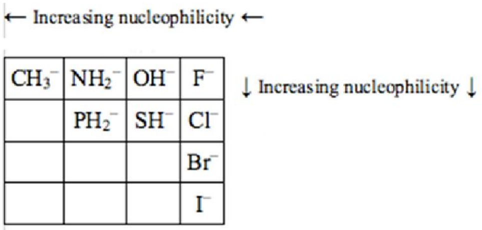
General consideration

Nucleophile

- A nucleophile is a chemical species that donates an electron pair to an electrophile to form a chemical bond in relation to a reaction.
- All molecules or ions with a free pair of electrons or at least one π bond.
- Because nucleophiles donate electrons, they are by definition Lewis bases.



← Increasing nucleophilicity ←

↓ Increasing nucleophilicity ↓

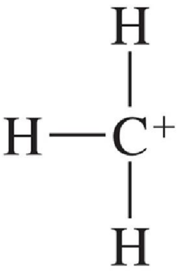
CH_3^-	NH_2^-	OH^-	F^-
	PH_2^-	SH^-	Cl^-
			Br^-
			I^-

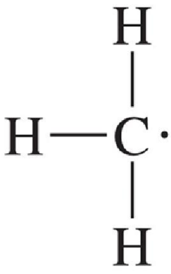
General consideration

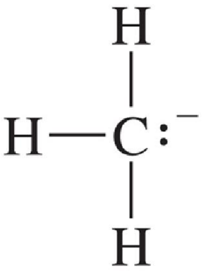
Electrophile

- An electrophile is a reagent attracted to electrons.
- Electrophiles are positively charged or neutral species having vacant orbitals that are attracted to an electron rich centers. It participates in a chemical reaction by accepting an electron pair in order to bond to a nucleophile.
- Because electrophiles accept electrons, they are Lewis acids

Intermediates in organic reactions

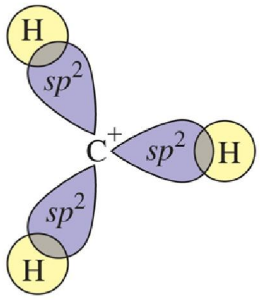

carbocation


radical

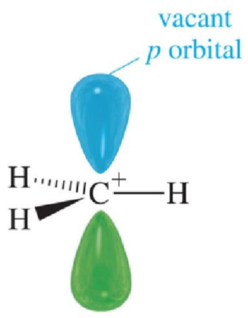

carbanion

Intermediates in organic reactions

Carbocations structure



top view

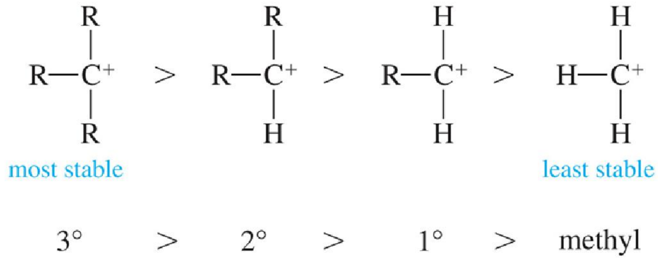


side view

- Carbon has 6 electrons, positively charged.
- Carbon is sp^2 hybridized with vacant *p* orbital.

Intermediates in organic reactions

Stability of carbocations



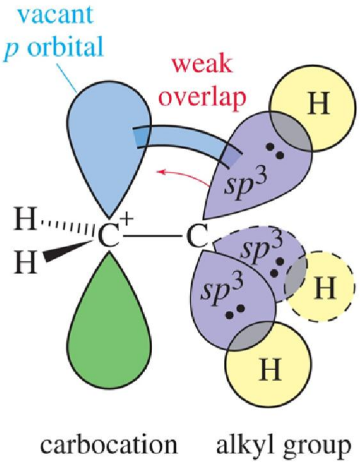
Stability of carbocations

Intermediates in organic reactions

Stability of carbocations

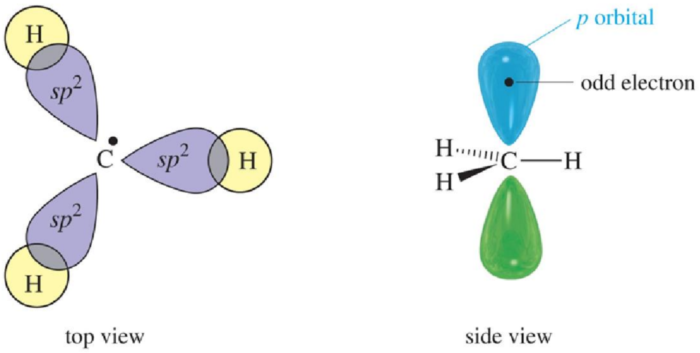
Stabilized by alkyl substituents in two ways:

1. ***Inductive effect***: Donation of electron density along the sigma bonds.
2. ***Hyperconjugation***: Overlap of sigma bonding orbitals with empty *p* orbital.



Intermediates in organic reactions

Carbon radicals

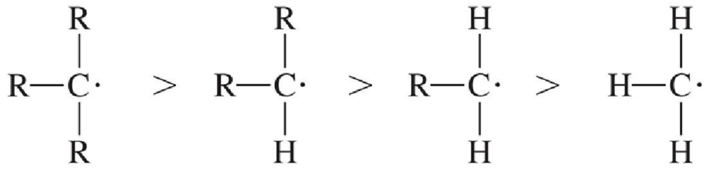


- Also electron-deficient.
- Stabilized by alkyl substituents.
- Order of stability:
  3° > 2° > 1° > methyl

Intermediates in organic reactions

Stability of carbon radicals

Stability of radicals



$R_3C\cdot > R_2CH\cdot > RCH_2\cdot > H_3C\cdot$

most stable

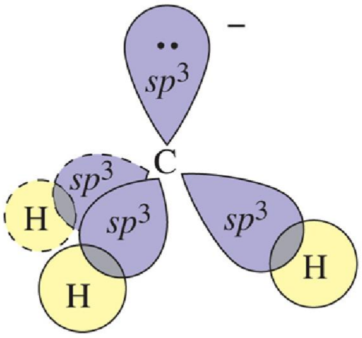
least stable

3° > 2° > 1° > methyl

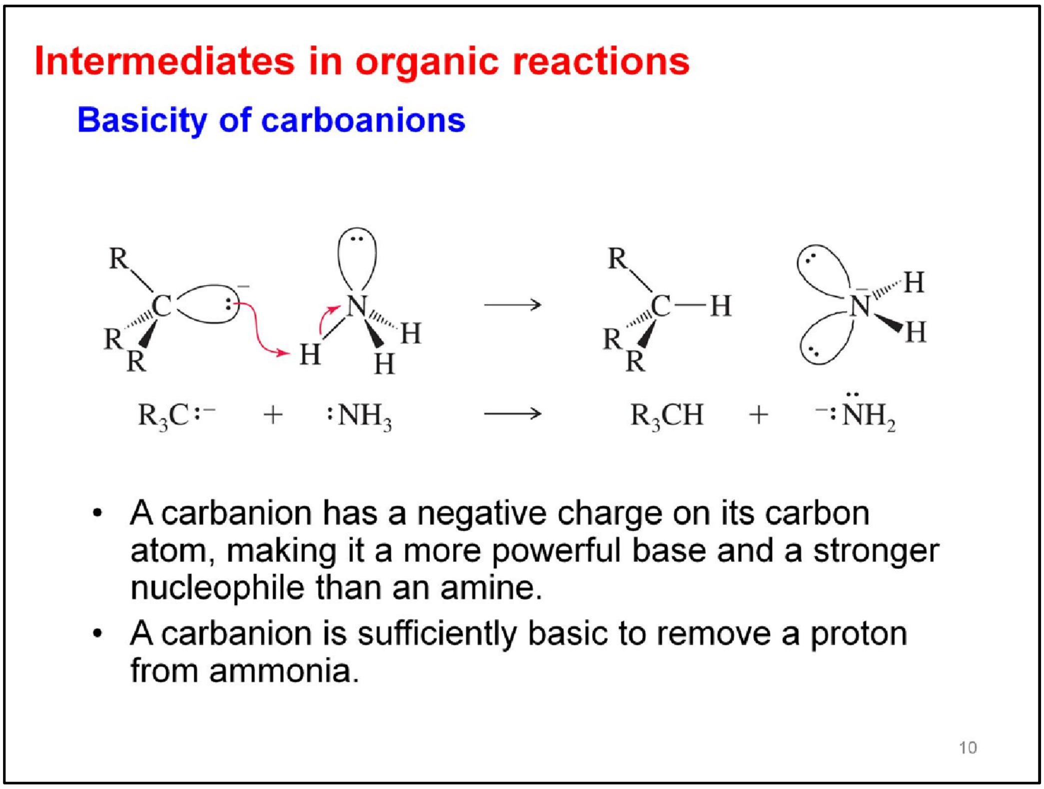
Intermediates in organic reactions

Carboanions structure

- Eight electrons on carbon: 6 bonding plus one lone pair.
- Carbon has a negative charge.
- Destabilized by alkyl substituents.
- Methyl >1° > 2 ° > 3 °



methyl anion



Intermediates in organic reactions

Basicity of carboanions

$$R_3C{:}^- \quad + \quad {:}NH_3 \quad \longrightarrow \quad R_3CH \quad + \quad {}^-{:}\ddot{N}H_2$$

- A carbanion has a negative charge on its carbon atom, making it a more powerful base and a stronger nucleophile than an amine.
- A carbanion is sufficiently basic to remove a proton from ammonia.

Figure: 04_16-02UN.jpg

Title:
Reactivity of a Carbanion

Caption:
Like amines, carbanions are nucleophilic and basic. A carbanion has a negative charge on its carbon atom, however, making it a more powerful base and a stronger nucleophile than an amine. For example, a carbanion is sufficiently basic to remove a proton from ammonia.

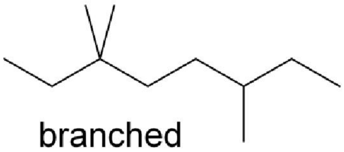
Notes:
Carbanions are a stronger base than amines, so they can deprotonate amines easily.

Alkanes

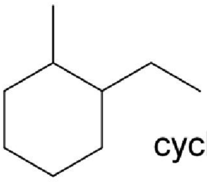
General formula C_nH_{2n+2}

Contains only C – H and C – C σ bonds.

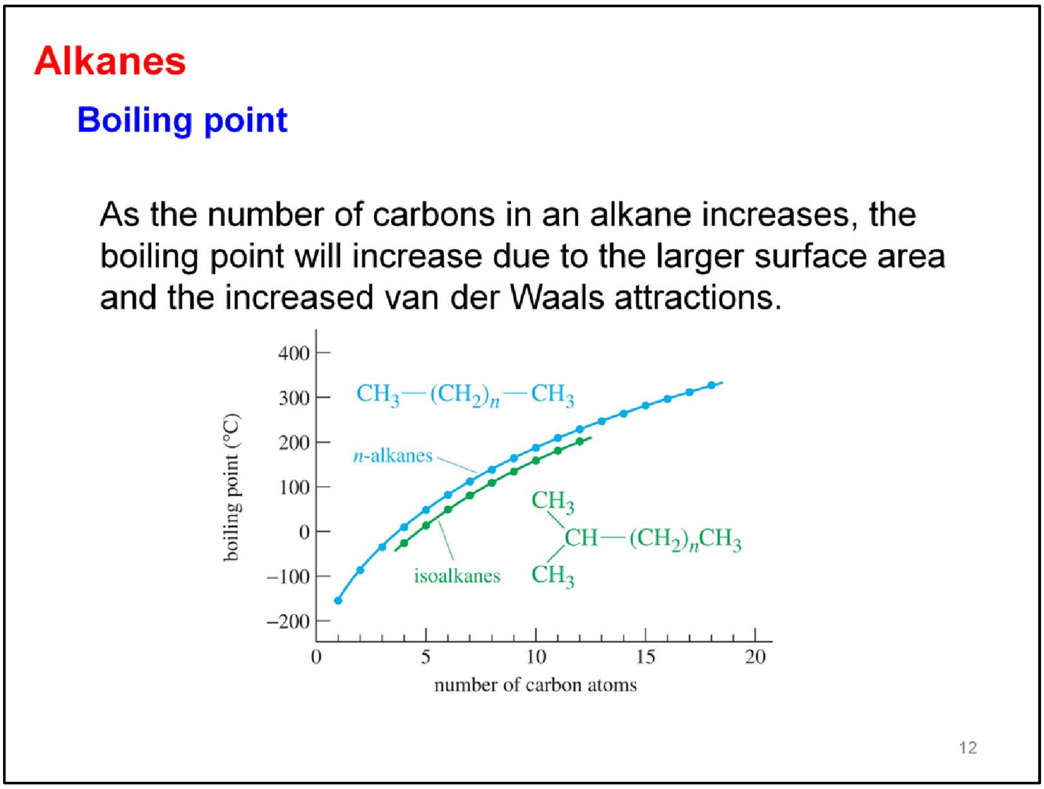
linear



branched



cyclic



Alkanes

Boiling point

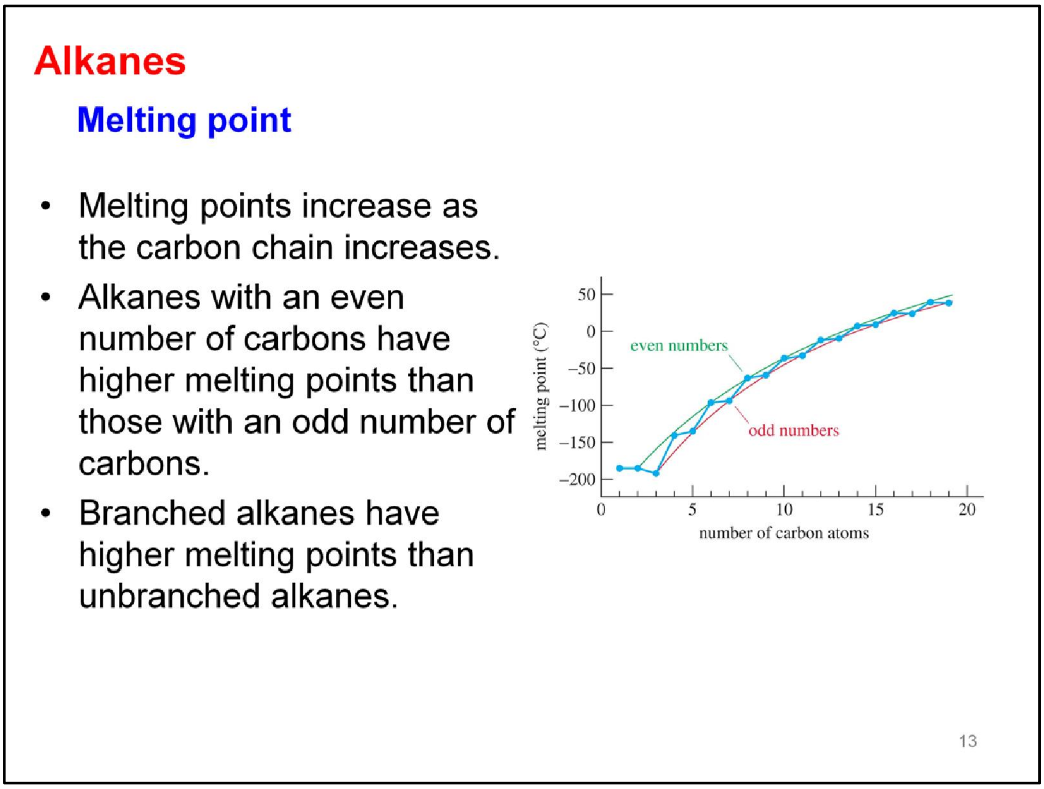
As the number of carbons in an alkane increases, the boiling point will increase due to the larger surface area and the increased van der Waals attractions.

Figure: 03_03.jpg

Title:
Boiling Points of Branched and Unbranched Alkanes

Caption:
Alkane boiling points. Comparison of the boiling points of the unbranched alkanes (blue) with those of some branched alkanes (red). Because of their smaller surface areas, branched alkanes have lower boiling points than unbranched alkanes.

