
Sodium (Na) is a very strong reducing agent, and will reduce alkynes (but not alkenes). Selective for the *trans*-alkene. The NH_3 provides the hydrogens in the final product.

Addition of Hydrogen bromide to form gem-dibromides



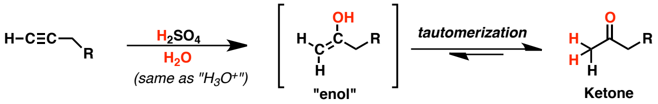
Markovnikoff

Addition of Hydrogen chloride to form gem-dichlorides



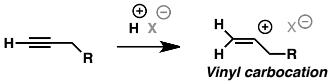
Markovnikoff

Acid-catalyzed Hydration to provide ketones



Markovnikoff

The key intermediate in all three of these reactions is an intermediate *vinyl carbocation* which is formed upon protonation of the alkyne by strong acid. The carbocation forms on the more substituted side of the carbon, according to Markovnikoff's rule.

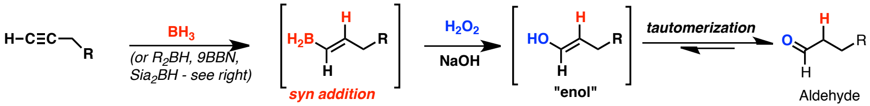


Vinyl carbocation

This carbocation will then be attacked by the nucleophile in question, leading to the formation of substituted products.

tautomerization (keto-enol tautomerization *in this case)* is the interconversion of enols and aldehydes/ketones through the movement of a proton and the shifting of bonding electrons. It is an equilibrium which generally favors the *keto* form.

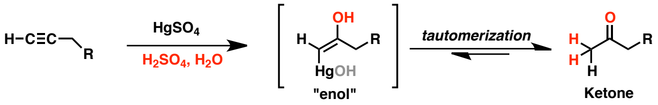
Hydroboration to form aldehydes



Anti-Markovnikoff

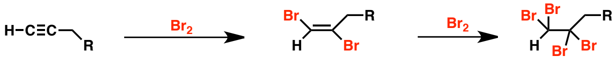
Note: Hydroboration on internal alkynes will give mixture of ketones.

Oxymercuration to provide ketones



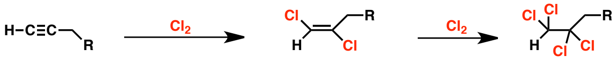
Markovnikoff

Bromination



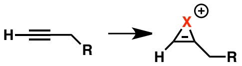
first addition is *trans*

Chlorination



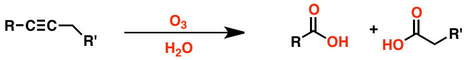
first addition is *trans*

The first intermediate in each of these three reactions is a cyclic ion, which undergoes attack by a nucleophile at the more substituted carbon (Markovnikoff)



X = Hg, Br, or Cl

Ozonolysis



If R = H , then one product will be CO_2 [O=C=O]

Omissions, Mistakes, Suggestions?

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Common Reaction Patterns (Org 1)

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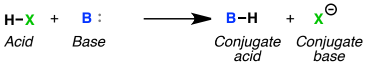
Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

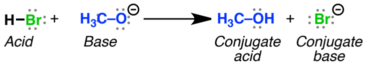
Pattern #1 - Acid Base Reactions

Generic example:



Bonds Formed	Bonds Broken
B–H	H–X

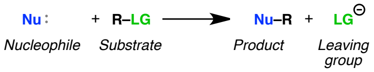
Specific example:



Notes: Favorable acid base reactions will involve a stronger acid and a stronger base reacting to give a weaker acid and weaker base. Relative strengths of acids and bases can be obtained through consulting a pKa table

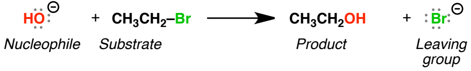
Pattern #2 - Nucleophilic Substitution Reactions

Generic example:



Bonds Formed	Bonds Broken
C–Nu	C–LG

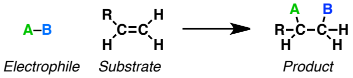
Specific example:



Notes: Substitution reactions can proceed through two pathways. The S_N2 pathway is concerted, and C-Nu bond formation occurs at the same time as C-LG bond breakage. Steric hindrance is paramount. In the S_N1 pathway, the leaving group leaves first to give a carbocation, which is then attacked by a nucleophile. In the S_N1 pathway rearrangements can occur depending on carbocation stability. Good nucleophiles tend to have a loosely held lone pair of electrons. Good leaving groups are weak bases.

