312 112 Basic Organic Chemistry

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Topics:  Alkynes, Aromatic Compounds, Stereochemistry

- Introduction  - Physical Properties

- Nomenclature  - Preparation and Reactions
References:


Online References:

1). http://academic.csuohio.edu/hehemannd/
(Dr. David G. Hehemann, Cleveland State University)

2). http://www.tamug.tamu.edu/mars/chem227/aromatics.htm
(Dr. Melanie Lesko, Texas A&M University at Galveston)

3). http://www.uncwil.edu/chem/chm212martin/
(Dr. Martin, University of North Carolina at Wilmington)

(Dr. Steve Glover, The University of New England)
Alkynes

H₃C≡C≡C≡C≡C≡C≡C≡C═O

Capillin
(Active against skin fungi)

HC≡C─C─CH₂CH₃
OH

3-Methyl-1-pentyn-3-ol
(Hypnotic)

CH₃

HO

17-Ethynylestradiol
(A birth control agent)

NH₂

An amphetamine analog
(Active in the central nervous system)
Structure of Alkynes

1. The functional group is a triple bond.

   a. The triple bond is composed of two $\pi$ bonds and a $\sigma$ bond.

      i. The $\pi$ bonds are oriented perpendicular to each other.
      ii. The two $\pi$ bonds are electron-rich, they undergo electrophilic addition like alkenes.

   b. The general formula is: $C_nH_{2n-2}$

      \[
      \begin{array}{c}
      R \quad \text{C} \equiv \text{C} \quad R \\
      \end{array}
      \]

      \[
      \begin{array}{c}
      R = \text{H, alkyl}
      \end{array}
      \]
**Acetylene**
*(Ethyne)*

* The strength of the carbon-carbon triple bond is about 837 kJ/mol.
* It is the strongest and the shortest known carbon-carbon bond.
Nomenclature: The alkynes are named according to 2 systems

1. They are considered to be derived from acetylene by replacement of one or both hydrogen atoms by alkyl groups.

- Ethylacetylene
  \[ \text{H} \equiv \text{C} \equiv \text{C} - \text{C}_2\text{H}_5 \]

- Dimethylacetylene
  \[ \text{H}_3\text{C} \equiv \text{C} \equiv \text{C} - \text{CH}_3 \]

- Isopropylmethylacetylene
  \[ \text{H}_3\text{C} \equiv \text{C} \equiv \text{C} - \text{CH} (\text{CH}_3)_2 \]

2. For more complicated alkynes, the IUPAC names are used.
IUPAC names for Alkynes

1. The rules are exactly the same as for the naming of alkenes, except that the ending \textit{-yne} replaces \textit{-ene}.

2. The parent structure is the longest continuous chain that contains the triple bond.

3. Numbering provides the lowest number for the triple bond.

\[ \text{H}_3\text{C} \equiv \text{C} \equiv \text{C} \equiv \text{CH} \equiv \text{CH}_3 \]

4-Methyl-2-pentyne
4-Bromo-2-hexyne

CH₂≡CHCH₂CH₂CH≡CH

4-Penten-1-yne

CH₂=CHCH₂CH₂CH≡CH

4,4-Dimethyl-2-pentyne

H₃C─C─CH₂─C≡C─CH

CH₃

4-Methyl-4-pentyn-2-ol

H₃C─C─CH₂─C≡C─CH

OH

CH₃

* Triple bonds have priority over double bonds.

* An -OH (hydroxyl group) has priority over the triple bond.
Physical Properties of Alkynes

1. The alkynes have physical properties that are essentially the same as those of the alkanes and alkenes.

2. They are insoluble in water but quite soluble in the usual organic solvents of low polarity.

3. They are less dense than water.

4. Their boiling points show the usual increase with the increasing carbon number.
**Preparation of Alkynes**

**Dehydrohalogenation of alkyl dihalides.**

- Treatment of a dihalide with strong base, leads to elimination of HX (X = Cl, Br).
- Just like alkene synthesis.
- The reaction can take place twice with a dihalide to form an alkyne.

\[
\text{Cl} \quad \text{H} \quad \text{C} \quad \text{H} \quad + \quad \text{KOH} \quad \rightarrow \quad \quad \text{C} \equiv \text{C}
\]
\[ \text{H}_3\text{CHC}≡\text{CH}_2 \xrightarrow{\text{Br}_2} \text{H}_3\text{CHC}−\text{CH}_2 \]

\[ \xrightarrow{\text{NaNH}_2} \text{H}_3\text{CC}≡\text{CH} \xrightarrow{\text{KOH}} \text{H}_3\text{CHC}≡\text{CH} + \text{KBr} + \text{H}_2\text{O} \]
Reaction of Alkynes

1. Addition Reactions

1.1 Addition of Hydrogen (Reduction to Alkenes)

\[
\text{RC≡CR'} \xrightarrow{YZ} \text{RC} = \text{CR'} \xrightarrow{YZ} \text{RC} - \text{CR'}
\]

\[
\text{RC≡CR'} \xrightarrow{\text{Na, NH}_3(\text{liq})} \text{H}_2 \xrightarrow{\text{Lindlar catalyst}} \text{R} = \text{C} = \text{C}_{\text{R'}}
\]

Anti

Syn
• The *trans* alkene can be obtained by using Li or Na / liquid NH$_3$ as the reducing agent.