Notes:
The only intermolecular force of nonpolar molecules are London dispersion forces which result from induced dipole attractions. Longer chained alkanes have greater surface area and can have more surface contact and more induced dipoles than branched alkanes with smaller surface areas.



Alkanes

Melting point

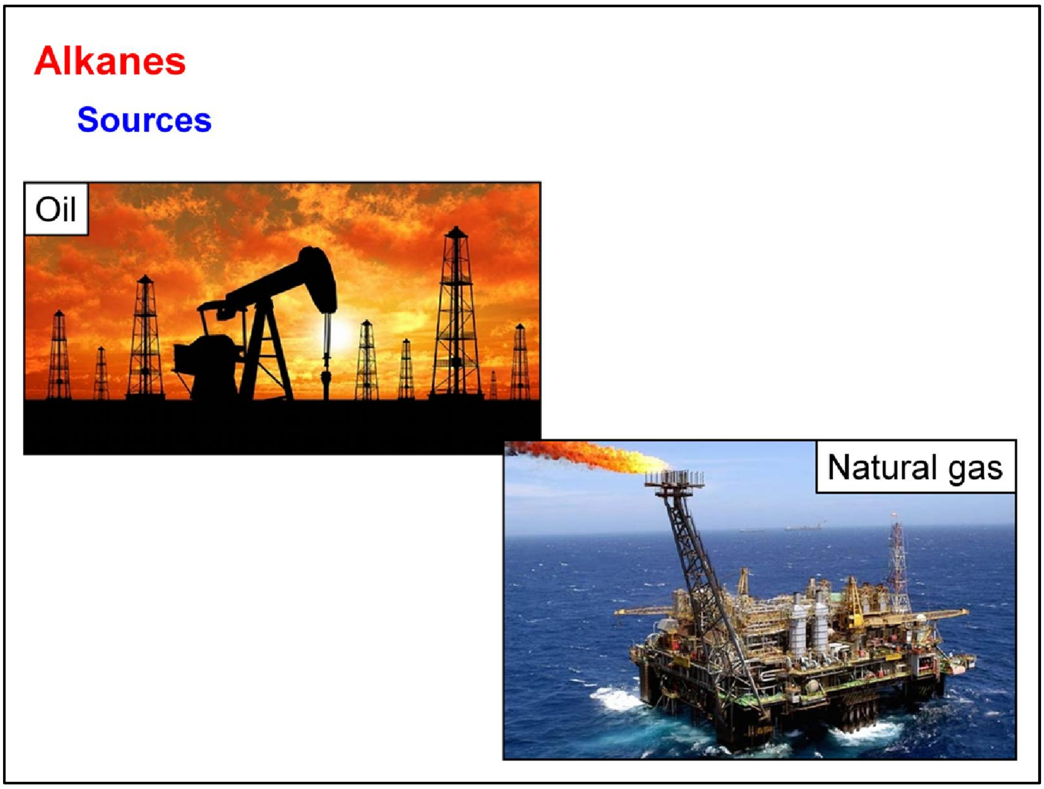
- Melting points increase as the carbon chain increases.
- Alkanes with an even number of carbons have higher melting points than those with an odd number of carbons.
- Branched alkanes have higher melting points than unbranched alkanes.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkanes

Sources

Oil

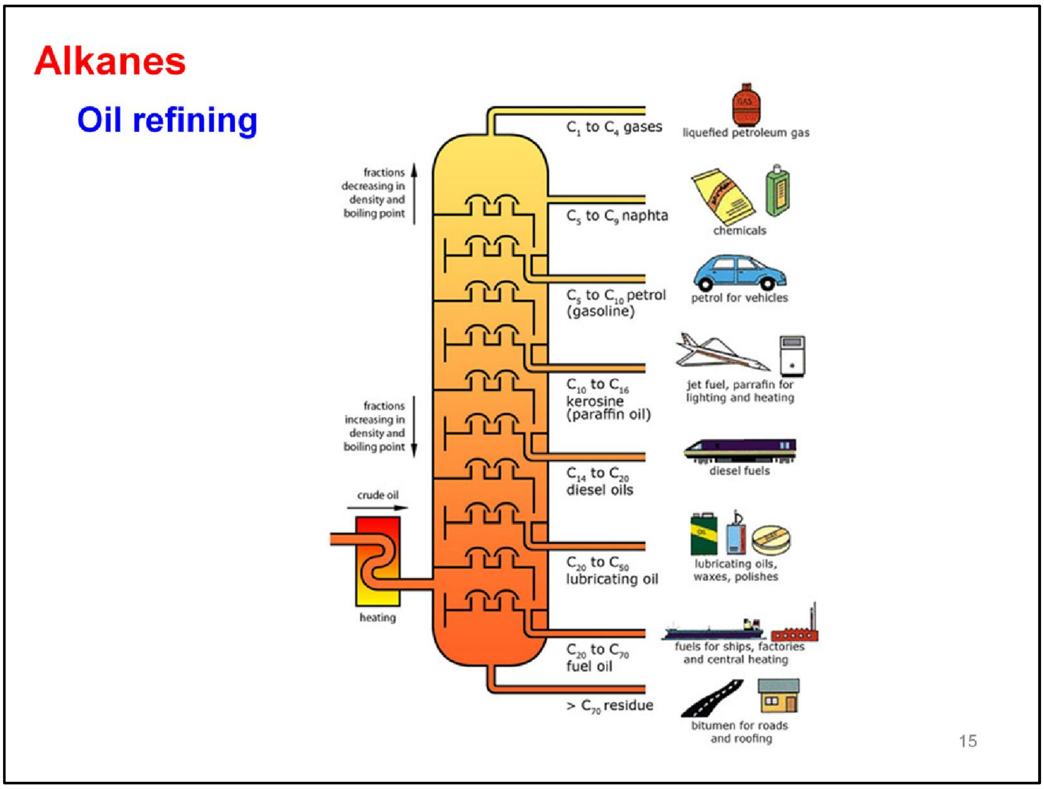
Natural gas

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkanes

Oil refining

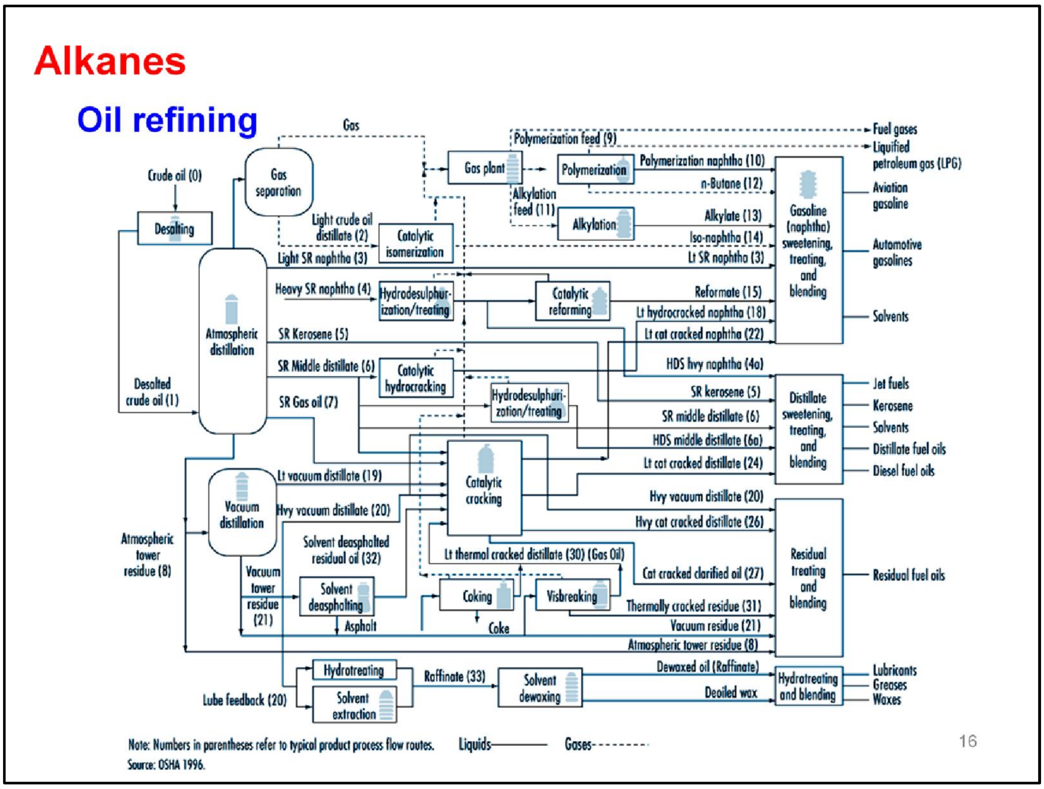
15

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkanes

Oil refining

Note: Numbers in parentheses refer to typical product process flow routes.

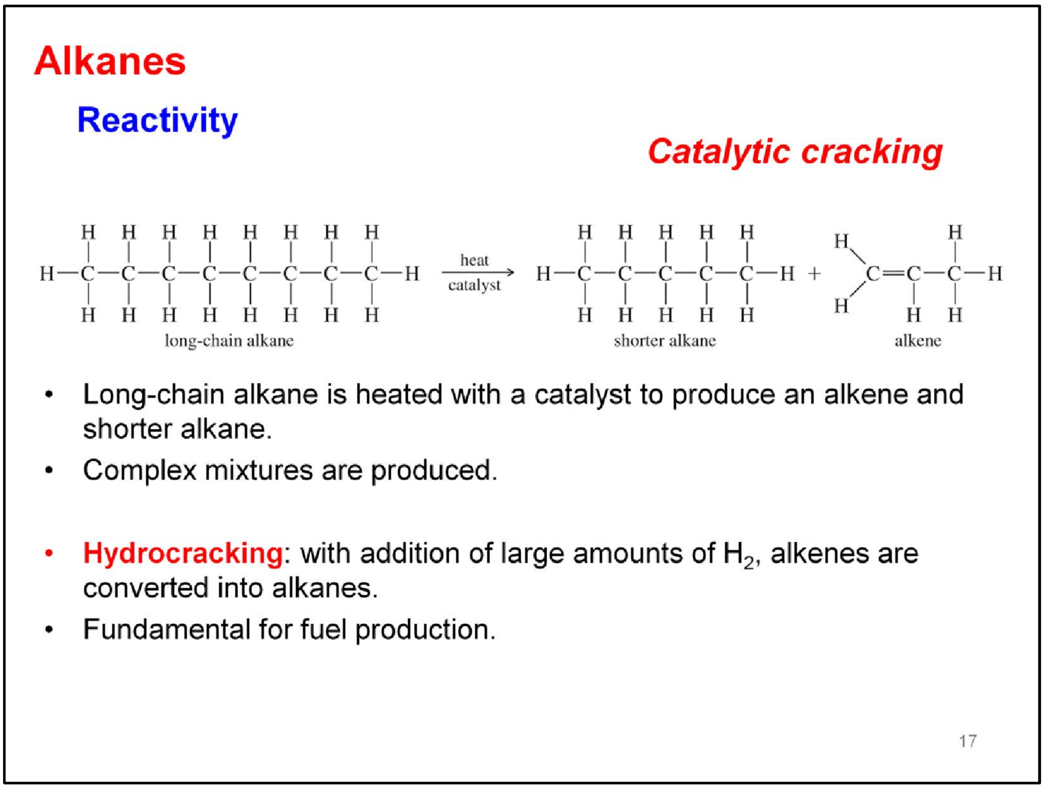
Source: OSHA 1996.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkanes

Reactivity

Catalytic cracking

- Long-chain alkane is heated with a catalyst to produce an alkene and shorter alkane.
- Complex mixtures are produced.

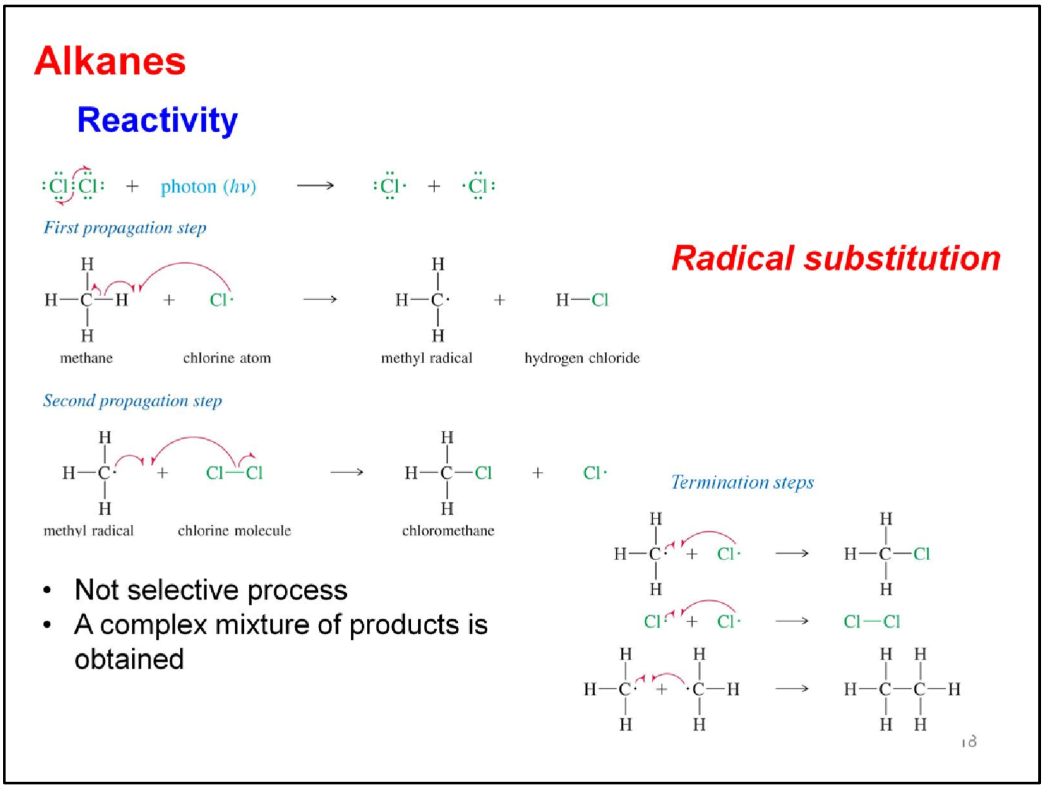
- **Hydrocracking**: with addition of large amounts of H_2, alkenes are converted into alkanes.
- Fundamental for fuel production.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkanes

Reactivity

Radical substitution

- Not selective process
- A complex mixture of products is obtained

Figure: 03_04.jpg

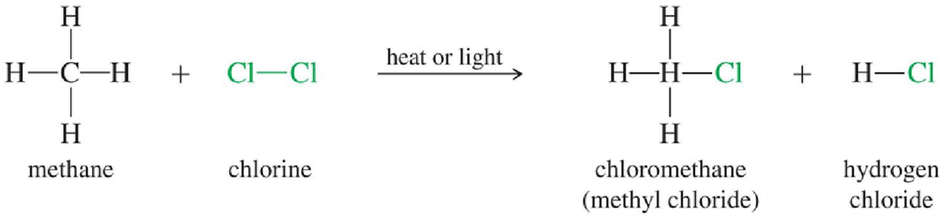
Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

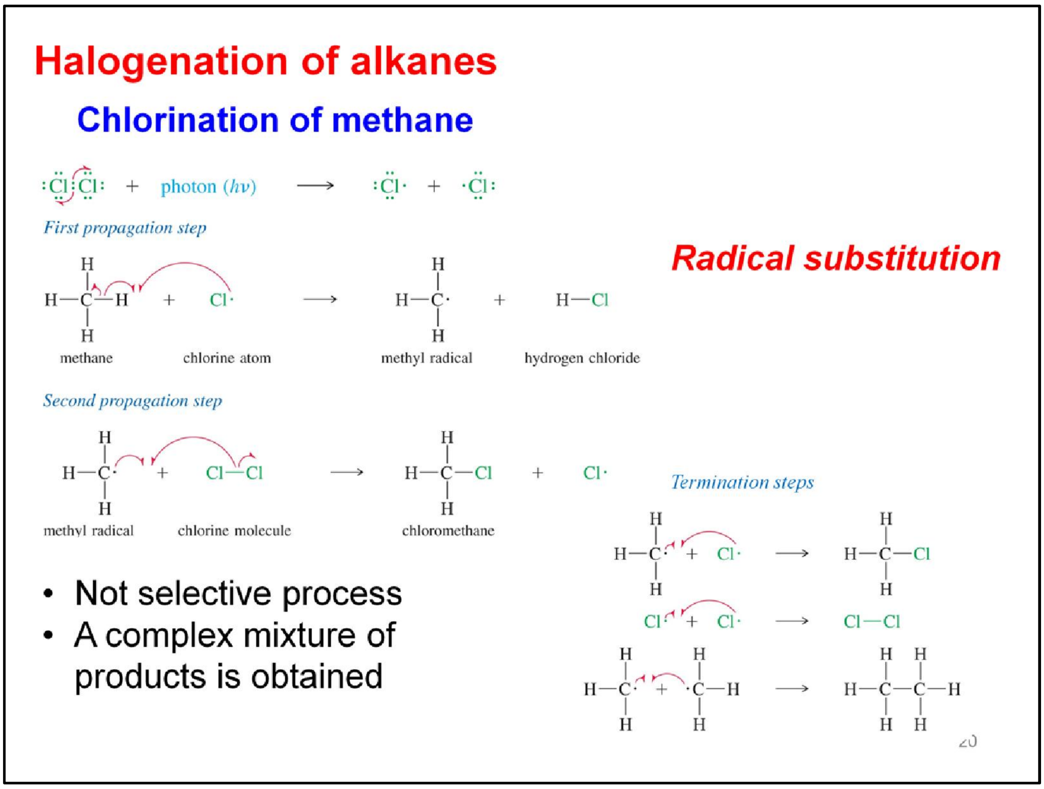
Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

Halogenation of alkanes

Chlorination of methane



- Requires heat or light for initiation.
- The most effective wavelength is blue, which is absorbed by chlorine gas.
- Many molecules of product are formed from absorption of only one photon of light (chain reaction).