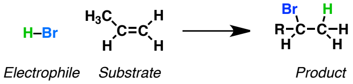
Pattern #3 - Electrophilic Addition

Generic example:



Bonds Formed	Bonds Broken
C–A	C–C (π)
C–B	A–B

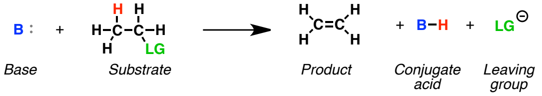
Specific example:



Notes: Note that every addition reaction involves breakage of a C-C π bond and formation of two new single bonds to C. For stepwise addition reactions, the tendency will be to place positive charge on the carbon best able to accept it (i.e. the carbon attached to the most carbon atoms). This gives rise to "Markovnikoff's rule", where H always adds to the least substituted carbon. [Notable exception is hydroboration-oxidation, which is "anti-Markovnikoff".] Stereochemistry of the two new bonds can be syn, anti, or a mixture of both, depending on mechanistic pathway.

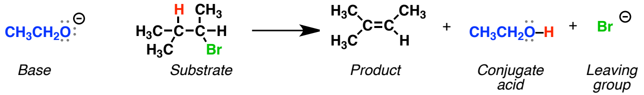
Pattern #4 - Elimination Reactions

Generic example:



Bonds Formed	Bonds Broken
C–C (π)	C–H
B–H	C–LG

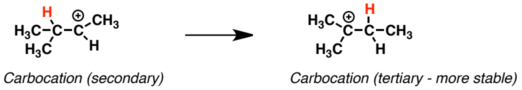
Specific example:



Notes: Note that every elimination reaction involves the formation of a new C–C π bond. Since alkene stability increases as the number of attached carbons increases, eliminations tend to favor formation of the more substituted alkene ("Zaitsev's rule"). An important exception is when more hindered bases (such as *t*-BuO(–) are used, which gives the less substituted alkene. Two dominant mechanisms for elimination are the concerted pathway (E2) which occurs in one step, requiring *anti*-periplanar arrangement of H and leaving group. The second pathway is the stepwise E1 pathway, which occurs with loss of leaving group followed by deprotonation. A third (rare) pathway involves deprotonation, followed by loss of leaving group, called the E1-conjugate base (E1cb) pathway.
All elimination reactions tend to be favored by heat.

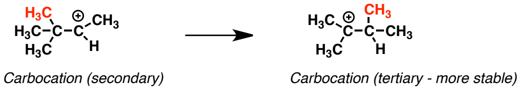
Pattern #5 - Carbocation Rearrangements

Hydride shift example:



Bonds Formed	Bonds Broken
C–H	C–H

Alkyl shift example:

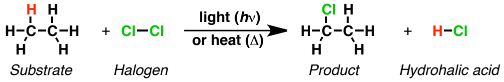


Bonds Formed	Bonds Broken
C–C	C–C

Notes: Rearrangements are favorable when the migration of hydride or alkyl leads to a more stable carbocation. Recall that carbocation stability proceeds in the order tertiary > secondary >> primary. Resonance can also stabilize carbocations. Hydrogen tends to migrate preferentially over carbon. Relief of ring strain can also be a major contributing factor with rearrangement reactions.

Pattern #6 - Free Radical Substitution

Generic example:

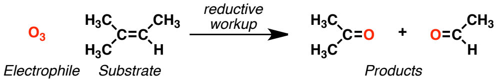


Bonds Formed	Bonds Broken
C–Cl	C–H
H–Cl	Cl–Cl

Notes: Free radical reactions proceed in three steps; initiation, propagation, and termination. Light ($h\nu$) or heat (Δ) is used to initiate the reaction. Chlorine is quite unselective relative to bromine, which will only react with tertiary and allylic/benzylic C-H bonds (which are weakest). Iodine does not perform this reaction.
If multiple equivalents of chlorine are present, chlorination can occur multiple times until all C-H bonds are replaced with C-Cl.