1. When lithium or sodium are dissolved in liquid ammonia an intensely blue solution results.

2. These solutions are composed of the *metal cations* and dissolved *electrons* which produce the blue color.

3. When an alkyne is added to this solution, an electron adds to one of the $\pi$ bonds to produce a *radical anion*.

\[
\begin{align*}
R-\overset{\text{e}}{C\equiv C}\overset{\Theta}{R} \quad \overset{(\text{Li})}{\xrightarrow{\text{e}^\Theta}} \quad R-\overset{\cdot}{C}\equiv \overset{\cdot}{C}\overset{\Theta}{R} + \overset{\cdot}{\text{Li}^+} 
\end{align*}
\]
4. The radical anion abstract a hydrogen from the solvent, ammonia leading to a $\textit{radical}$.

$$R\cdot\ddot{\text{C}}\ddot{\text{C}}\dddot{\text{R}} + \text{H}\dddot{\text{NH}}_2 \rightarrow R\cdot\dddot{\text{C}}\dddot{\text{C}}R + \text{NH}_2^-$$

5. The radical then reacts with a second dissolved electron to form an anion which again abstracts a hydrogen to give the final product.

$$R\cdot\dddot{\text{C}}\dddot{\text{C}}R \rightarrow R\cdot\dddot{\text{C}}\dddot{\text{C}}R + e^- \rightarrow R\cdot\dddot{\text{C}}\dddot{\text{C}}R + \text{H}\dddot{\text{NH}}_2 \rightarrow R\cdot\dddot{\text{C}}\dddot{\text{C}}R$$

$$R\cdot\dddot{\text{C}}\dddot{\text{C}}R + \text{H}\dddot{\text{NH}}_2 \rightarrow R\cdot\dddot{\text{C}}\dddot{\text{C}}R + \text{NH}_2^-$$
* The *cis* alkene can be obtained by using *Lindlar’s catalyst*.

* *Lindlar’s catalyst* is a form of Palladium (Pd) that has been deactivated by treatment with lead acetate and quinoline.

\[
\text{Surface of metal catalyst} \quad \text{H}_2 \quad \text{H} \quad \text{H}
\]

* When a Platinum (Pt) catalyst is used, the alkyne generally react with two molar equivalents of hydrogen to give an alkane.
1.2 Halogenation

\[ \text{C≡C} \xrightarrow{X_2} \text{C=CC} \xrightarrow{X_2} \text{C-C} \quad (X = \text{Cl, Br}) \]

**Mechanism**

\[ \text{C≡C} \xrightarrow{X_2} \begin{bmatrix} \text{C-} & \text{X}^{+} \end{bmatrix} \xrightarrow{X^-} \text{C=C} \quad (X = \text{Cl, Br}) \]
1.3 Hydrohalogenation

\[ \text{C≡C} \xrightarrow{HX} \text{C≡C} \xrightarrow{HX} \text{C−C} \quad (X = \text{Cl, Br, I}) \]

**Mechanism**

\[ \text{C≡C} + \text{HX} \xrightarrow{} \text{C}^+ \xrightarrow{X^-} \]

**Alkenyl Carbocation**
The second carbocation, with the halogen atom attached, is stabilized by the lone electrons on halogen atom.

The charge on the alkenyl carbocation is centered in an $sp^2$ orbital, this is relatively high energy.

These two factors lead to the fact that the second hydrogen attack occurs faster than the initial attack.
\[
\text{HCCCH + HCl} \quad \xrightarrow{\text{HgCl}_2} \quad \text{H}_2\text{CCHCl} \\
\text{H}_3\text{CCHCCCH}_2\text{CH}_3 + \text{HCl} \quad \xrightarrow{\text{NH}_4\text{Cl}, \text{CH}_3\text{COOH}} \quad \text{ClCHCCCH}_2\text{CH}_3 \\
\text{H}_3\text{CCHCCCH + 2Br}_2 \quad \xrightarrow{\text{CCl}_4} \quad \text{CH}_3\text{CH}_2\text{CBr}_2\text{CHBr}_2
\]
1.4 Hydration

* Terminal alkynes

\[
\begin{align*}
\text{H–C≡C–R} & \xrightarrow{\text{HgSO}_4, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{H–C–C–R} \\
\end{align*}
\]

* Other alkynes

\[
\begin{align*}
\text{CH}_3–\text{C≡C–R} & \xrightarrow{\text{HgSO}_4, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{CH}_3–\text{C–C–R} + \text{CH}_3–\text{C–C–R} \\
\end{align*}
\]

\[
\begin{align*}
\text{R–C≡C–R} & \xrightarrow{\text{HgSO}_4, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{R–C–C–R} \\
\end{align*}
\]
* Markovnikov regiochemistry is found for the hydration with the OH group adding to the more highly substituted carbon and the H attaching to the less highly substituted carbon.

* The intermediate in the reaction, a vinyl alcohol, then rearranges to a ketone in a process called tautomerism.

\[
\begin{align*}
\text{Enol tautomer} & \quad \longleftrightarrow \\ 
\text{(less favored)} & \quad \text{Keto tautomer} \\
\text{(more favored)} & \\
\end{align*}
\]
Mechanism

R–C≡C–H → [-H⁺]

R–C≡C–H

Hg⁺SO₄²⁻

R–C≡C–H

H₂O

Hg⁺SO₄²⁻

R–C≡C–H

H₂O

H⁺

R–C≡C–H

Hg⁺SO₄²⁻

R–C≡C–H

R–C≡C–H

R–C≡C–H

R–C≡C–H
1.5 Hydroboration/ Oxidation

* Hydroboration of symmetrically substituted internal alkynes gives vinylic boranes.