Halogenation of alkanes

Chlorination of methane

Radical substitution

- Not selective process
- A complex mixture of products is obtained

Figure: 03_04.jpg

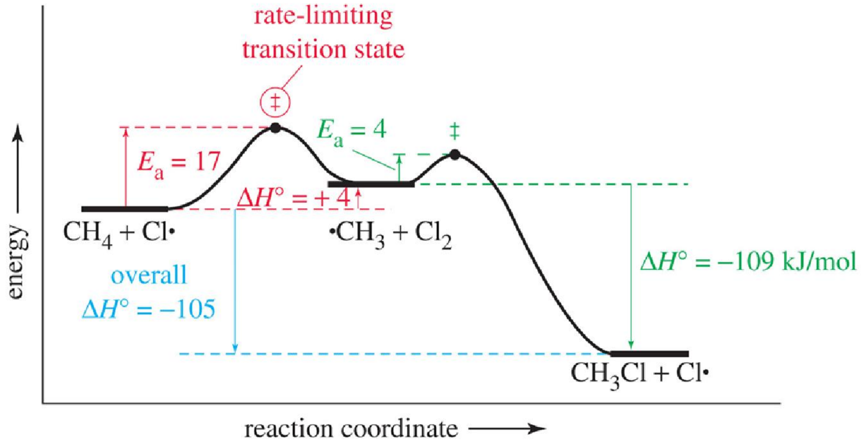
Title:
Melting Points of Alkanes

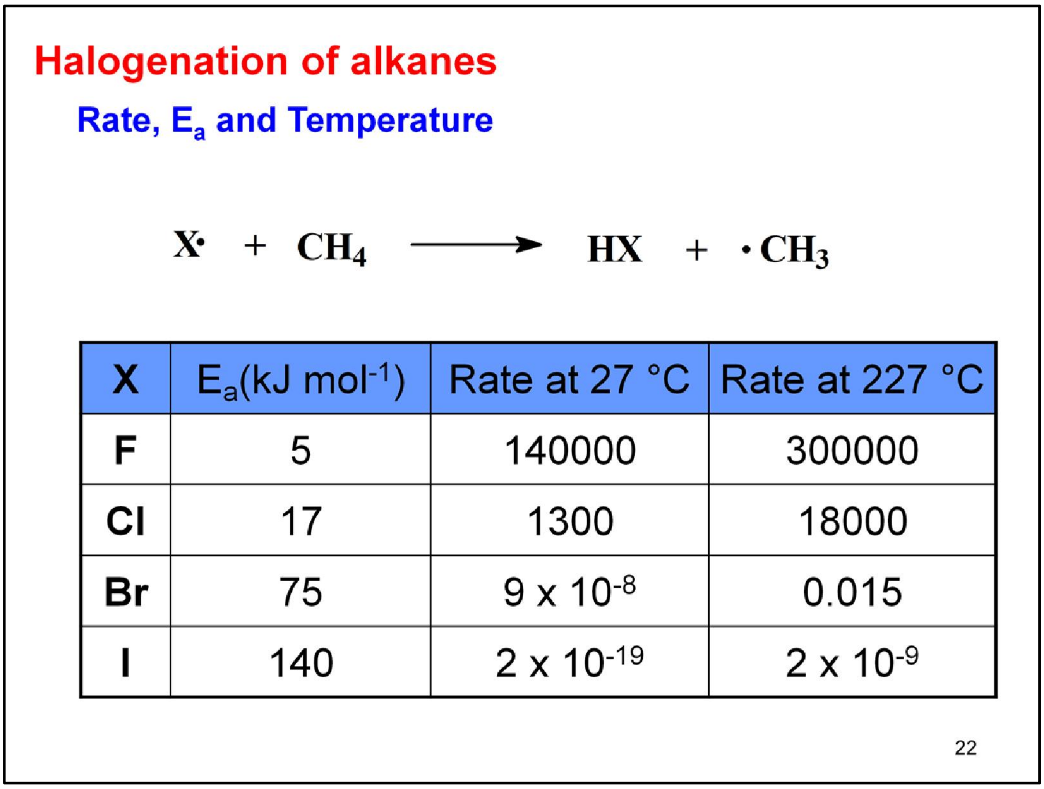
Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

Halogenation of alkanes

Energy Diagram for the Chlorination of Methane





Halogenation of alkanes

Rate, E_a and Temperature

$$X\cdot + CH_4 \longrightarrow HX + \cdot CH_3$$

X	E_a(kJ mol^{-1})	Rate at 27 °C	Rate at 227 °C
F	5	140000	300000
Cl	17	1300	18000
Br	75	9×10^{-8}	0.015
I	140	2×10^{-19}	2×10^{-9}

Halogenation of alkanes

Conclusions

- With increasing E_a, rate decreases.
- With increasing temperature, rate increases.
- Fluorine reacts explosively.
- Chlorine reacts at a moderate rate.
- Bromine must be heated to react.
- Iodine does not react (detectably).

Halogenation of alkanes

Chlorination of propane

Initiation: Splitting of the chlorine molecule

$$Cl_2 + h\nu \longrightarrow 2\,Cl\cdot$$

First propagation step: Abstraction (removal) of a primary or secondary hydrogen

$$CH_3{-}CH_2{-}CH_3 + Cl\cdot \longrightarrow \underset{\text{primary radical}}{\cdot CH_2{-}CH_2{-}CH_3} \text{ or } \underset{\text{secondary radical}}{CH_3{-}\dot{C}H{-}CH_3} + HCl$$

Second propagation step: Reaction with chlorine to form the alkyl chloride

$$\underset{\text{primary radical}}{\cdot CH_2{-}CH_2{-}CH_3} + Cl_2 \longrightarrow \underset{\substack{\text{primary chloride}\\ \text{(1-chloropropane)}}}{Cl{-}CH_2{-}CH_2{-}CH_3} + Cl\cdot$$

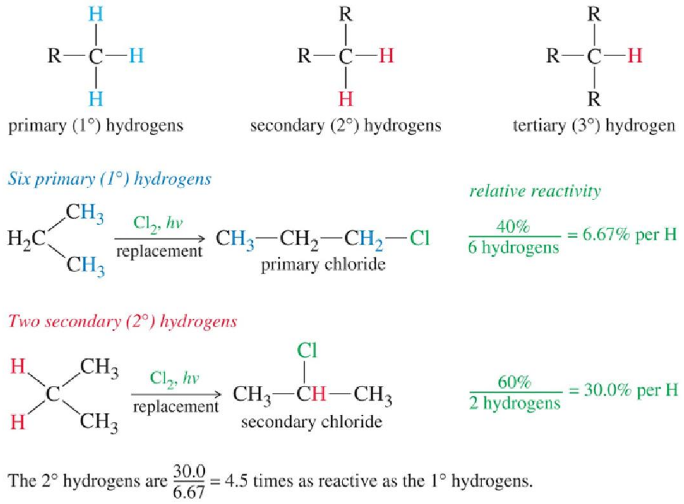
40%

$$\text{or } \underset{\text{secondary radical}}{CH_3{-}\dot{C}H{-}CH_3} + Cl_2 \longrightarrow \underset{\substack{\text{secondary chloride}\\ \text{(2-chloropropane)}}}{CH_3{-}\overset{\overset{\displaystyle Cl}{|}}{C}H{-}CH_3} + Cl\cdot$$

60%

Halogenation of alkanes

Primary, Secondary and Tertiary Hydrogens



$H_2C(CH_3)_2 \xrightarrow[\text{replacement}]{Cl_2,\ h\nu} CH_3{-}CH_2{-}CH_2{-}Cl$ (primary chloride)

$\frac{40\%}{6\ \text{hydrogens}} = 6.67\%$ per H

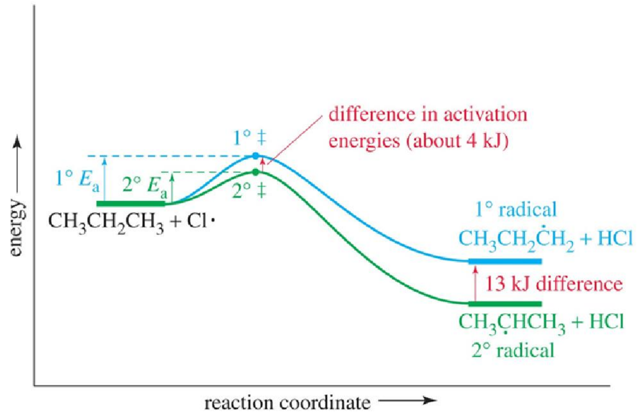
$H_2C(CH_3)_2 \xrightarrow[\text{replacement}]{Cl_2,\ h\nu} CH_3{-}CH(Cl){-}CH_3$ (secondary chloride)

$\frac{60\%}{2\ \text{hydrogens}} = 30.0\%$ per H

The 2° hydrogens are $\frac{30.0}{6.67} = 4.5$ times as reactive as the 1° hydrogens.

Halogenation of alkanes

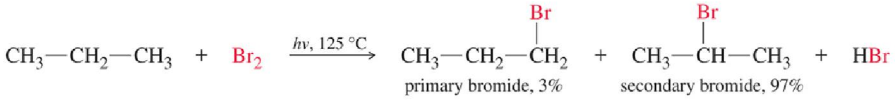
Chlorination Energy Diagram



Lower E_a, faster rate, so more stable intermediate is formed faster.

Halogenation of alkanes

Bromination of Propane



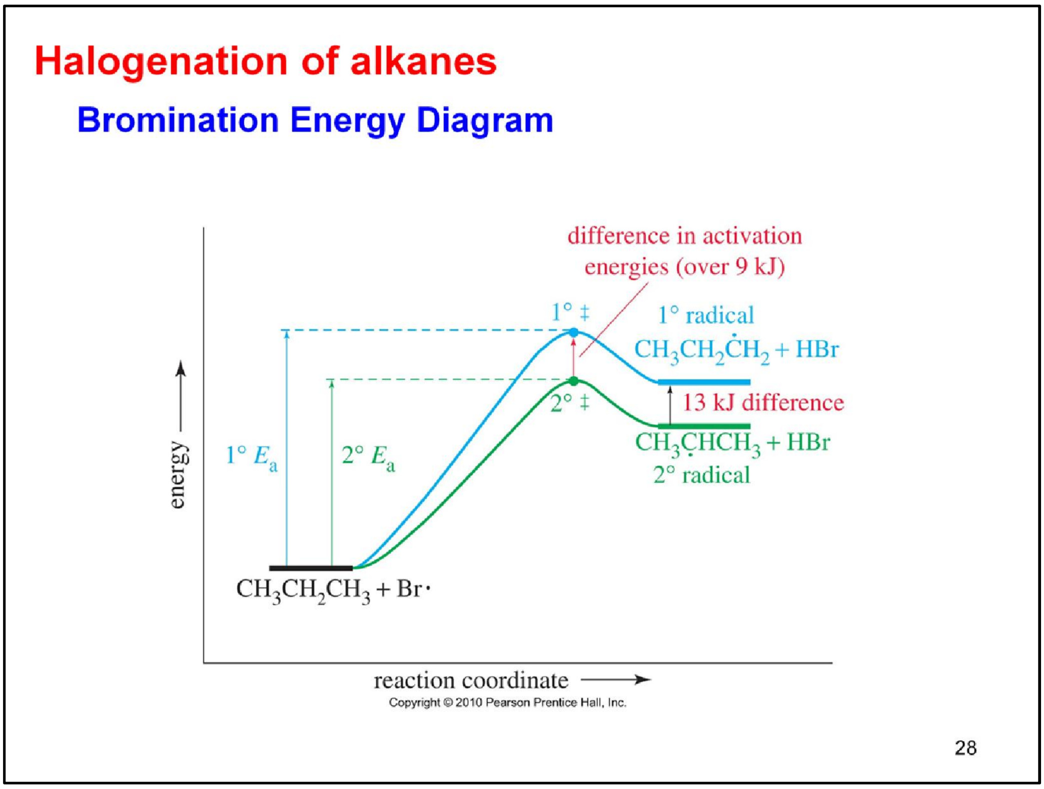
$$CH_3-CH_2-CH_3 + Br_2 \xrightarrow{h\nu,\ 125\ ^\circ C} \underset{\text{primary bromide, 3\%}}{CH_3-CH_2-\overset{Br}{\overset{|}{C}}H_2} + \underset{\text{secondary bromide, 97\%}}{CH_3-\overset{Br}{\overset{|}{C}}H-CH_3} + HBr$$

Relative reactivity

six primary hydrogens $\frac{3\%}{6} = 0.5\%$ per H

two secondary hydrogens $\frac{97\%}{2} = 48.5\%$ per H

The 2° hydrogens are $\frac{48.5}{0.5} = 97$ times as reactive as the 1° hydrogens.