Pattern #7 - Oxidative Cleavage

Specific example:



Bonds Formed	Bonds Broken
C–O (2)	C–C (2)
C–O (π) (2)	C–C (π) (2)

Notes: Oxidation of C-C multiple bonds (π bonds) can be achieved with ozone (O_3) or potassium permanganate ($KMnO_4$). With ozone, reductive workup (using Zn or dimethyl sulfide) leaves all C-H bonds intact. With $KMnO_4$or O_3 using oxidative workup, sp^2 hybridized C–H bonds are oxidized to C–OH.
A different type of oxidative cleavage can occur with vicinal diols using $NaIO_4$, HIO_4, or $Pb(OAc)_4$. These oxidants will cleave C–C single bonds and form C–O (π) bonds

Omissions, Mistakes, Suggestions?

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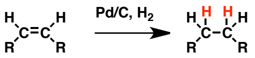
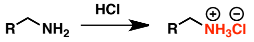
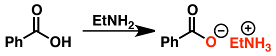
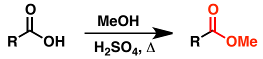
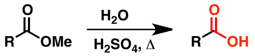
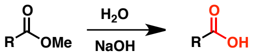
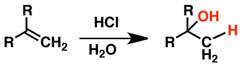
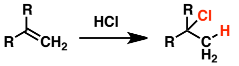
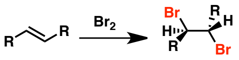
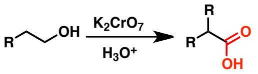
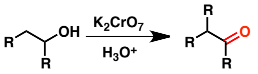
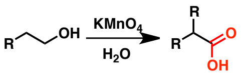
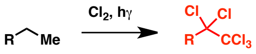
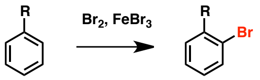
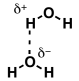
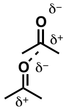
Introduction to Chemical Reactivity, Nomenclature, Boiling Points, and Water Solubility

http://masterorganicchemistry.com

Reactant #1	Reactant #2	Product	Example	Notes
Alkene	Pd/C + H_2	Alkane		cis addition (hydrogens go on same side of alkene)
Amine	Acid	Ammonium salt		amines but NOT amides (amides are *not* basic on nitrogen)
Carboxylic acid	Base	Salt (Carboxylate salt)		
Carboxylic acid	Alcohol, acid, heat	Ester		Alcohols used as solvent
Ester	Water, acid, heat	Carboxylic acid		This is the reverse of the above reaction. Here we use water as solvent.
Ester	Water, base	Carboxylic acid		This is called ester hydrolysis or *saponification*
Alkene	Water, acid	Alcohol		alcohol forms on most substituted carbon (Markovnikov rule) proceeds through carbocation
Alkene	Strong acid	Alkyl halide		halide adds to most substituted carbon (Markovnikov rule) proceeds through carbocation
Alkene	Br_2	Dibromide		Results in *trans* product
Alcohol	K_2CrO_7	Carboxylic acid (primary alcohol) OR ketone (secondary alcohol)		
				Note that secondary alcohols stop at the ketone stage
Alcohol	$KMnO_4$	Carboxylic acid (primary alcohol)		
Alkane	Cl_2, hν (or peroxides)	Alkyl chloride		Free-radical reaction (number of new C–Cl bonds depends on # of equivalents)
Benzene derivative	Br_2, $FeCl_3$	Aryl bromide		Also gives 1,4 (**para**) product but **never** 1,3 (**meta**) product
Thiol	"Oxidant"	Disulfide	$R\text{-}SH \xrightarrow{[ox]} RS\text{–}SR$	

- Boiling point increases with strength of the intermolecular interactions.
- Water solubility increases with polarity.

The Four Types of Intermolecular Bonding in Organic Chemistry

Name	Type of Interaction	Found in	Example	Strength	Notes
Ionic	Attraction between point charges	Salts	$NH_4^{\oplus}Cl^{\ominus}$	Strongest	gives rise to greatest water solubility (most polar) also highest boiling points
Hydrogen Bonding	Attraction between positively charged H and negatively charged O, N or F.	Water, alcohols carboxylic acids amides, amines		2nd strongest	2nd greatest for effect on water solubility and boiling points
Dipole-Dipole	Attraction between dipole moments caused by differences in electronegativity	ketones, aldehydes, esters, alkyl halides, etc. - any molecule with a strongly electronegative element (O, N, F, Cl, Br)		2nd weakest	Increases as electronegativity difference increases 3rd greatest for effect on water solubilty and boiling points
Van Der Waals (London forces)	Attraction between temporary dipoles	Hydrocarbons	Name	Weakest	Increases with surface area (increasing length of carbon chains) worst for water solubility (least polar) best for solubility in non-polar solvents (e.g. pentane)