* The vinylic boranes are oxidized by basic hydrogen peroxide to yield ketones (via enols)

* The reaction occurs in **anti-Markovnikov** fashion.
2. Reactions as Acids

\[
2 \ce{R-C≡C-H} + 2 \ce{Na} \rightarrow 2 \ce{R-C≡C^\ominus Na^\oplus} + \ce{H_2}
\]
Sodium acetylide

\[
\ce{R-C≡C-H} + \ce{LiNH_2} \rightarrow \ce{R-C≡C^\ominus Li^\oplus} + \ce{HNH_2}
\]
Lithium acetylide

\[
\ce{R-C≡C-H} + \ce{Ag^+} \rightarrow \ce{R-C≡C-Ag}
\]
Precipitate

\[
\ce{R-C≡C-H} + \ce{Ag^+} \rightarrow \ce{R-C≡C-H} + \ce{Ag^+} + \ce{HNO_3}
\]
Table 1. Acidity of Simple Hydrocarbons

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>$K_a$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyne</td>
<td>HC≡CH</td>
<td>$10^{-25}$</td>
<td>25</td>
</tr>
<tr>
<td>Alkene</td>
<td>H$_2$C═CH$_2$</td>
<td>$10^{-44}$</td>
<td>44</td>
</tr>
<tr>
<td>Alkane</td>
<td>H$_3$C—CH$_3$</td>
<td>$10^{-60}$</td>
<td>60</td>
</tr>
</tbody>
</table>

Stronger acid

Weaker acid
Reactions of metal acetylides with primary alkyl halides

* Lithium or sodium acetylides can react with primary alkyl halides

* The alkyl group becomes attached to the triply bonded carbon, and a new, larger alkynes has been generated.

\[
\text{RC≡C−Li} \quad \overset{\text{R'X}}{\longrightarrow} \quad \text{RC≡C−R'} + \text{LiBr}
\]

\[
\text{HC≡C−Li} \quad \overset{\text{CH}_3\text{CH}_2\text{Br}}{\longrightarrow} \quad \text{HC≡C−CH}_2\text{CH}_3 + \text{LiBr}
\]
* Acetylide ion alkylation is limited to the use of primary alkyl bromides and iodides.
* Acetylides ions are sufficiently strong bases to cause dehydrohalogenation instead of substitution when they react with secondary and tertiary alkyl halides.
3. Oxidative cleavage

An internal alkyne

\[ \text{R} - \text{C}=\text{C} - \text{R}' \xrightarrow{\text{KMnO}_4 \text{ or O}_3} \text{R} - \text{C} = \text{O} + \text{R}' - \text{C} = \text{O} \]

A terminal alkyne

\[ \text{R} - \text{C}=\text{C} - \text{H} \xrightarrow{\text{KMnO}_4 \text{ or O}_3} \text{R} - \text{C} = \text{O} + \text{C} = \text{O} \]
Organic Synthesis

* Prepare octane from 1 pentyne

\[
\text{1. } \text{NaNH}_2, \text{NH}_3 \\
\text{2. } \text{BrCH}_2\text{CH}_2\text{CH}_3, \text{THF}
\]

H\textsubscript{2}/Pt in Ethanol

* Prepare \textit{cis}-2-hexene from 1 pentyne

\[
\text{1. } \text{NaNH}_2, \text{NH}_3 \\
\text{2. } \text{CH}_3\text{Br}, \text{THF}
\]

H\textsubscript{2}/Pd in Ethanol
Aromatic Compounds

The original meanings of Aliphatic = Fatty, Aromatic = Fragrant

Benzene
- From coal distillate

Benzaldehyde
- From cherries, peaches, and almonds

Toluene
- From Tolu balsam

“Benzene and compounds that resemble benzene in chemical behavior”

!! Benzene has been found to cause bone-marrow depression and consequent leukopenia.
Estrone
(Female Steroidal Hormone)

Penicillin V

Vitamin E

Morphine
(Analgesic)
2-Acetyloxybenzoic acid (Aspirin, Bayer Aspirin)

2-[4-(2-Methylpropyl)-phenyl]propanoic acid (Ibuprofen)

N-(4-Hydroxyphenyl)acetamide (Acetaminophen, Tylenol)

The Painkillers
Nomenclature

* Monosubstituted Benzenes (IUPAC)

- Monosubstituted aromatics are named using \textit{-benzene} as the parent name.
- Alkyl substituted benzenes are named according to the chain length of the alkyl group.
- If the alkylsubstituent has six carbons or fewer, it will be named as \textit{alkylbenzene}.

\begin{itemize}
  \item Fluorobenzene
  \item Nitrobenzene
  \item Ethylbenzene
\end{itemize}
* **Monosubstituted Benzenes (Some Common Names)**

- Toluene
- Phenol
- Aniline
- Cumene
- Acetophenone
- Styrene
* If the alkyl substituent is larger than the ring (more than six carbons), the compound is named as a phenyl-substituted alkane.

A phenyl group

2-Phenylheptane

A benzyl group

Benzylbromide
* Disubstituted Benzenes

- Disubstituted benzenes can be named one of two ways.
- Each method describes the relationship of the two groups on the six membered aromatic ring.
  - Using the prefixes ortho-, meta-, or para-.
  - Systematic numbering of the aromatic ring.

- The common names for monosubstituted benzenes can be used as parent names for disubstituted aromatics.
ortho-Dichlorobenzene

1,2-Dichlorobenzene

meta-Dinitrobenzene

1,3-Dinitrobenzene

para-Diiodobenzene

1,4-Diiodobenzene
ortho-Xylene (o-Xylene)
meta-Xylene (m-Xylene)
para-Cresol (p-Cresol)
ortho-Iodoaniline
meta-Nitrobenzoic acid
para-Bromotoluene
* Polysubstituted Benzenes*

- Polysubstituted benzenes are named by numbering the position of each substituent on the ring.
- The numbering is carried out to give the substituents the lowest possible numbers.
- A substituted carbon is always C#1.
- For rings with common names, the carbon bearing the substituent responsible for the common name is C #1.
4-Bromo-1,2-dimethylbenzene

2-Chloro-1,4-dinitrobenzene

4-Bromo-2-ethyl-1-nitrobenzene

1-Bromo-3-ethyl-4-nitrobenzene

(Wrong ???)