Halogenation of alkanes

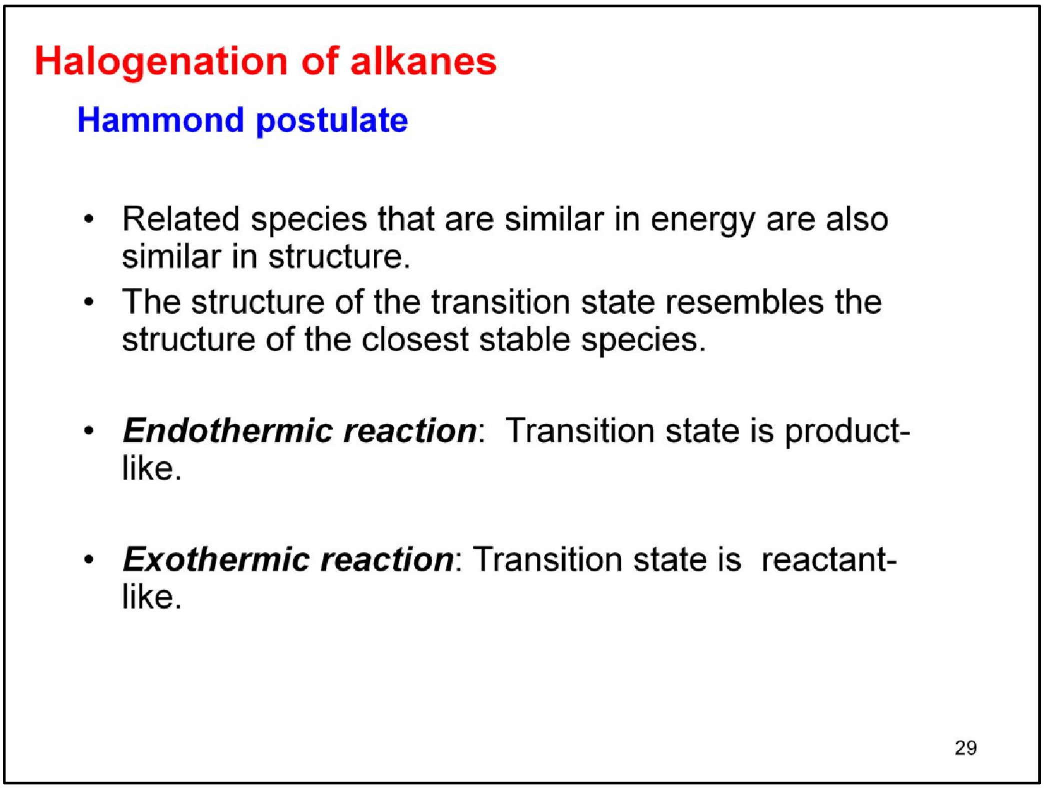
Bromination Energy Diagram

Figure: 04_10.jpg

Title:
Energy Diagram for the Bromination of Propane

Caption:
Reaction-energy diagram for the first propagation step in the bromination of propane. The energy difference in the transition states is nearly as large as the energy difference in the products.

Notes:



Halogenation of alkanes

Hammond postulate

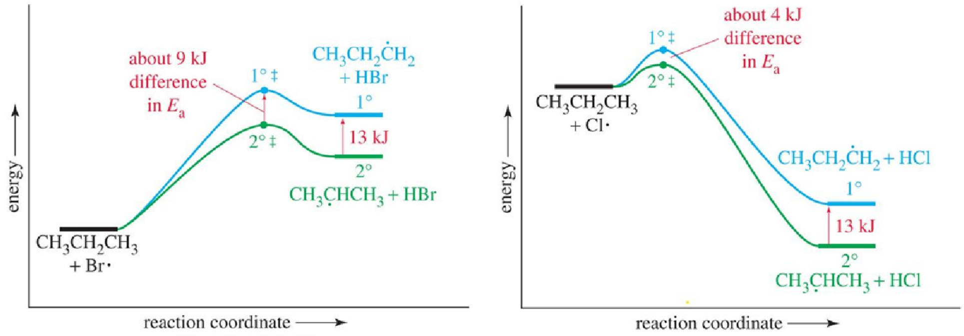
- Related species that are similar in energy are also similar in structure.
- The structure of the transition state resembles the structure of the closest stable species.

- ***Endothermic reaction***: Transition state is product-like.

- ***Exothermic reaction***: Transition state is reactant-like.

Halogenation of alkanes

Energy Diagrams: Chlorination Versus Bromination

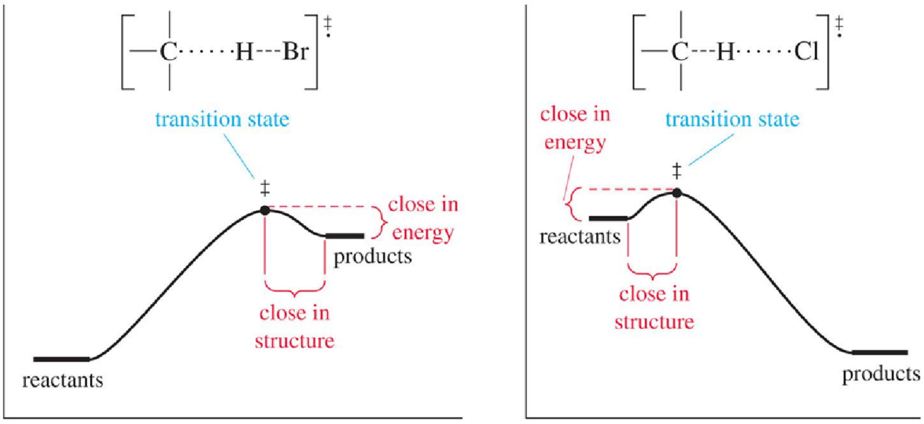


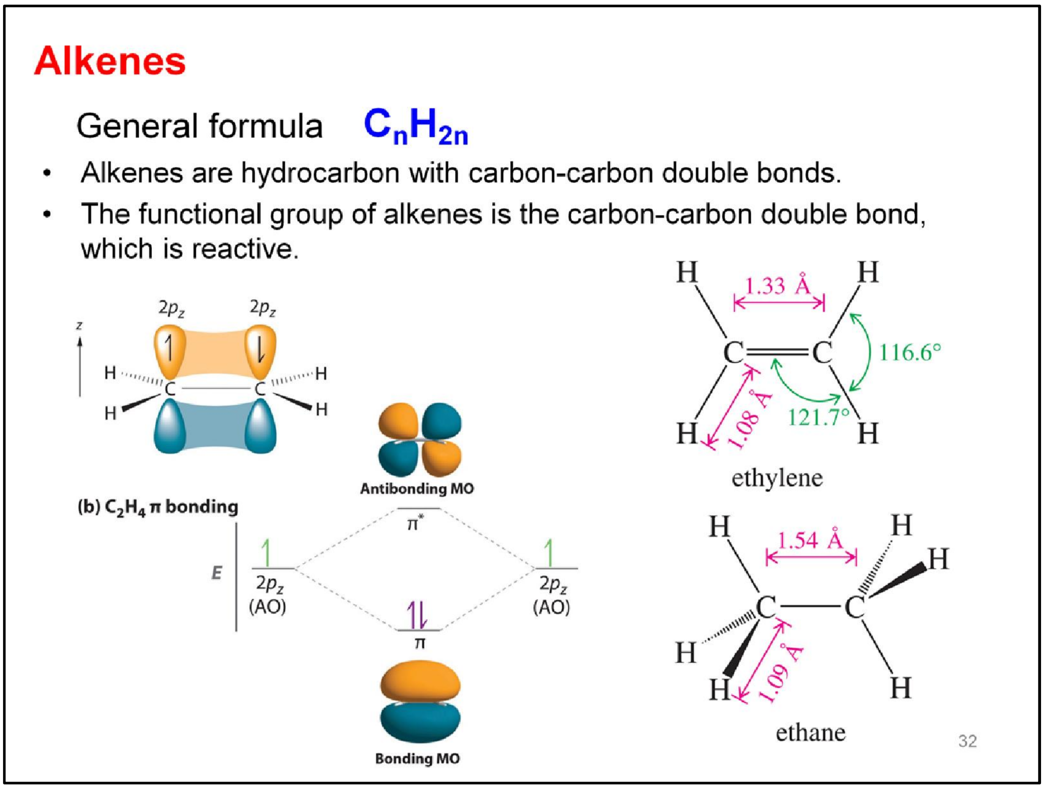
(a) BROMINATION
endothermic
TS close to products
large difference in E_a

(b) CHLORINATION
exothermic
TS close to reactants
small difference in E_a

Halogenation of alkanes

Endothermic and Exothermic Diagrams





Alkenes

General formula C_nH_{2n}

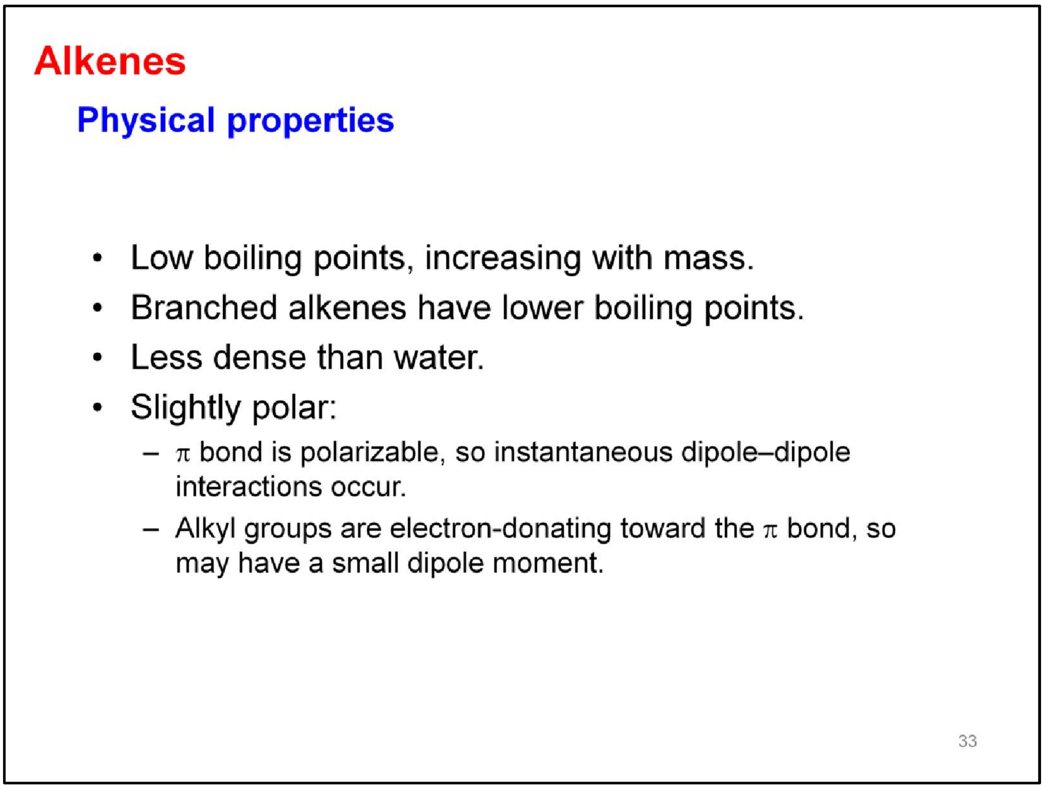
- Alkenes are hydrocarbon with carbon-carbon double bonds.
- The functional group of alkenes is the carbon-carbon double bond, which is reactive.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkenes

Physical properties

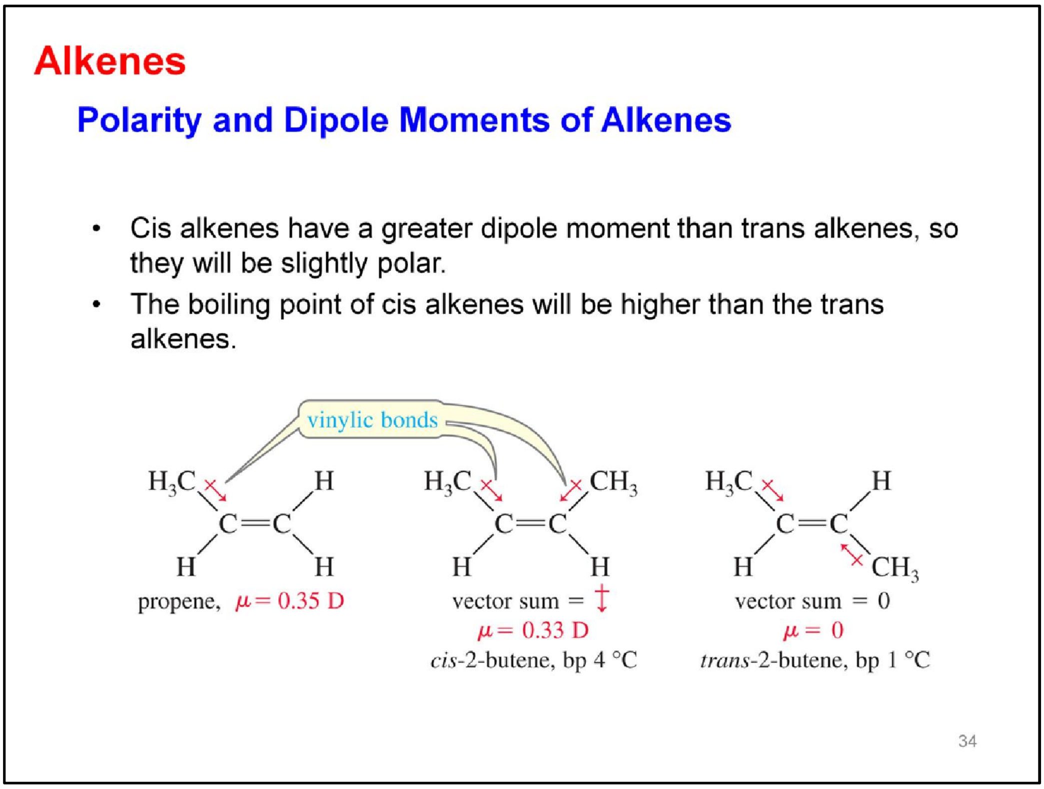
- Low boiling points, increasing with mass.
- Branched alkenes have lower boiling points.
- Less dense than water.
- Slightly polar:
  - π bond is polarizable, so instantaneous dipole–dipole interactions occur.
  - Alkyl groups are electron-donating toward the π bond, so may have a small dipole moment.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkenes

Polarity and Dipole Moments of Alkenes

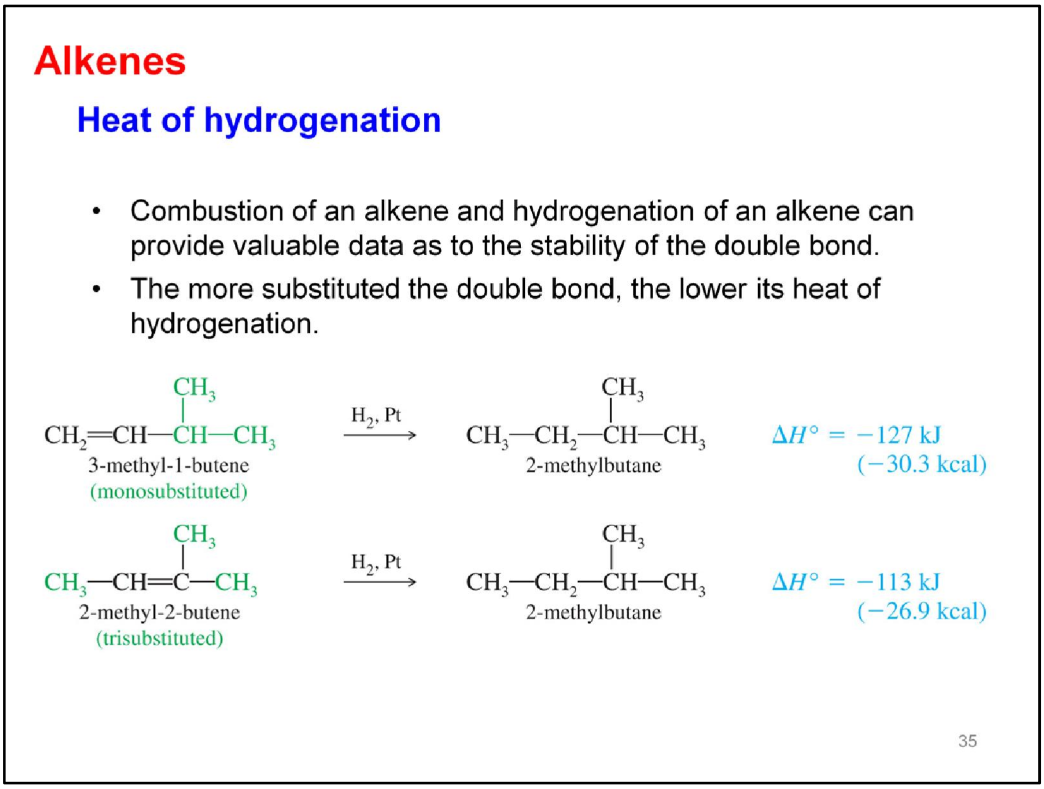
- Cis alkenes have a greater dipole moment than trans alkenes, so they will be slightly polar.
- The boiling point of cis alkenes will be higher than the trans alkenes.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkenes