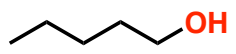
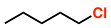
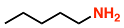
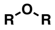
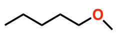
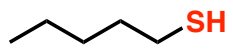
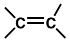
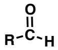
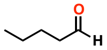
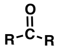
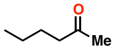
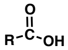
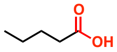
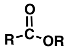
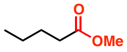
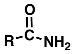
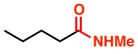
# Carbons	Root
1	**Meth-**
2	**Eth-**
3	**Prop-**
4	**But-**
5	**Pent-**
6	**Hex-**
7	**Hept-**
8	**Oct-**
9	**Non-**
10-	**Dec-**

Primary carbon: attached to ONE carbon atom

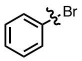
Secondary: attached to TWO carbon atoms

Tertiary: attached to THREE carbon atoms

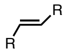
Quaternary: attached to FOUR carbon atoms

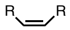
Functional Group	Name	Example	Name
R–	Alkyl		Pentane
–OH	Hydroxyl		Pentanol or pentyl alcohol
–Cl, –Br, –F, –I	Halide		Pentyl chloride
$–NH_2$	Amine		Pentylamine
	Ether		Pentyl methyl ether
–SH	Thiol		Pentane thiol
	Alkene		Pentene
 $R\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}H$	Aldehyde		Pentanal
 $R\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}R$	Ketone		Butyl methyl ketone OR 2-pentanone
 $R\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}OH$	Carboxylic acid		Pentanoic acid
 $R\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}OR$	Ester		Methyl pentanoate
 $R\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}NH_2$	Amide		N-methyl pentamide

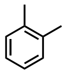
Other important nomenclature terms to remember

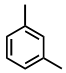

Phenyl (e.g. phenyl bromide)

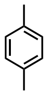

isopropyl e.g. isopropanol


Trans


Cis


1,2 *ortho*


1,3 *meta*


1,4 *para*

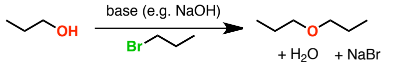
Introduction to Alcohols and Ethers

"Master Organic Chemistry"
masterorganicchemistry.com
2015 Version

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

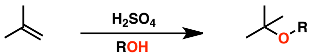
Ethers from alcohols and alkyl halides

The Williamson Ether synthesis: alcohol, base, alkyl halide (or tosylate)



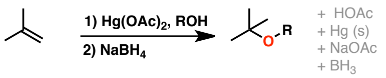
This is an S_N2 reaction; it works best for primary alkyl halides (and alkyl tosylates)

Ethers from alkenes



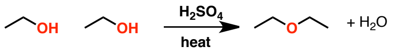
The reaction is similar to the hydration of alkenes with aqueous acid. Acid leads to the formation of a carbocation, which is then trapped by the alcohol as solvent.
Carbocation rearrangements (hydride and alkyl shifts) can occur in certain cases.

Ethers from alkenes through oxymercuration



The reaction is similar to the hydration of alkenes with aqueous acid. The **key difference** is that it does **not** proceed through a carbocation, so **no rearrangements** can occur.

Ethers from alcohols through dehydration

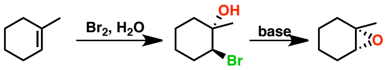


Strong acid (and heat) leads to protonation of the alcohol, followed by nucleophilic attack of a second molecule of alcohol to give the ether. Only practical for the synthesis of *symmetrical* ethers.

Epoxides from alkenes

m-CPBA (meta-chloroperoxybenzoic acid, a peroxyacid) converts alkenes to epoxides, a cyclic ether. Other peroxyacids can be used (e.g. CH_3CO_3H)

Epoxides from halohydrins



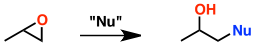
Formation of the halohydrin from the alkene is stereospecific for the **trans** product. Deprotonation of the alcohol by base results in S_N2 (with inversion at carbon bearing the leaving group) to give the epoxide.

Opening of epoxides

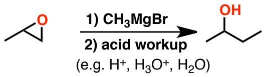
Due to ring strain, epoxides are highly reactive towards nucleophiles. They will react with nucleophiles under both acidic and basic conditions. However the *patterns* are different.