3-Bromo-5-chloronitrobenzene
2,4,6-Trinitrotoluene (TNT)

2,6-Dibromophenol

2,4,6-Trbromoaniline
Polynuclear Aromatic Hydrocarbons

Napthalene

Anthracene

2-Napthol (α-Naphthol)

6-Amino-2-napthalenesulfonic acid
Stability of Benzene

- $C_6H_6$ indicates that several double bonds must be present and should react the same way as alkenes.
Benzene shows none of the behavior characteristic of alkenes.

Benzene does not undergo electrophilic addition reactions.
Table 1. Heats of Hydrogenation of Cyclic Alkenes

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>$\Delta H^0_{\text{hydrog}}$ (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexene</td>
<td>Cyclohexane</td>
<td>120</td>
</tr>
<tr>
<td>1,3-Cyclohexadiene</td>
<td>Cyclohexane</td>
<td>232</td>
</tr>
<tr>
<td>Benzene</td>
<td>Cyclohexane</td>
<td>208</td>
</tr>
</tbody>
</table>

H$_2$/Metal Catalyst
C-C Bonds are 1.54 Å
C=C Bonds are 1.34 Å
1.5 Bonds on average
Representation of Benzene: The Resonance Approach

1.5 Bonds on average
Napthalene is Aromatic
Aromaticity and The Huckel 4n + 2 Rule

Criteria for simple aromatics

- Follow Huckel's rule, having 4n+2 electrons in the delocalized cloud.
- Are able to be planar and are cyclic.
- Every atom in the circle is able to participate in delocalizing the electrons by having a $p$ orbital or an unshared pair of electrons.
n=0, 2 electrons:

\[ \text{cyclopropenyl cation} \]

n=1, 6 electrons:

- benzene
- pyridine
- pyrrole
- furan
- thiophene
- cyclopentadienyl anion
- cycloheptatrienyl cation or tropylium ion
n=2, 10 electrons:

- naphthalene
- benzothiophene
- indole
- benzofuran
- quinoline
- azulene
Compounds that are "anti-aromatic"

- Cyclobutadiene: 4 electrons
- Cyclooctatetraene: 8 electrons (relaxes to a non-planar form)
- Nonplanar: 8 electrons

These two structures each have 12 electrons, so entire structure could not be aromatic (left could act like 2 separate benzenes). If made into anion at arrow adds 2 electrons, atom can participate and total of 14 electrons is aromatic.
Chemistry of Benzene

- Benzene undergoes substitution reactions with electrophile, in contrast with the corresponding reaction of alkenes.
- Proceeding by addition of the electrophile and then by proton loss to regenerate the aromatic ring.
- Many different substituents can be introduced onto the aromatic ring:

  - Halogenation: $X = -F, -Cl, -Br, -I$
  - Nitration: $-\text{NO}_2$ / Sulfonation: $-\text{SO}_3\text{H}$
  - Alkylation: $-\text{R}$ (alkyl group)
  - Acylation: $-\text{COR}$ (acyl group)
Mechanism of Electrophilic Aromatic Substitution
Substitution Electrophilic Reactions
1). Halogenation of Benzene: The need for a catalyst

Benzene is unreactive in the presence of halogens, because halogens are not electrophilic enough to disrupt the aromaticity.

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
& \quad \text{FeBr}_3 \\
& \quad \text{A weak electrophile}
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
& \quad \text{FeBr}_3 \\
& \quad \text{A strong electrophile}
\end{align*}
\]

- Activation of Bromine by the Lewis Acid; FeCl\textsubscript{3}.
Electrophilic attack on Benzene by Activation Bromine

Bromobenzene Formation.

Bromobenzene Formation.
**Chlorination**

\[
\text{C}_6\text{H}_5\text{H} + \text{Cl}_2 \xrightarrow{\text{FeCl}_3} \text{C}_6\text{H}_4\text{Cl} + \text{HCl}
\]

**Iododination**

\[
\text{C}_6\text{H}_5\text{H} + \text{I}_2 \xrightarrow{\text{CuCl}_2} \text{C}_6\text{H}_4\text{I} + \text{HI}
\]
2). Nitration of Benzene: The attack by nitronium ion

\[
\text{Nitric Acid} + \text{Sulfuric Acid} \rightleftharpoons \text{Nitronium Ion}
\]

\[
\text{Benzene} + \text{Nitronium Ion} \rightarrow \text{Nitrobenzene}
\]
3). Sulfonation of Benzene

\[ 2H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4 \]

Sulfonation is reversible

[Diagram showing the process of sulfonation]

\[ \text{H}_2O,\ \text{cat. H}_2SO_4,\ 100 \degree C \]

[Diagram showing the reverse reaction]
Benzenesulfonic acids have important use.

- Aromatic Detergent Synthesis

- Sulfa Drugs

![Detergent](image1)

![Sulfadiazine](image2)

*Sulfadiazine (Antimalarial drug)*

![Sulfathoxazole](image3)

*Sulfathoxazole (Antibacterial agent)*
4). Friedel-Craft Alkylation

* Haloalkane reacts with benzene in the presence of aluminium halide
* Limitations of Friedel-Craft Alkylation

An aryl halide (ArX)

An vinyl halide

Y = -NO₂, -CN, -SO₃H, -COCH₃, -COOH, -COOCH₃, -NR₃

\[ \text{Ph} + \text{H₃C-C-CH₂Cl} \xrightarrow{\text{AlCl₃}} \text{Ph-C-CH₂CH₂CH₃} \]
Cl_{AlCl_3} 

\text{(Primary (1\textdegree) Carbocation)} \quad \text{(Secondary (2\textdegree) Carbocation)}
5). Friedel-Craft Acylation

\[
\text{苯} + RCOCl \xrightarrow{\text{AlCl}_3} \text{苯} - \text{RCO} + \text{HCl}
\]

\[
\text{RCOCl} + \text{AlCl}_3 \rightleftharpoons \text{RCOCl}_{\text{AlHCl}_3}
\]

Acylium ion

\[
\left[ \begin{array}{c}
\text{RCO}^+ \rightleftharpoons \text{RCO}^+ \\
\text{RCO}^+ \rightleftharpoons \text{RCO}^+ \\
\end{array} \right] + \text{ClAlCl}_3
\]
Substitution Electrophilic Reactions

Other reagents for carbocation formation:
To practice your brain.....

\[
\begin{align*}
&\text{CH}_3 \\
&\text{HNO}_3/\text{H}_2\text{SO}_4 \\
&\text{Cl}_2/\text{FeCl}_3 \\
&\text{OH} \\
&\text{Bromination}
\end{align*}
\]
Reactivity of Aromatic Rings

Substituents already present on the ring have two effects.