Heat of hydrogenation

- Combustion of an alkene and hydrogenation of an alkene can provide valuable data as to the stability of the double bond.
- The more substituted the double bond, the lower its heat of hydrogenation.

$$\underset{\substack{\text{3-methyl-1-butene}\\ \text{(monosubstituted)}}}{CH_2{=}CH{-}\overset{\displaystyle CH_3}{\overset{|}{C}H}{-}CH_3} \xrightarrow{H_2,\ Pt} \underset{\text{2-methylbutane}}{CH_3{-}CH_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}H}{-}CH_3} \qquad \begin{array}{r} \Delta H^\circ = -127\ \text{kJ} \\ (-30.3\ \text{kcal}) \end{array}$$

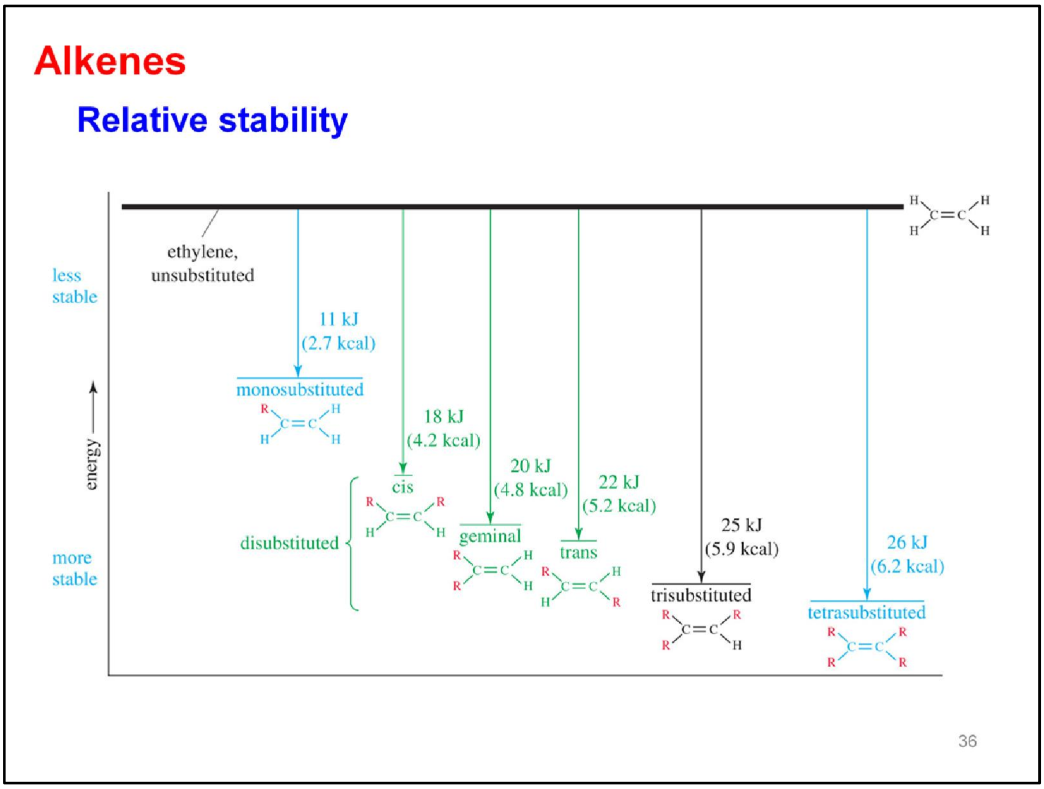
$$\underset{\substack{\text{2-methyl-2-butene}\\ \text{(trisubstituted)}}}{CH_3{-}CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH_3} \xrightarrow{H_2,\ Pt} \underset{\text{2-methylbutane}}{CH_3{-}CH_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}H}{-}CH_3} \qquad \begin{array}{r} \Delta H^\circ = -113\ \text{kJ} \\ (-26.9\ \text{kcal}) \end{array}$$

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkenes

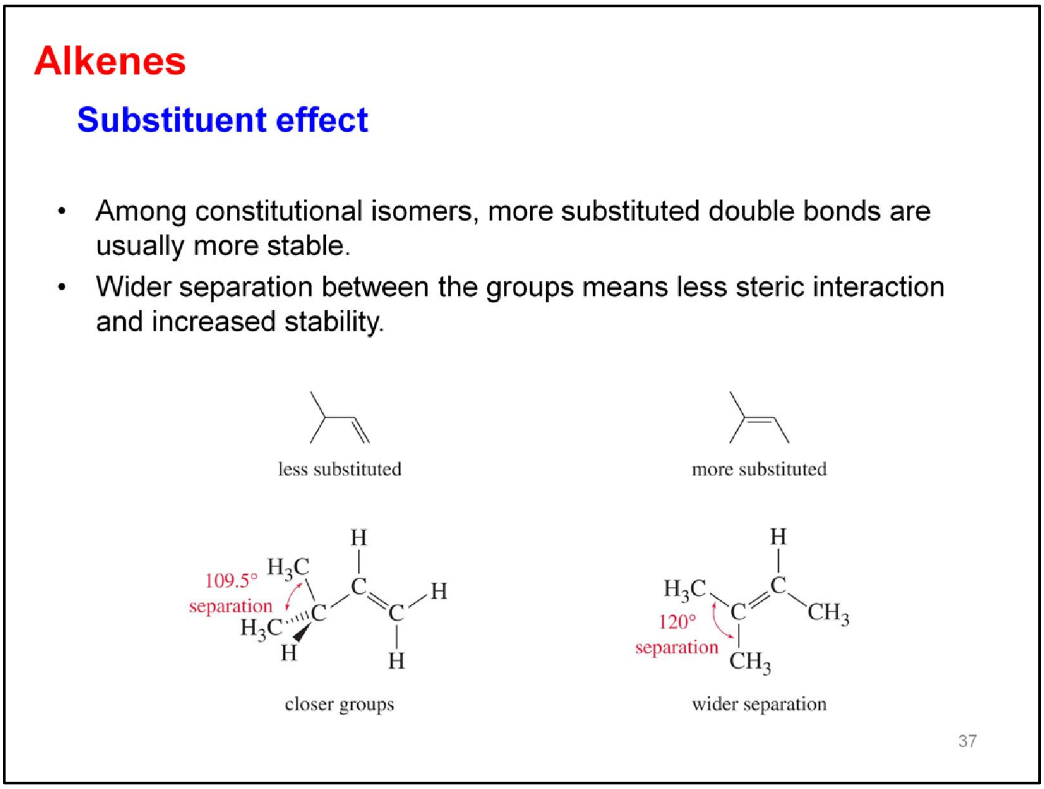
Relative stability

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkenes

Substituent effect

- Among constitutional isomers, more substituted double bonds are usually more stable.
- Wider separation between the groups means less steric interaction and increased stability.

less substituted

more substituted

closer groups

wider separation

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

Alkenes

Commercial use of ethylene

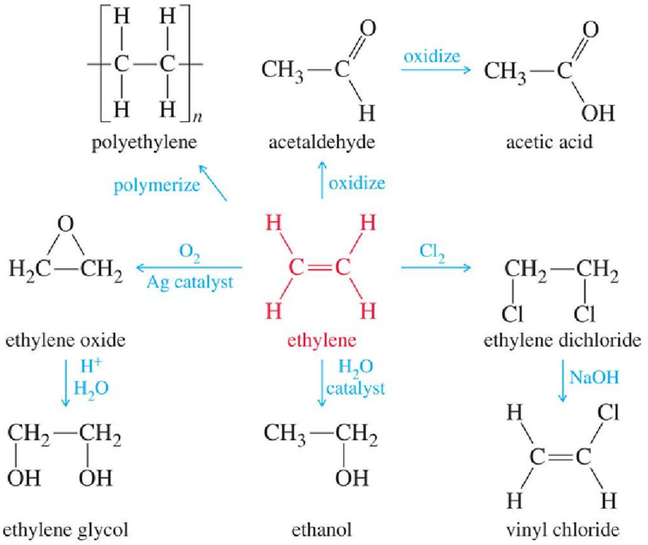
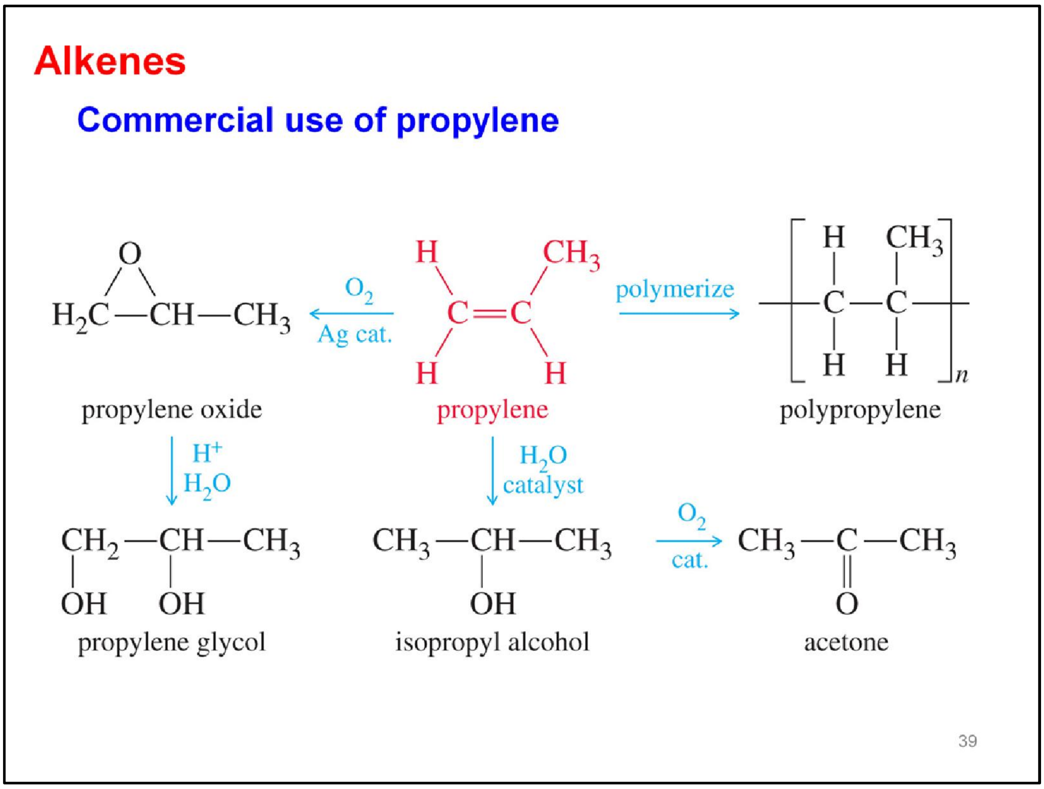


Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkenes

Commercial use of propylene

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

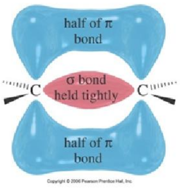
Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

Alkenes

Reactivity: ELECTROPHILIC ADDITION

- Electrons in π bond are loosely held.
- The double bond acts as a nucleophile attacking electrophilic species.
- Carbocations are intermediates in the reactions.
- These reactions are called ***electrophilic additions***.



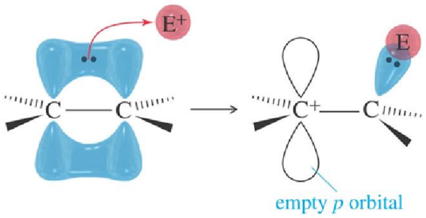


Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

Alkenes

Reactivity: ELECTROPHILIC ADDITION

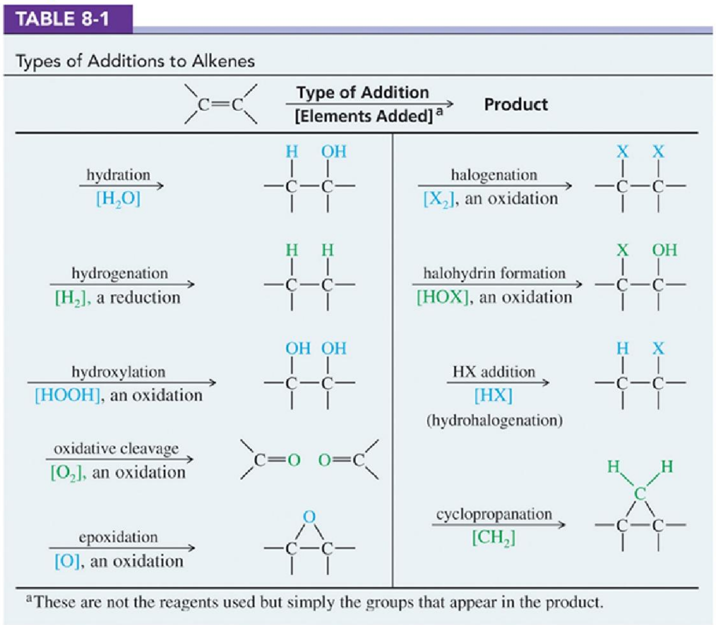


TABLE 8-1

Types of Additions to Alkenes

Type of Addition [Elements Added][a]	Type of Addition [Elements Added][a]
hydration [H_2O]	halogenation [X_2], an oxidation
hydrogenation [H_2], a reduction	halohydrin formation [HOX], an oxidation
hydroxylation [HOOH], an oxidation	HX addition [HX] (hydrohalogenation)
oxidative cleavage [O_2], an oxidation	cyclopropanation [CH_2]
epoxidation [O], an oxidation	

[a] These are not the reagents used but simply the groups that appear in the product.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

Electrophilic addition

Types of additions

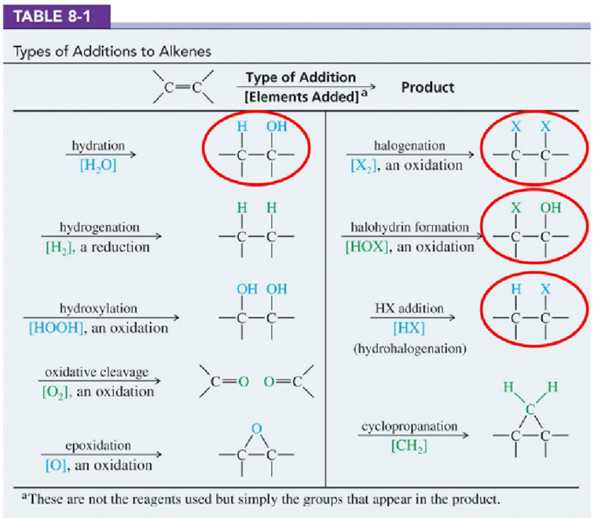


TABLE 8-1

Types of Additions to Alkenes

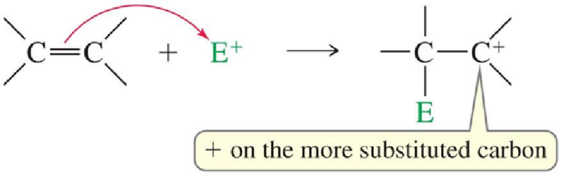
Type of Addition	[Elements Added][a]
hydration	$[H_2O]$
hydrogenation	$[H_2]$, a reduction
hydroxylation	[HOOH], an oxidation
oxidative cleavage	$[O_2]$, an oxidation
epoxidation	[O], an oxidation
halogenation	$[X_2]$, an oxidation
halohydrin formation	[HOX], an oxidation
HX addition (hydrohalogenation)	[HX]
cyclopropanation	$[CH_2]$

[a] These are not the reagents used but simply the groups that appear in the product.

Electrophilic addition

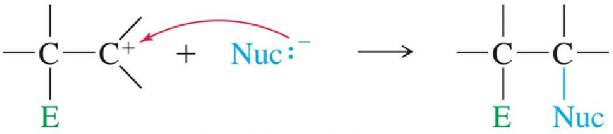
General mechanism

- Step 1: Pi electrons attack the electrophile.



+ on the more substituted carbon

- Step 2: Nucleophile attacks the carbocation.