Under basic conditions

Under basic conditions, nucleophiles will attack epoxides at the ***least sterically hindered position*** (primary [fastest] > secondary > tertiary [slowest]) The reaction is essentially an S_N2 reaction!

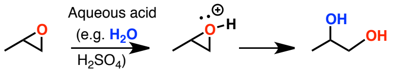


Example: reaction of epoxides with Grignard reagents

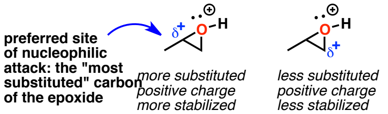


Under acidic conditions

Under acidic conditions, the epoxide oxygen is protonated:

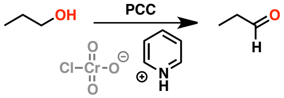


The nucleophile will attack the carbon best able to stabilize positive charge - which is the more substituted carbon
Just like Markovnikov's rule!



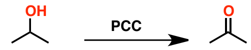
Oxidation of alcohols

Oxidation of primary alcohols to aldehydes



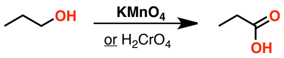
PCC = pyridinium chlorochromate

Oxidation of secondary alcohols to ketones



Can also use $KMnO_4$ or H_2CrO_4 (or DMP or Swern, see right)

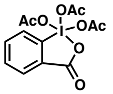
Oxidation of primary alcohols to carboxylic acids



Common source of confusion:
Another way of writing H_2CrO_4 is $K_2Cr_2O_7$ / H_2SO_4 or $Na_2Cr_2O_7$/H_2SO_4

Alternative reagents for oxidation of primary alcohols to aldehydes and secondary alcohols to ketones (not seen in all courses):

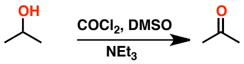
Dess-Martin Periodinane (DMP)



- oxidizes primary alcohols to aldehydes
- oxidizes secondary alcohols to ketones

Swern oxidation

- oxidizes primary alcohols to aldehydes
- oxidizes secondary alcohols to ketones



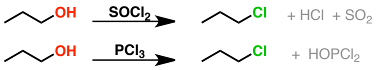
(often just written, "Swern")

$(COCl)_2$ is oxalyl chloride
DMSO is dimethyl sulfoxide
and NEt_3 is triethylamine (base)

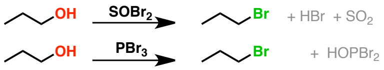
Conversion of alcohols to good leaving groups

The hydroxide group (HO^-) of alcohols is a strong base and a poor leaving group. Converting to a halogen or "sulfonate" (e.g. tosylate or mesylate) greatly facilitates substitution reactions.

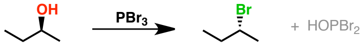
Alcohols to alkyl chlorides



Alcohols to alkyl bromides



One thing to note - these reactions occur with inversion of configuration. For example:



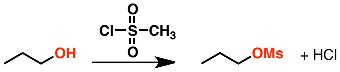
inversion!

Alcohols to alkyl halides by using acids

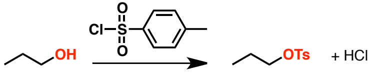
These reactions can proceed through an S_N1 or S_N2 pathway depending on the structure of the alcohol

Alcohols to tosylates and mesylates ("sulfonate esters")

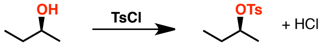
Methanesulfonyl chloride (mesyl chloride, MsCl)



p-toluenesulfonyl chloride (Tosyl chloride, TsCl)



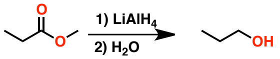
One thing to note - these reactions do not change the stereochemistry of the alcohol.



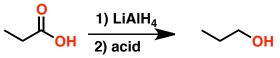
retention!

Alcohols through reduction

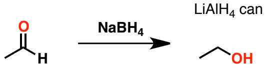
Reduction of esters by lithium aluminum hydride ($LiAlH_4$)



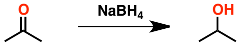
Reduction of carboxylic acids by lithium aluminum hydride ($LiAlH_4$)



Reduction of aldehydes by sodium borohydride ($NaBH_4$)
$LiAlH_4$ can also do this reaction.



Reduction of ketones by sodium borohydride ($NaBH_4$)
$LiAlH_4$ can also do this reaction.



Omissions, Mistakes, Suggestions?

james@masterorganicchemistry.com