- Reactivity: some make the ring more reactive than benzene, and some make it less reactive.

- Orientations: The nature of the substituent determines the position of the second substituent; 
  ortho-, meta-, or para-.
Substituents control:

- **Rate** of a second substitution—
  Activating groups cause faster than with benzene
  Deactivating groups cause slower reaction than with benzene

- **Position** of second substitution—
  Activators direct to *ortho/para* positions
  Deactivators direct to the *meta* position
• Donor groups result in electron-rich ring
  Easier to attack $E^+$ — faster

• Acceptor groups result in electron-deficient ring
  More difficult to attack $E^+$ — slower
Classification of substituents:

Substituent effects

**Activating ortho, para-directors**
- $\text{NH}_2$
- $\text{NHR}$
- $\text{NR}_2$
- $\text{OH}$
- $\text{OR}$
- $\text{NHCO}$
- $\text{R}$

**Deactivating ortho, para-director**
- $\text{X}^-$ (Halogen)

**Deactivating meta directors**
- $\text{O}$
- $\text{NR}_3$
- $\text{C}^\text{X}_8$
- $\text{CH}^\text{CR}^\text{COH}^\text{COR}$
- $\text{CN}$
- $\text{SOH}$
The powerful activating group will lead to a trisubstituted product in nearly quantitative yield.

\[
\begin{align*}
\text{OH} & \quad \text{Br}_2 (\text{xs}) \quad \text{H}_2\text{O} \\
\text{Br} & \quad \text{Br} \\
\text{Br} & \quad \text{Br}
\end{align*}
\] (No catalyst needed)

\[
\begin{align*}
\text{NH}_2 & \quad \text{Br}_2 (\text{xs}) \quad \text{H}_2\text{O} \\
\text{NH}_2 & \quad \text{Br}
\end{align*}
\] (No catalyst needed)
\[
\text{C}_6\text{H}_5 \overset{\text{HNO}_3, \text{H}_2\text{SO}_4}{\rightarrow} \begin{array}{c}
\text{C}_6\text{H}_4\text{CH}_3\text{NO}_2 \\
(59\%) \\
\text{C}_6\text{H}_4\text{CH}_3\text{NO}_2 \\
(37\%) \\
\text{C}_6\text{H}_4\text{CH}_3\text{NO}_2 \\
(4\%)
\end{array}
\]
Questions:

Why do electron-releasing groups direct ortho/para?

Why does this occur at a faster rate than it does on benzene?
Ortho/para substitution:

Charge dispersed onto D

para-attack

ortho-attack
Meta attack — D can less effectively stabilise intermediate (and transition state):

\[
\begin{align*}
&\text{D} & \text{D} & \text{D} \\
&\text{H} & \text{H} & \text{H} \\
&\text{E} & \text{E} & \text{E}
\end{align*}
\]
Why are halogens ortho/para-directing but deactivating?
Questions:

Why do electron-withdrawing groups direct *meta*?

Why does this occur at a *slower rate* than it does on benzene?
Control of ortho/para ratio

Steric effects:

toluene

\[ +\text{NO}_2 \rightarrow o/p = 58\% \]

\[ \text{A} - \text{butylbenzene} \]

\[ +\text{NO}_2 \rightarrow o/p = 16\% \]
Control of *ortho/para* ratio

- Inductive effects influence *ortho* more than *para* positions:
Trisubstitution – additivity effects

Consider:

• Relative **electronic effects** of substituents
  The group that stabilises the intermediate best will direct substitution

• Relative **steric** effects of the substituents
  Important when electronic effects are similar
• Stronger activating groups control the third substitution:

General order of directivity:

-\(\text{-NH}_2\), -\(\text{NR}_2\), -\(\text{OH}\), -\(\text{O}^-\) > -\(\text{OR}\), -\(\text{OCOR}\), -\(\text{NHCOR}\)
-\(\text{-R}\), -\(\text{-Ar}\) > -\(\text{-Halogen}\) > *meta* directing groups.
Directing groups reinforce each other — A single product is obtained:
• Stronger activating groups control the third substitution:
Examples of Electrophilic Substitution Reactions of Benzenes

1. \[ \text{H}_3\text{C}-\begin{array}{c} \text{CH}_3 \\ \text{AlCl}_3 \end{array} \text{(CH}_3\text{CO})_2\text{O} \rightarrow \text{H}_3\text{C}-\begin{array}{c} \text{CH}_3 \\ \text{H}_3\text{C} \end{array} \]

2. \[ \text{Cl}-\begin{array}{c} \text{Cl} \\ \text{H}_2\text{SO}_4 \end{array} \rightarrow \text{Cl}-\begin{array}{c} \text{Cl} \\ \text{Cl} \end{array} \]

3. \[ \text{O}_2\text{N}-\begin{array}{c} \text{CO}_2\text{H} \\ \text{H}_2\text{SO}_4 \end{array} \rightarrow \text{O}_2\text{N}-\begin{array}{c} \text{CO}_2\text{H} \\ \text{NO}_2 \end{array} \]