Electrophilic addition

Regioselectivity

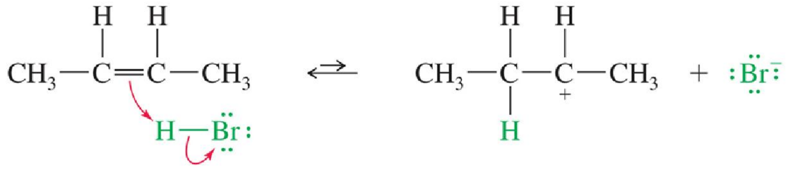
Markovnikov's Rule (extended)

In an electrophilic addition to the alkene, the electrophile adds in such a way that it generates the most stable intermediate.

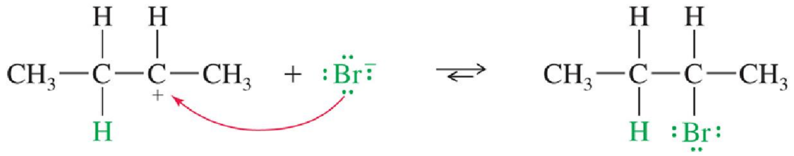
Electrophilic addition

Mechanism of addition of HX

Step 1: Protonation of the double bond.

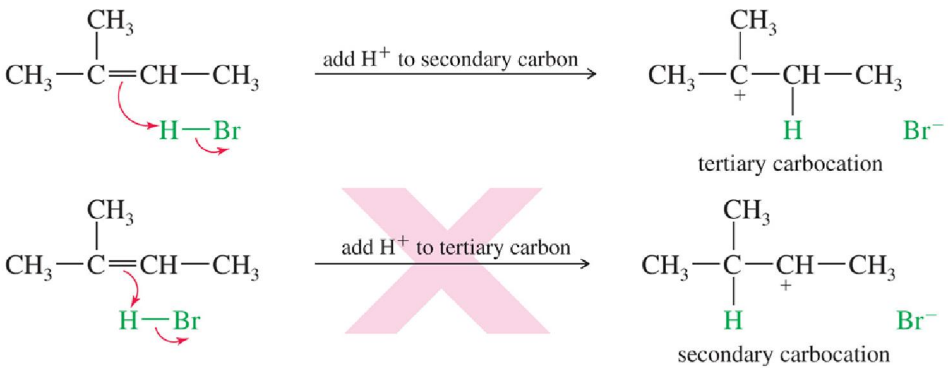


Step 2: Nucleophilic attack of the halide on the carbocation.



Electrophilic addition

Markovnikov's rule



The acid proton will bond to carbon 3 in order to produce the most stable carbocation possible.

Electrophilic addition

Free-radical addition of HBr

- In the presence of peroxides, HBr adds to an alkene to form the “anti-Markovnikov” product.
- Peroxides produce free radicals.
- Only HBr has the right bond energy.
- The HCl bond is too strong, so it will add according to Markovnikov’s rule, even in the presence of peroxide.
- The HI bond tends to break heterolytically to form ions, it too will add according to Markovnikov’s rule.

Electrophilic addition

Free-radical initiation

- The peroxide bond breaks homolytically to form the first radical:

$$R{-}O{-}O{-}R \xrightarrow{\text{heat}} R{-}O\cdot + \cdot O{-}R$$

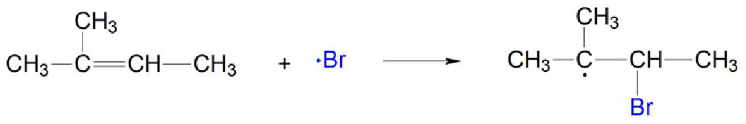
$$R{-}O\cdot + H{-}Br \longrightarrow R{-}O{-}H + Br\cdot$$

- Hydrogen is abstracted from HBr.

Electrophilic addition

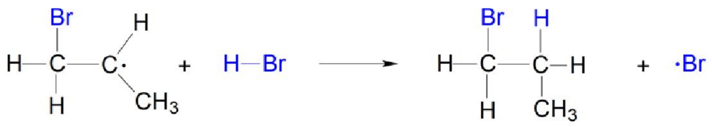
Propagation steps

- Bromine adds to the double bond forming the most stable radical possible:



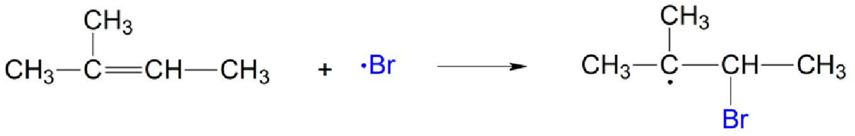
tertiary radical (more stable)

- Hydrogen is abstracted from HBr:



Electrophilic addition

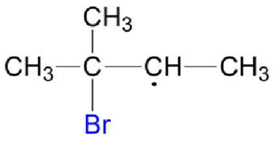
Anti-Markovnikov stereochemistry



$$CH_3-\overset{CH_3}{C}=CH-CH_3 + \cdot Br \longrightarrow CH_3-\overset{CH_3}{\underset{\bullet}{C}}-\underset{Br}{CH}-CH_3$$

tertiary radical (more stable)

- The intermediate tertiary radical forms faster because it is more stable.

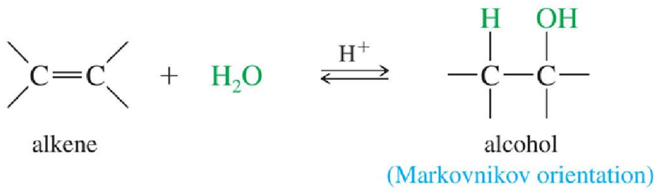


$$CH_3-\overset{CH_3}{\underset{Br}{C}}-\underset{\bullet}{CH}-CH_3$$

secondary radical (less stable)
not formed

Electrophilic addition

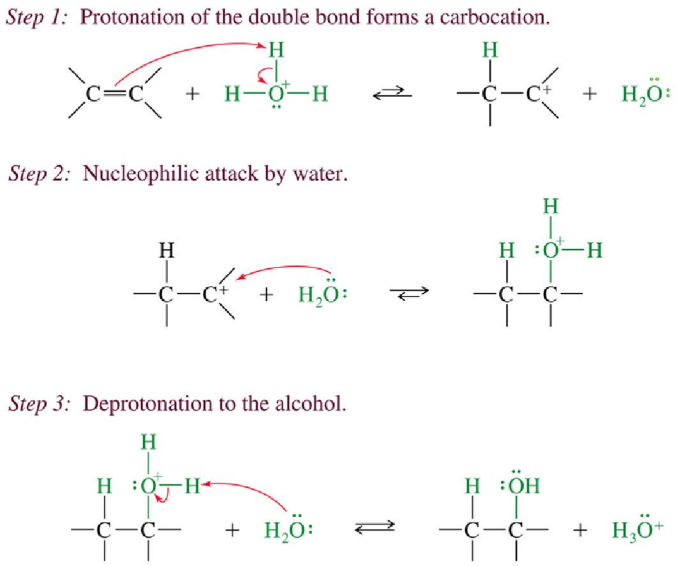
Hydration of alkenes


Hydration of an alkene

- The Markovnikov addition of water to the double bond forms an alcohol.
- Uses dilute solutions of H_2SO_4 or H_3PO_4 to drive equilibrium toward hydration.

Electrophilic addition

Mechanism for hydration



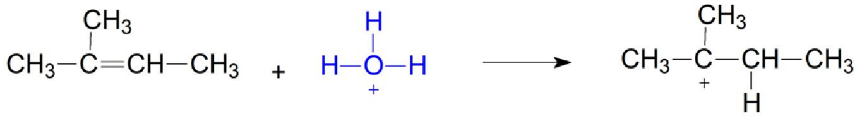
Step 1: Protonation of the double bond forms a carbocation.

Step 2: Nucleophilic attack by water.

Step 3: Deprotonation to the alcohol.

Electrophilic addition

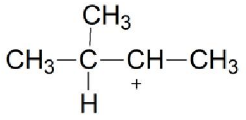
Orientation of hydration



$CH_3-\overset{CH_3}{C}=CH-CH_3 + H-\overset{H}{\underset{+}{O}}-H \longrightarrow CH_3-\overset{CH_3}{\underset{+}{C}}-\underset{H}{CH}-CH_3$

3°, more stable

The protonation follows Markovnikov’s rule: The hydrogen is added to the less substituted carbon in order to form the most stable carbocation.

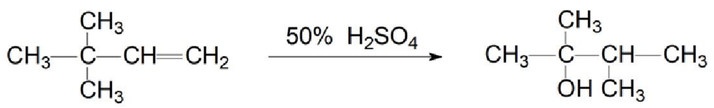


$CH_3-\overset{CH_3}{\underset{H}{C}}-\underset{+}{CH}-CH_3$

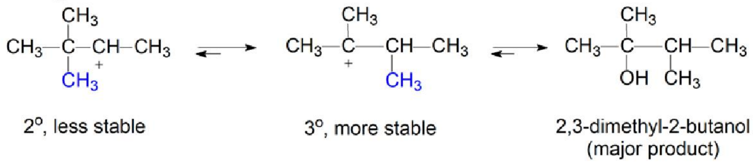
2° less stable,
not formed

Electrophilic addition

Rearrangements



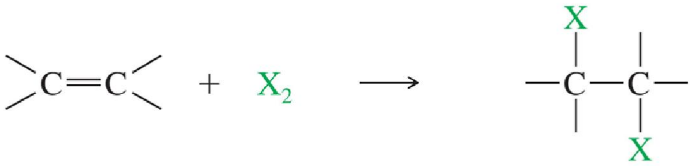
Rearrangement:



- Rearrangements can occur when there are carbocation intermediates.
- A methyl shift after protonation will produce the more stable tertiary carbocation.

Electrophilic addition

Addition of halogens



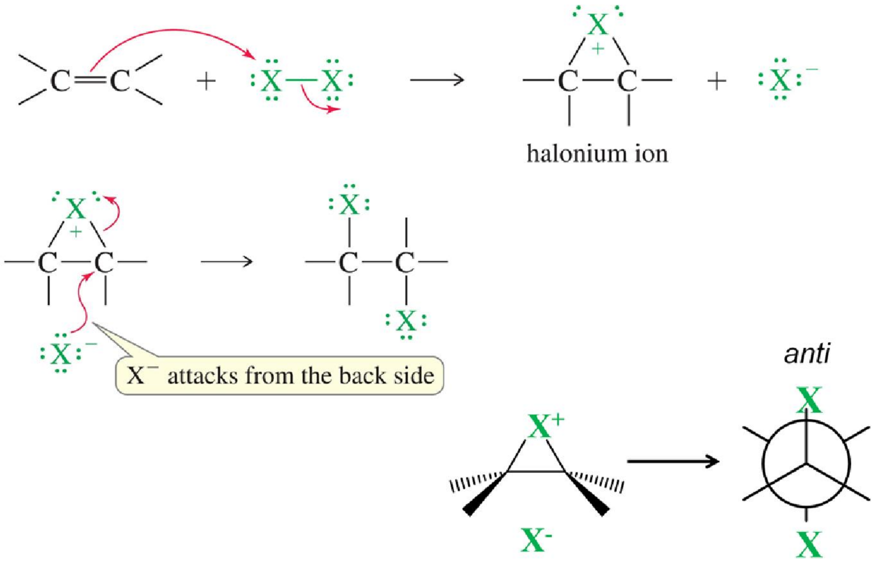
($X_2 = Cl_2, Br_2$, sometimes I_2)

usually anti addition

Cl_2, Br_2, and sometimes I_2 add to a double bond to form a vicinal dibromide.

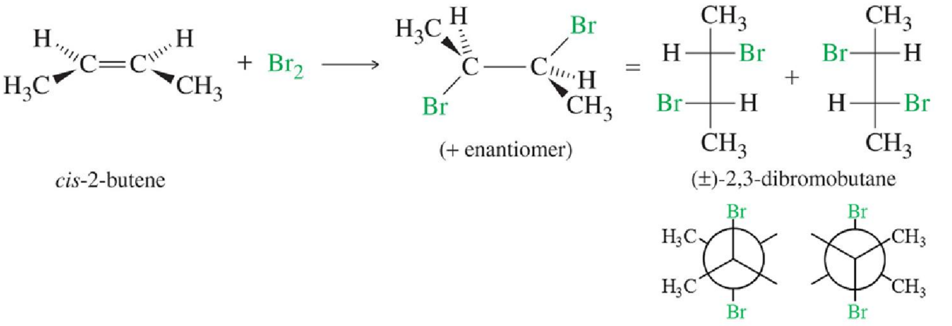
Electrophilic addition

Mechanism of addition of halogens



Electrophilic addition

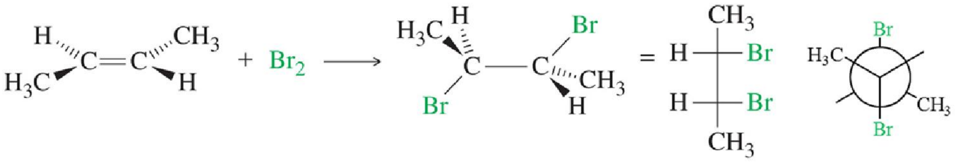
Examples of stereospecificity



cis-2-butene

(+ enantiomer)

(±)-2,3-dibromobutane

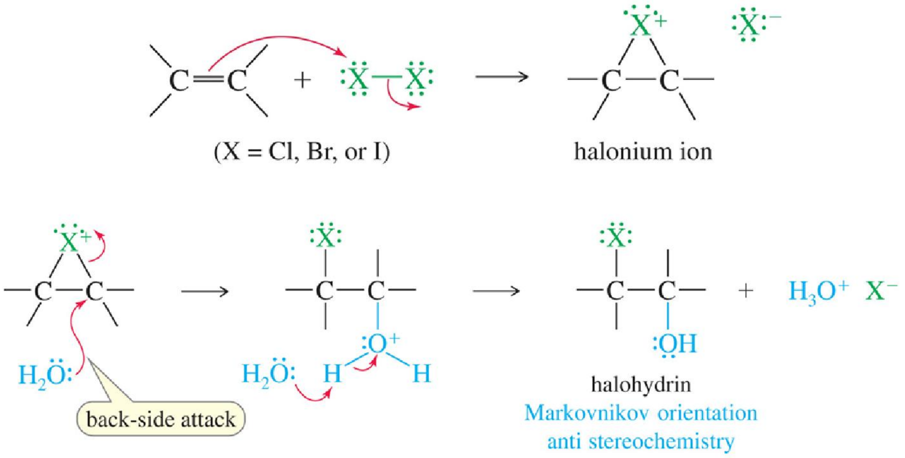


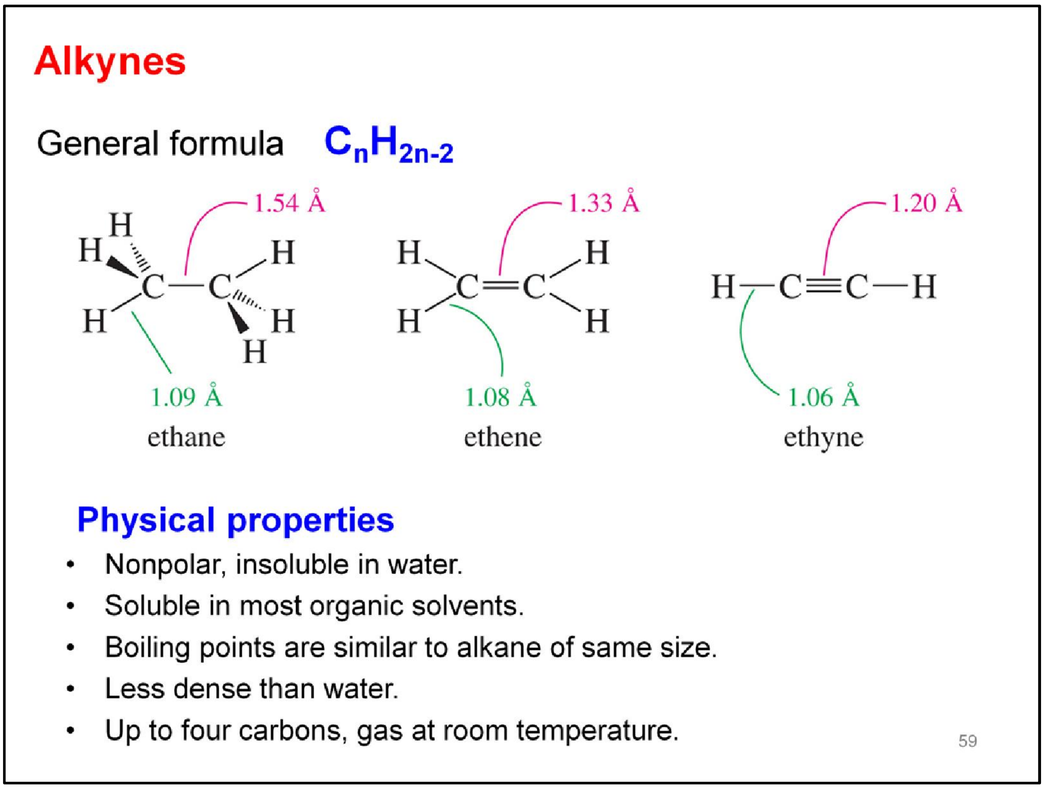
trans-2-butene

meso-2,3-dibromobutane

Electrophilic addition

Mechanism of halohydrin formation





Alkynes

General formula C_nH_{2n-2}

Physical properties

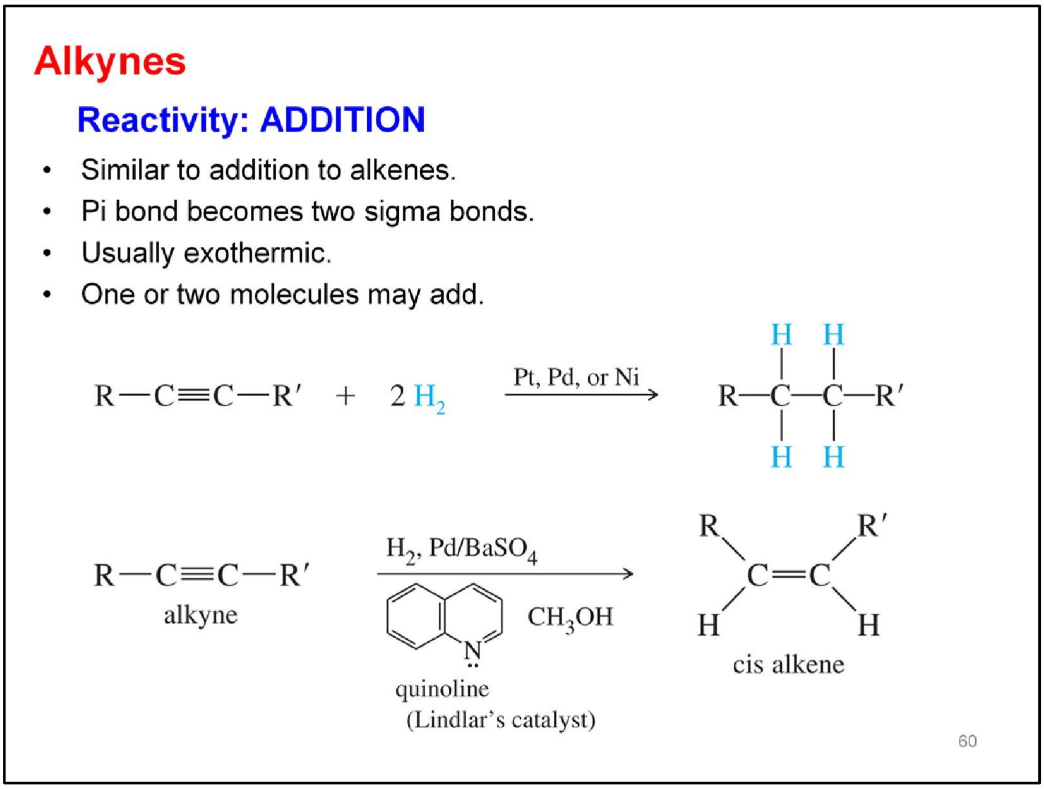
- Nonpolar, insoluble in water.
- Soluble in most organic solvents.
- Boiling points are similar to alkane of same size.
- Less dense than water.
- Up to four carbons, gas at room temperature.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkynes

Reactivity: ADDITION

- Similar to addition to alkenes.
- Pi bond becomes two sigma bonds.
- Usually exothermic.
- One or two molecules may add.

$$R-C\equiv C-R' + 2\,H_2 \xrightarrow{\text{Pt, Pd, or Ni}} R-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-R'$$

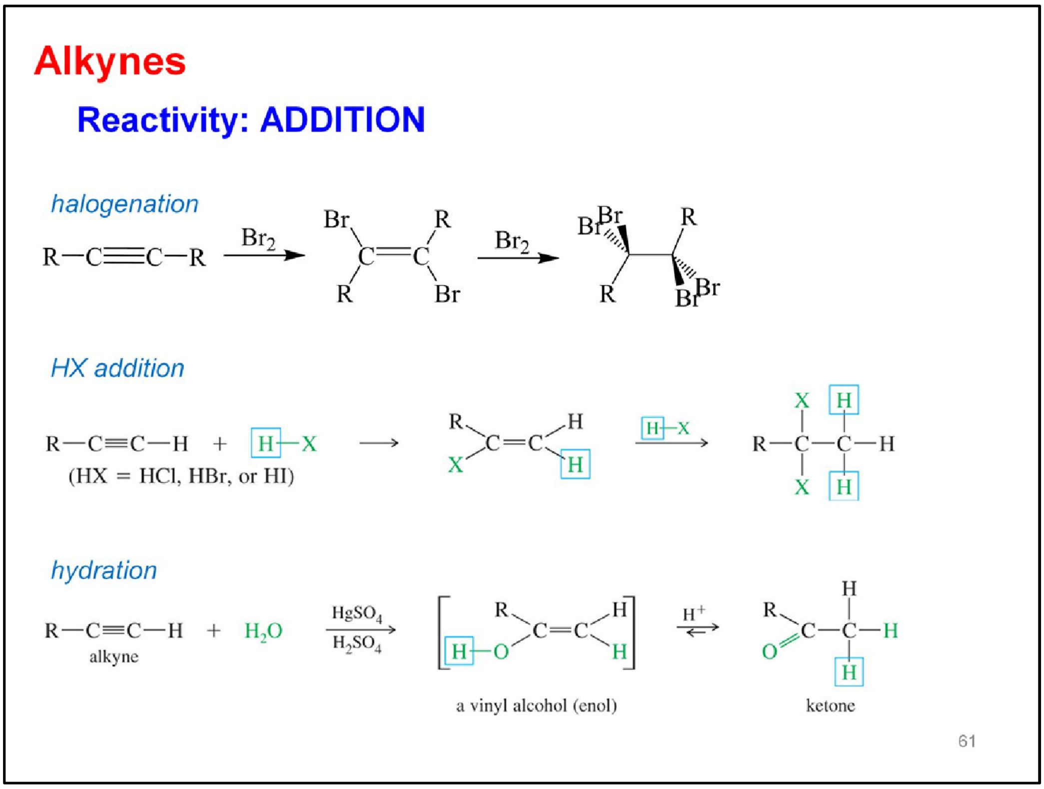
$$R-C\equiv C-R' \xrightarrow[\text{CH}_3\text{OH}]{H_2,\ \text{Pd/BaSO}_4}$$

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkynes

Reactivity: ADDITION

halogenation

HX addition

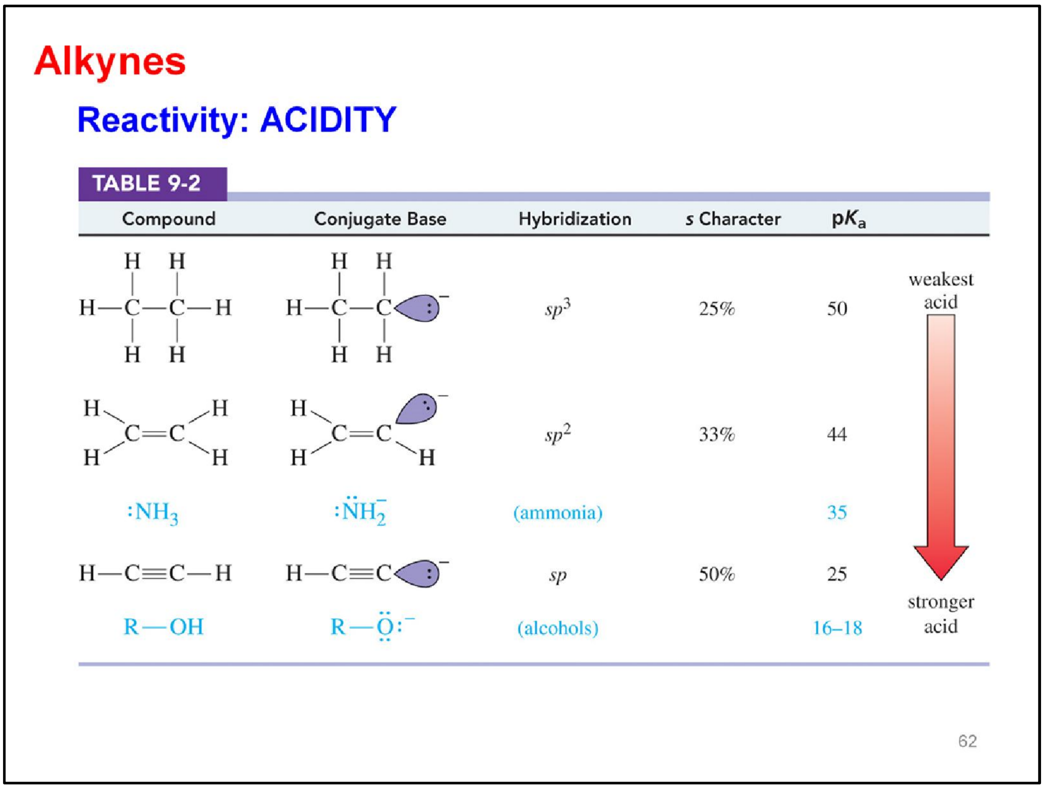
hydration

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkynes

Reactivity: ACIDITY

TABLE 9-2

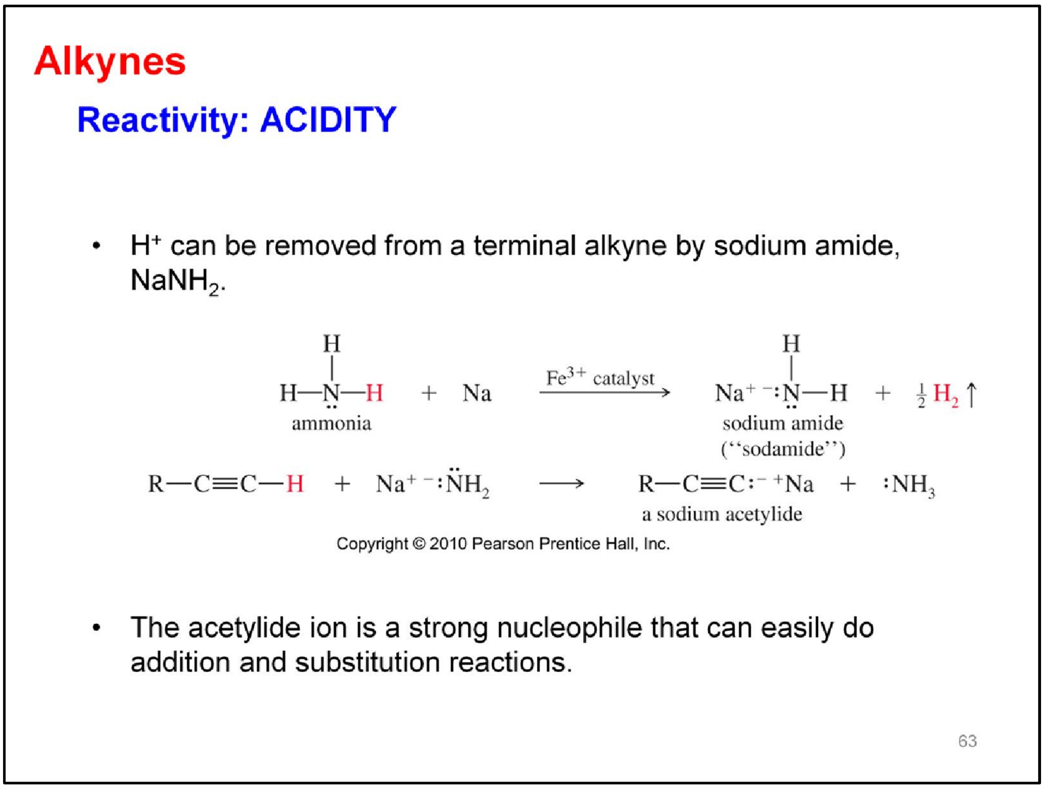
Compound	Conjugate Base	Hybridization	s Character	pK_a	
H H H—C—C—H H H	H H H—C—C:$^-$ H H	sp^3	25%	50	weakest acid
H H C=C H H	H C=C:$^-$ H H	sp^2	33%	44	
:NH_3	:$\ddot{N}H_2^-$	(ammonia)		35	
H—C≡C—H	H—C≡C:$^-$	sp	50%	25	
R—OH	R—$\ddot{O}$:$^-$	(alcohols)		16–18	stronger acid

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkynes

Reactivity: ACIDITY

- H^+ can be removed from a terminal alkyne by sodium amide, $NaNH_2$.

$$\mathrm{H{-}\overset{\displaystyle H}{\underset{..}{N}}{-}H} + \mathrm{Na} \xrightarrow{\mathrm{Fe^{3+}\ catalyst}} \mathrm{Na^{+}\ {}^{-}{:}\overset{\displaystyle H}{\underset{..}{N}}{-}H} + \tfrac{1}{2}\,\mathrm{H_2}\uparrow$$

ammonia

sodium amide
(“sodamide”)

$$\mathrm{R{-}C{\equiv}C{-}H} + \mathrm{Na^{+}\ {}^{-}{:}\ddot{N}H_2} \longrightarrow \mathrm{R{-}C{\equiv}C{:}^{-}\ {}^{+}Na} + \mathrm{{:}NH_3}$$

a sodium acetylide

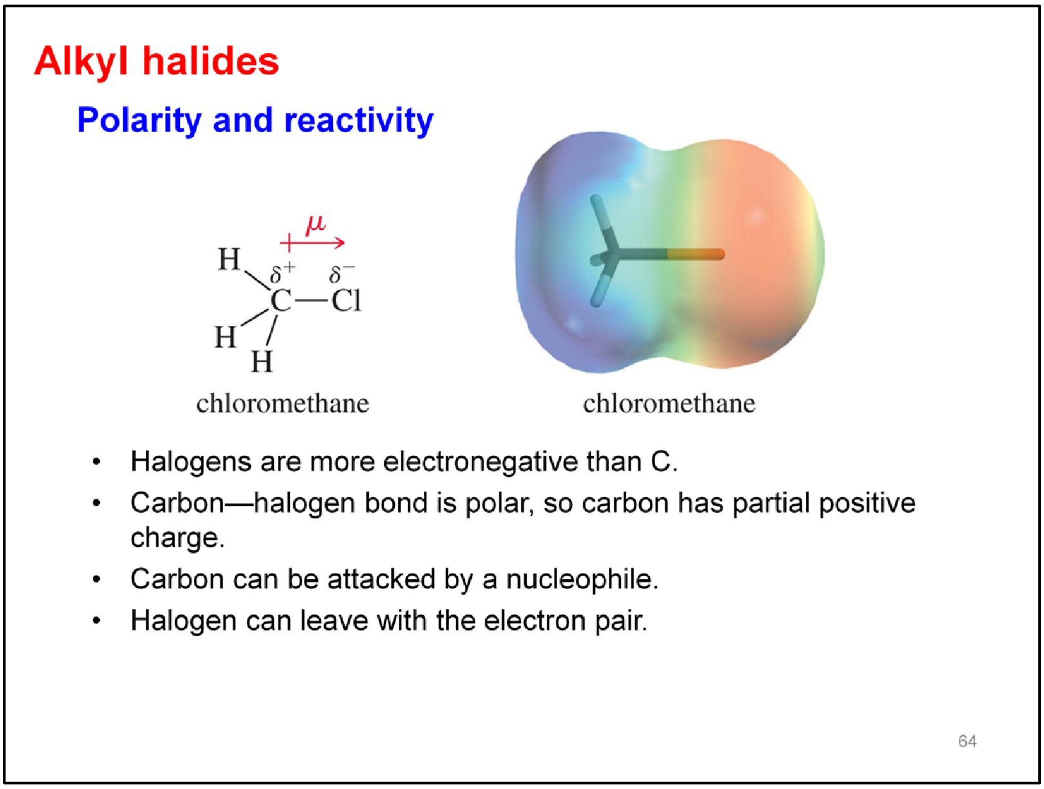
- The acetylide ion is a strong nucleophile that can easily do addition and substitution reactions.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkyl halides