4. \[ \text{Br}-\begin{array}{c} \text{NO}_2 \\ \text{H}_2\text{SO}_4 \end{array} \rightarrow \text{Br}-\begin{array}{c} \text{NO}_2 \\ \text{SO}_3\text{H} \end{array} \]

5. \[ \text{NO}_2-\begin{array}{c} \text{OH} \\ \text{Fe} \end{array} \rightarrow \text{NO}_2-\begin{array}{c} \text{Br} \\ \text{Br} \end{array} \]

6. \[ \text{SO}_2\text{NH}_2-\begin{array}{c} \text{N}-(\text{CH}_3)_2 \\ 2\text{Cl}_2 \end{array} \rightarrow \text{SO}_2\text{NH}_2-\begin{array}{c} \text{Cl} \\ \text{N}-(\text{CH}_3)_2 \end{array} \]
Nucleophilic Substitution

$\text{ArS}_N1\text{ type:}$

Only under special conditions with outstanding leaving group — diazonium ion
Nucleophilic Substitution

ArS$_N$2 mechanism:

slow

intermediate $\sigma$-complex

fast

$-$X$^\text{-}$

+ X$^\text{-}$
• The more nitro groups (electron-withdrawing groups), the easier the reaction:

\[
\begin{align*}
\text{R}_1 &= \text{NO}_2, \text{R}_2 = \text{R}_3 = \text{H} & 130^\circ \\
\text{R}_1 &= \text{R}_2 = \text{NO}_2, \text{R}_3 = \text{H} & 100^\circ \\
\text{R}_1 &= \text{R}_2 = \text{R}_3 = \text{NO}_2 & 35^\circ \\
\end{align*}
\]
Reactivity of Polynuclear Aromatics

- Naphthalene reacts at the 1, 4, 5 or 8
Aromatic-Aliphatic Compounds

➤ Halogenation

\[
\begin{align*}
\text{CH}_3 & \quad \xrightarrow{\Delta \text{ or } hv} \quad \text{CH}_2\text{Cl} \\
\text{CH}_2\text{CH}_3 & \quad \xrightarrow{\text{Cl}_2} \quad \text{CHClCH}_3 + \text{CH}_2\text{CH}_2\text{Cl}
\end{align*}
\]
Oxidation

1) KMnO₄, OH-, Δ
2) H₃O⁺

COOH
* The sense of the directing power of substituents can be changed.

![Chemical Structures]

**Nitro** (Meta Director) → Zn(Hg), HCl, or H₂, Ni, or Fe, HCl → **Amino** (Ortho, Para Director)

**NO₂**

**NH₂**

**F₃C—C—OOH**
CH₂R

Zn(Hg), HCl, Δ or H₂/Pd in Ethanol

CrO₃, H₂SO₄, H₂O

Alkanoyl (Meta Director)

Alkyl (Ortho, Para Director)
**Stereochemistry**

is the study of the three-dimensional structure of molecules.

- **Stereoisomers**
- **Stereoselective and Stereospecific Reactions**
- **Enantiotopic and Diastereotopic Ligands and Faces**

**Stereoisomers**

*Isomers*: Different compounds that have the same molecular formula.

*Stereoisomers*: Isomers that have the same bonding sequence but differ in the orientation of their atoms in space.
ISOMERS

CONSTITUTIONAL ISOMERS
Isomers with different order of attachment of atoms in their molecules

STEREOISOMERS
Differ only in arrangement of atoms in space

CONFIGURATIONAL ISOMERS
Can be interconverted only by breaking and reforming bonds

CONFORMATIONAL ISOMERS
Can be converted by rotation about a bond

OPTICAL ISOMERS
Differ in 3-D relation of substituent about one or more atoms

GEOMETRIC ISOMERS
Substituents differ in spatial arrangement due to restricted rotation in ring/π bond

ENANTIOMERS
Stereoisomers with nonsuperimposable mirror images

DIASTEREOMERS
Molecules that are not mirror images of each other

(http://www.paccd.cc.ca.us/instadm/phycidv/psganapa/chem8a/STEREOCHEMISTRY.htm)
Conformational Isomers

Different spatial orientations of the atoms of a molecule that result from rotations or twisting about single bonds.

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \quad n\text{-Butane} \]
From 3D to 2D structures:

- **In/Out of A Plane**
- **Fisher Projection**
- **Newman Projection**
- **Sawhorse Formula**
How many conformers can \( n \)-butane have?

A. Staggered (Anti) conformation

B. Eclipsed conformation

C. Staggered (Gauche) conformation

D. Eclipsed conformation
Dr. William Reusch (http://www.cem.msu.edu/~reusch/VirtualText/sterisom.htm#isom4)
Ring Conformations

Cyclohexane

Boat Conformation

Twist Boat Conformation

Chair Conformation

Axial

Equatorial
Important aspects of conformational stereoisomerism

- Most conformational interconversions in simple molecules occur rapidly at room temperature. Isolation is impossible.

- Staggered conformations about carbon-carbon single bonds are more stable than the corresponding eclipsed conformations. The higher energy of eclipsed bonds is known as eclipsing strain.

- In butane the gauche-conformer is less stable than the anti-conformer by about 0.9 kcal/mol. This is due to steric hindrance.
Configurational Isomers: 1) Geometrical Isomers

- Alkenes may exist as a pair of configurational stereoisomers, often designated *cis* (on this side) and *trans* (across).
- Each carbon of the double bond must have two different substituent groups (one may be hydrogen).

\[ \text{cis-2-pentene} \quad \text{trans-2-pentene} \]
Sometimes it is very hard to identify *cis*- or *trans*- alkenes

A completely unambiguous system, based on a set of group priority rules, assigns a Z (German, zusammen for together) or E (German, entgegen for opposite) to designate the stereoisomers.

- Z is equivalent to *cis* and E is equivalent to *trans*.
Assign priorities to double bond substituents by looking at the atoms attached directly to the double bond carbons.

- The higher the atomic number of the immediate substituent atom, the higher the priority.
  For example, H– < C– < N– < O– < Cl–. (priority increases left to right)
  (Different isotopes of the same element are assigned a priority according to their atomic mass.)
If two substituents have the same immediate substituent atom, move to the next atom (away from the double bond) until a difference is found.

For example, $\text{CH}_3^- < \text{C}_2\text{H}_5^- < \text{ClCH}_2^- < \text{BrCH}_2^- < \text{CH}_3\text{O}^-$

Once the relative priorities of the two substituents on each of the double bond carbons has been determined, a \textit{cis} orientation of the higher priority pair is designated Z, and a \textit{trans} orientation is termed E.
(Z)-1-bromo-3-chloro-4-isopropyl-3-heptene

(Z)-configuration

higher priority groups on same side

E isomer

Z isomer
Configurational Isomers: 2) Optical Isomers

2.1) **Enantiomers**: non-superimposable (different) mirror images; most of chemical and physical properties are identical.

2.2) **Diastereomers**: are stereoisomers that are not mirror images (all stereoisomers except enantiomers) and have different chemical and physical properties.
(-)-limonene (lemon oil)

(+)-limonene (oranges)

(-)-carvone (spearmint)

(+)-carvone (caraway)

180° rotation
Late 50’s, thalidomide was prescribed as an analgesic for morning sickness and used extensively in Europe and Canada despite strong warning that it not be used by pregnant women.

By 1961, it was recognized as the cause for numerous birth defects (~7-10,000 in 28 countries).
Although two enantiomers have identical boiling points and melting points, they rotate the plane of polarized light in opposite directions. A **polarimeter** is used to measure the optical rotations of enantiomers.

(http://www.cem.msu.edu/~reusch/VirtualText/sterism2.htm#isom12)
Each enantiomer of a stereoisomeric pair is **optically active** and has an equal but opposite-in-sign specific rotation.

One enantiomer will rotate polarized light in a clockwise direction, termed **dextrorotatory** (+), and its mirror-image partner in a counter-clockwise manner, termed **levorotatory** (−).

It is common practice to convert the observed rotation, $\alpha$, to a **specific rotation**, $[\alpha]$. 
Specific rotation, $[\alpha] = \text{amount (degrees) that a substance rotates plane polarized light expressed in a standard form.}$

$$[\alpha]_\lambda^T = \frac{\alpha}{c \cdot l}$$

- temp
- exptl rotation
- wavelength of light; usually sodium D line, $\lambda = 589 \text{ nm}$
- conc of sample in g/mL
- sample path length in decimeters (dm)
Carvone from caraway:  $[\alpha]_D = +62.5^\circ$

Carvone from spearmint:  $[\alpha]_D = -62.5^\circ$

Lactic acid from muscle tissue:  $[\alpha]_D = +2.5^\circ$

Lactic acid from sour milk:  $[\alpha]_D = -2.5^\circ$

(R)-(-)-lactic acid  (S)-(+)-lactic acid
How can one identify enantiomerism?

All objects may be classified with respect to *chirality* (from the Greek *cheir* = hand):

**Chiral** = Objects that are different from their mirror image; i.e. golf clubs, scissors; enantiomers are chiral.

**Achiral** = Objects that are identical with their mirror image; i.e. a pencil, a T-shirt.
Achiral molecules have either one or both of the following:

- Plane of symmetry
- Center of symmetry

Chiral molecule: (R)-lactic acid

Achiral molecule: water

\[(R)-(-)-\text{lactic acid}\]  \[\text{Water (H}_2\text{O)}\]
Achiral Objects and Molecules
Chiral molecules have **chiral center** (or stereo or stereogenic center): an atom attached to 4 different atoms or groups.
Can you indicate stereocenters?

- Methylcyclohexane
- Methylcyclohexane
- Menthol
- Camphor
- Nicotine
- Penicillin V
Designating the Configuration of Stereogenic Centers

The CIP system of nomenclature.

(R. S. Cahn, C. K. Ingold and V. Prelog)

- Each stereogenic center in a molecule is assigned a prefix (R or S), according to whether its configuration is right- or left-handed.

- The symbol $R$ comes from the Latin *rectus* for right, and $L$ from the Latin *sinister* for left.
The assignment of the prefixes depends on the application of two rules:

- The Sequence Rule
- The Viewing Rule

**Right-Handed**

**Left-Handed**
The Sequence Rule (*The same as E-Z assignment*)

✓ Assign sequence priorities to the four substituents by looking at the atoms attached directly to the chiral stereogenic carbon atom.

✓ The higher the atomic number of the immediate substituent atom, the higher the priority; H– < C– < N– < O– < Cl–.

✓ If two substituents have the same immediate substituent atom, evaluate atoms progressively further away from the chiral center until a difference is found.

i.e. CH₃– < C₂H₅– < ClCH₂– < BrCH₂– < CH₃O–.
If double or triple bonded groups are encountered as substituents, they are treated as an equivalent set of single-bonded atoms. i.e. \( \text{C}_2\text{H}_5^- \text{ is treated as } \text{CH}_2=\text{CH}^- \text{ is treated as } \text{HC}≡\text{C}^- \)

\[
\begin{align*}
\text{H} & \quad \text{C}≡\text{C} & \text{H} & \quad \text{IS TREATED AS} & \quad \text{H} & \quad \text{C} & \quad \text{C} & \quad \text{R} \\
\text{R} & \quad \text{C} & \quad \text{C} & \quad \text{H} & \quad \text{C} & \quad \text{C} & \quad \text{R} & \quad \text{IS TREATED AS} & \quad \text{C} & \quad \text{C} & \quad \text{R} \\
\text{O} & \quad \text{C} & \quad \text{H} & \quad \text{IS TREATED AS} & \quad \text{O} & \quad \text{C} & \quad \text{H} & \quad \text{O} & \quad \text{O}
\end{align*}
\]
The Viewing Rule

✓ The chiral center must be viewed from the side opposite the lowest priority group.

✓ Numbering the substituent groups from 1 to 4, with 1 being the highest and 4 the lowest in priority sequence, and put a viewer's eye on the side opposite substituent #4.

✓ If the progression from 1 to 3 is clockwise, the configuration at the stereocenter is $R$. Conversely, the counterclockwise progression is assigned as $S$. 
Assign Priorities

Twist the lowest priority to the back

Rotate Priorities

(R)-Lactic acid
2-Bromobutane

Priorities

View & Assign

(S)-2-Bromobutane
If you have troubles looking at the stereocenter, try Fischer Projections.

Press flat

A Simple Mental Exercise for Fisher Projection
Only two kinds of motions are allowed for Fischer projection.

1) Rotation on page $180^\circ$ is allowed for Fischer projection.

2) One group can be held steady while the other three rotate in either a clockwise or a clockwise direction.
Assigning $R, S$ configurations to Fischer projections.

✓ Assign priorities to the four substituents in the usual way.

✓ Perform one of the two allowed motions to place the group of lowest (4th) priority at the top of the Fischer projection if it is necessary.

✓ Determine the direction of rotation in going from priority 1 to 2 to 3, and assign $R$ (clockwise) or $S$ (counterclockwise).
Lactic acid

2-Bromobutane
Compounds Having Two or More Stereogenic Centers

(-)-Ephedrine

(1R), (2S)-(-)-Ephedrine
Can you assign absolute configurations of these compounds?

(+)-Ephedrine

(+)-Pseudoephedrine

(-)-Pseudoephedrine

(+)-Pseudoephedrine and (-)-Pseudoephedrine are diastereomers of (+)-Ephedrine.
Diastereomers

✓ Stereoisomers that are not mirror images of each other.

✓ Diastereomers have similar chemical properties.

✓ Diastereomers have different physical properties: melting points, boiling points, solubilities in solvent, etc.

✓ Diastereomers can be separated by fractional distillation, or crystallization.
Diastereomers

(-)-Ephedrine

(+)-Ephedrine

Diastereomers

(+)-Pseudoephedrine

(-)-Pseudoephedrine
### Relationships Between Stereoisomers

<table>
<thead>
<tr>
<th>Stereoisomers</th>
<th>Enantiomeric with</th>
<th>Diastereomeric with</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1$R$), (2$S$)-(−)-Ephedrine</td>
<td>(1$S$), (2$R$)-(+)</td>
<td>(1$S$), (2$S$)-(+) Pseudoephedrine</td>
</tr>
<tr>
<td></td>
<td>(2$S$)-(+)</td>
<td>(1$R$), (2$R$)-(−) Pseudoephedrine</td>
</tr>
</tbody>
</table>

Cahn-Ingold-Prelog $R/S$ notation = Specifies absolute configuration of a chiral center;
there is no correspondence between $R$ and + or $S$ and −
(+)-Tartaric Acid:  \([\alpha]_D = +12^\circ\)  m.p. 170 °C

(−)-Tartaric Acid:  \([\alpha]_D = -12^\circ\)  m.p. 170 °C

meso-Tartaric Acid:  \([\alpha]_D = 0^\circ\)  m.p. 140 °C
Meso Isomer:

an achiral molecule with 2 or more chiral centers and an internal plane of symmetry; the molecule is achiral.

(2S, 3R)-(+)-Tartaric Acid

\[
\begin{align*}
\text{COOH} & \\
\text{HO} & \quad \text{S} \\
\text{HO} & \quad \text{R} \\
\text{COOH} & 
\end{align*}
\]

(2R, 3S)-(+)-Tartaric Acid

\[
\begin{align*}
\text{COOH} & \\
\text{H} & \quad \text{R} \\
\text{H} & \quad \text{S} \\
\text{COOH} & 
\end{align*}
\]

Identical
Number of stereoisomers = a molecule with $n$ stereogenic centers (and for which a meso isomer isn’t possible) will have $2n$ stereoisomers.

![(+)-glucose](image)

# of chiral centers = 4

total # of stereoisomers = $2^4 = 16$
Racemix Mixtures (Racemate)

- A 50:50 mixture of the two enantiomers.
- Denote by the symbol (±) or prefix $d, l$.
- Must show zero optical rotation (optically inactive).

**Enantiomeric Excess (ee)**

$$ee = \left( \frac{\text{specific rotation of the mixture}}{\text{specific rotation of the pure enantiomer in excess}} \right) \times 100$$

$$ee = \left( \frac{\text{moles of major enantiomer} - \text{moles of other enantiomer}}{\text{Total moles of both enantiomers}} \right) \times 100$$
Let's suppose that we have a reaction mixture which we measure for rotation, and the observed specific rotation of the reaction mixture is measured to be $+8.52^\circ$. The specific rotation of the $S$-configured enantiomer was said to be $-15.00^\circ$. Determine the enantiomeric excess.

\[
enantiomeric \text{ excess} = \left( \frac{+8.52}{+15.00} \right) \times (100) = 56.8\%\text{ in excess of } R\text{-isomer}
\]

This means that 56.8% of the entire mixture is in excess of the $R$-configured isomer.
Resolution of Racemic Mixtures

There are two basic ways that one can separate the enantiomers in a racemic mixture:

✓ Biological Resolution: Uses a microbe which metabolizes one specific enantiomer leaving the other alone.

✓ Chemical Resolution: The racemate is converted to two diastereoisomers. Once separated the diastereoisomeric forms are converted back to enantiomers in separate containers.