Polarity and reactivity

chloromethane

chloromethane

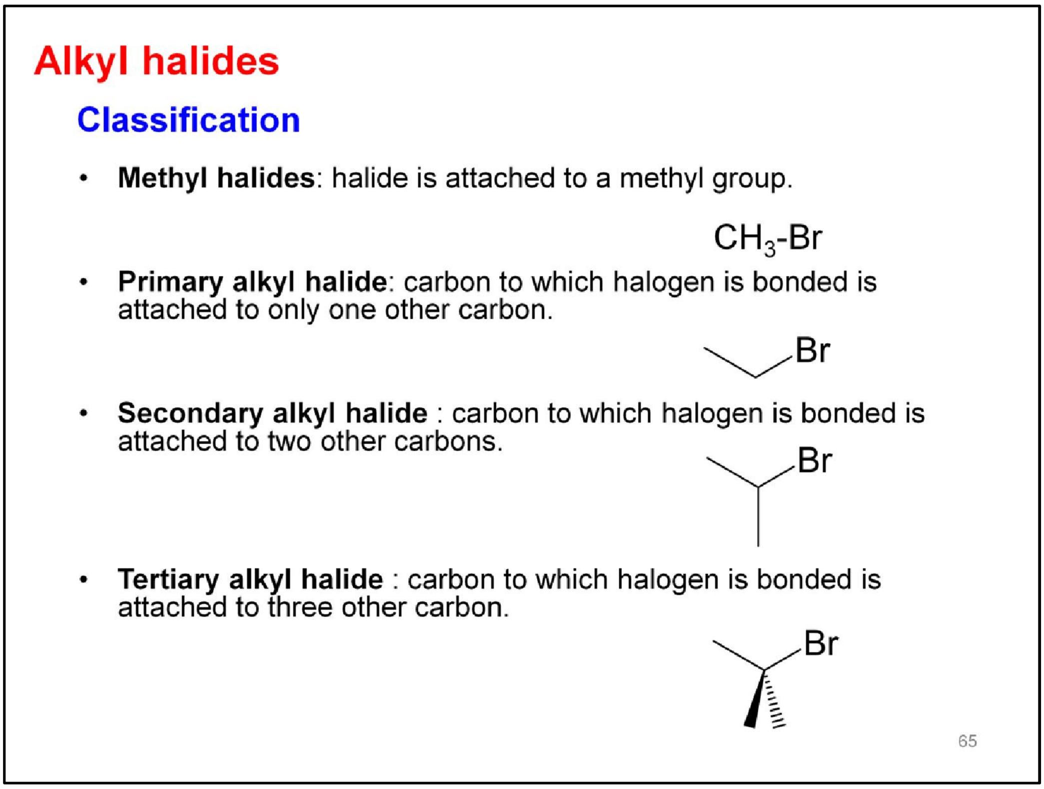
- Halogens are more electronegative than C.
- Carbon—halogen bond is polar, so carbon has partial positive charge.
- Carbon can be attacked by a nucleophile.
- Halogen can leave with the electron pair.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkyl halides

Classification

- **Methyl halides**: halide is attached to a methyl group.

CH_3-Br

- **Primary alkyl halide**: carbon to which halogen is bonded is attached to only one other carbon.

- **Secondary alkyl halide** : carbon to which halogen is bonded is attached to two other carbons.

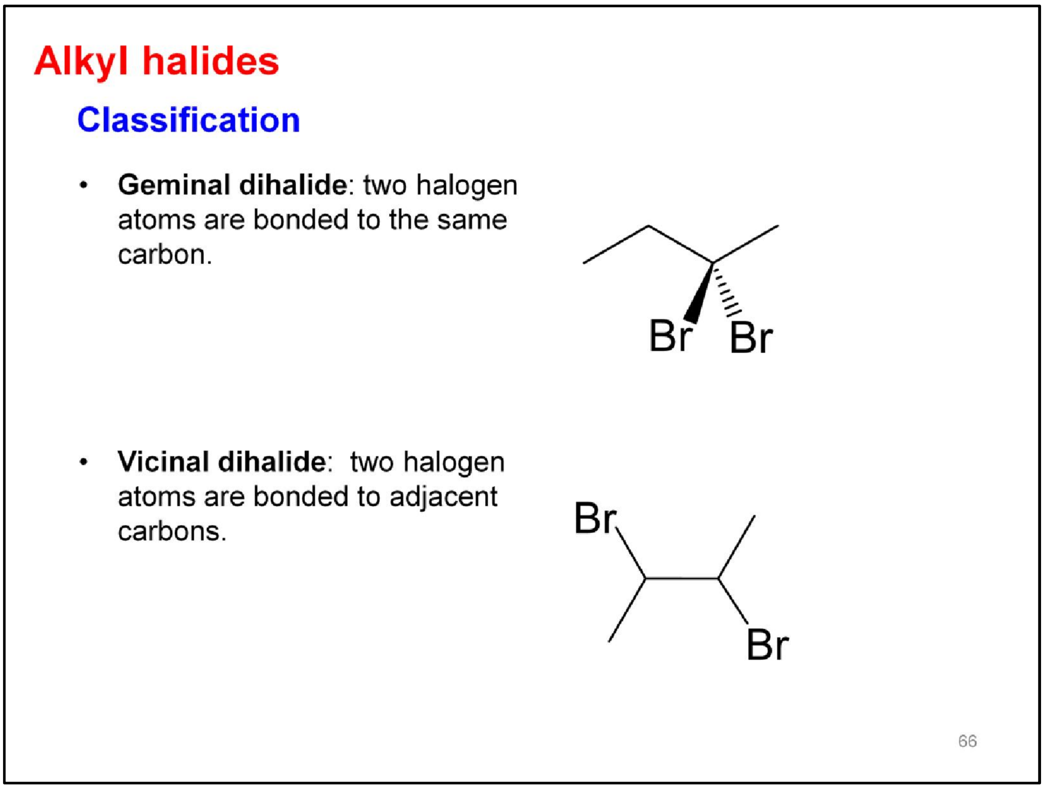
- **Tertiary alkyl halide** : carbon to which halogen is bonded is attached to three other carbon.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkyl halides

Classification

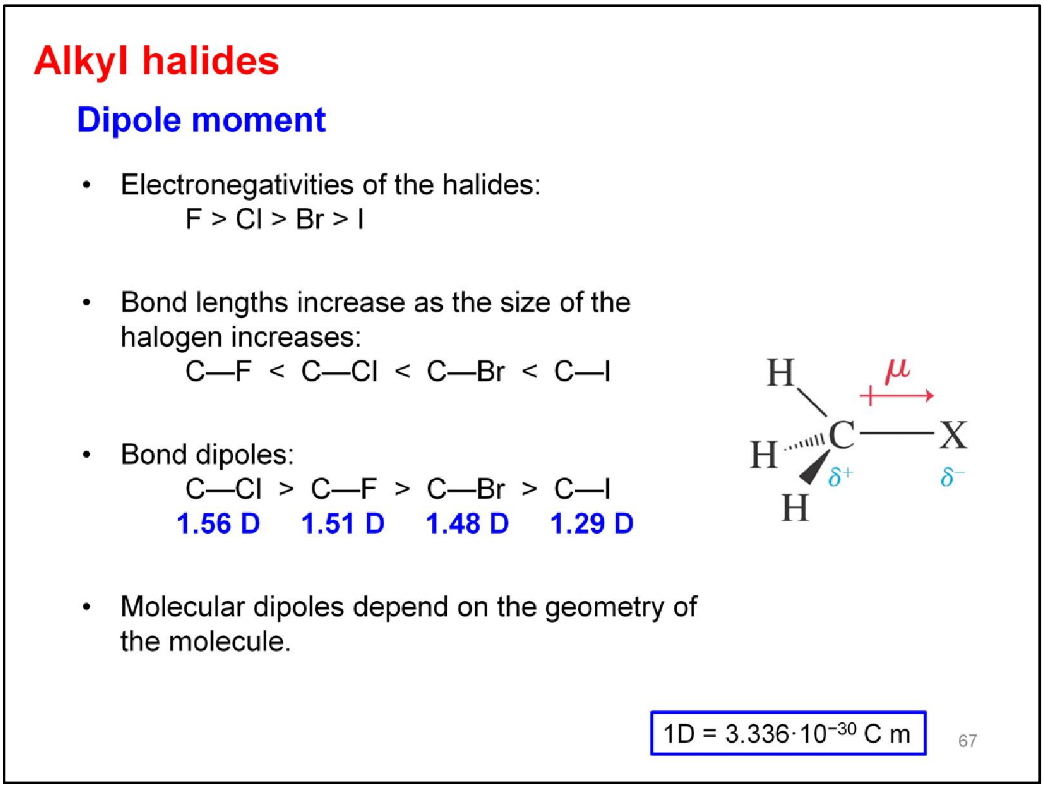
- **Geminal dihalide**: two halogen atoms are bonded to the same carbon.
- **Vicinal dihalide**: two halogen atoms are bonded to adjacent carbons.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkyl halides

Dipole moment

- Electronegativities of the halides:
  F > Cl > Br > I
- Bond lengths increase as the size of the halogen increases:
  C—F < C—Cl < C—Br < C—I
- Bond dipoles:
  C—Cl > C—F > C—Br > C—I
  1.56 D 1.51 D 1.48 D 1.29 D
- Molecular dipoles depend on the geometry of the molecule.

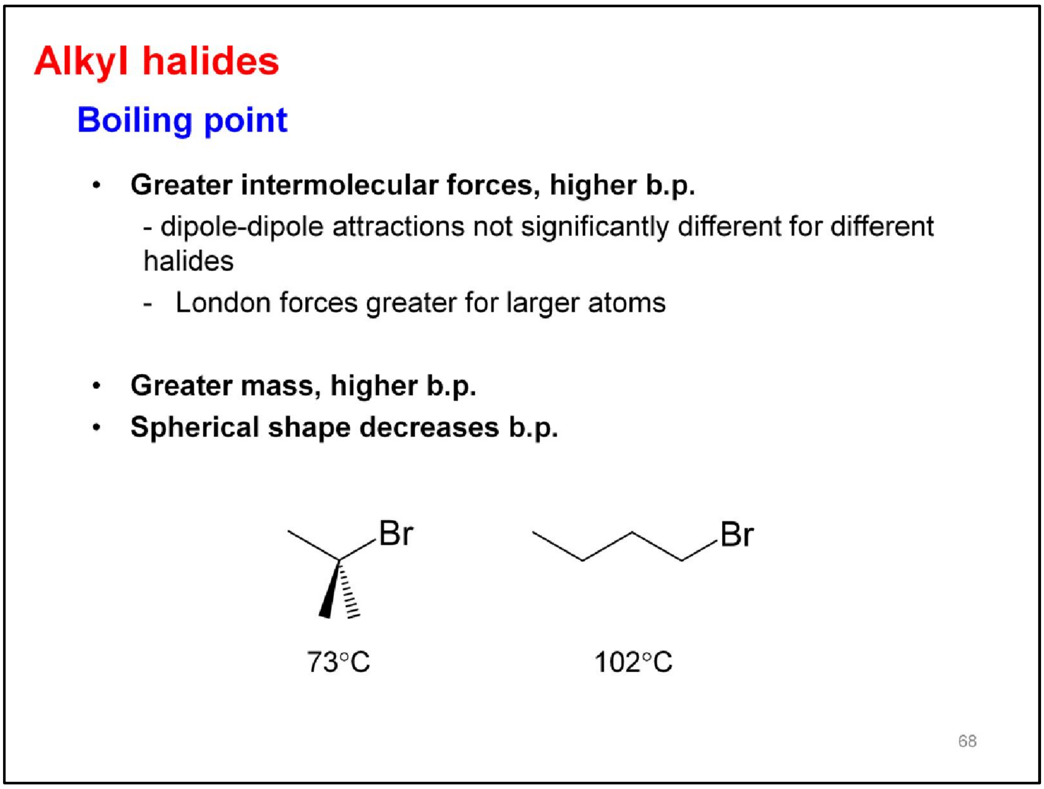
$1D = 3.336 \cdot 10^{-30}$ C m

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkyl halides

Boiling point

- **Greater intermolecular forces, higher b.p.**
  - dipole-dipole attractions not significantly different for different halides
  - London forces greater for larger atoms
- **Greater mass, higher b.p.**
- **Spherical shape decreases b.p.**

73°C

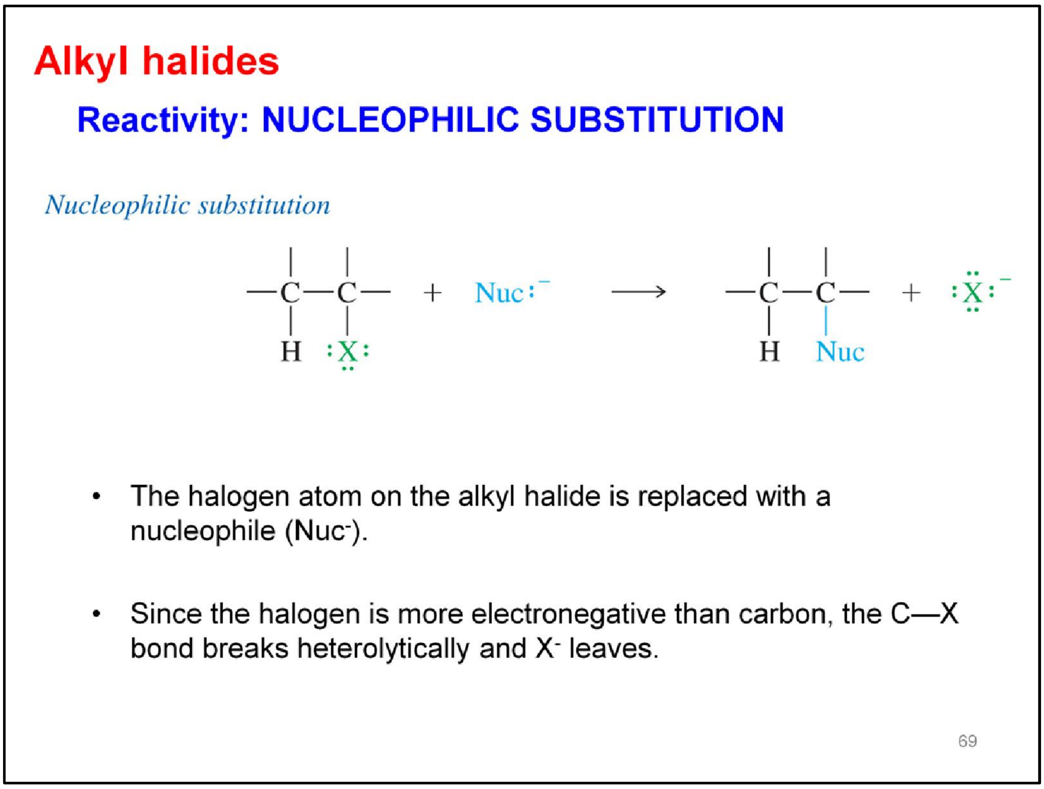
102°C

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkyl halides

Reactivity: NUCLEOPHILIC SUBSTITUTION

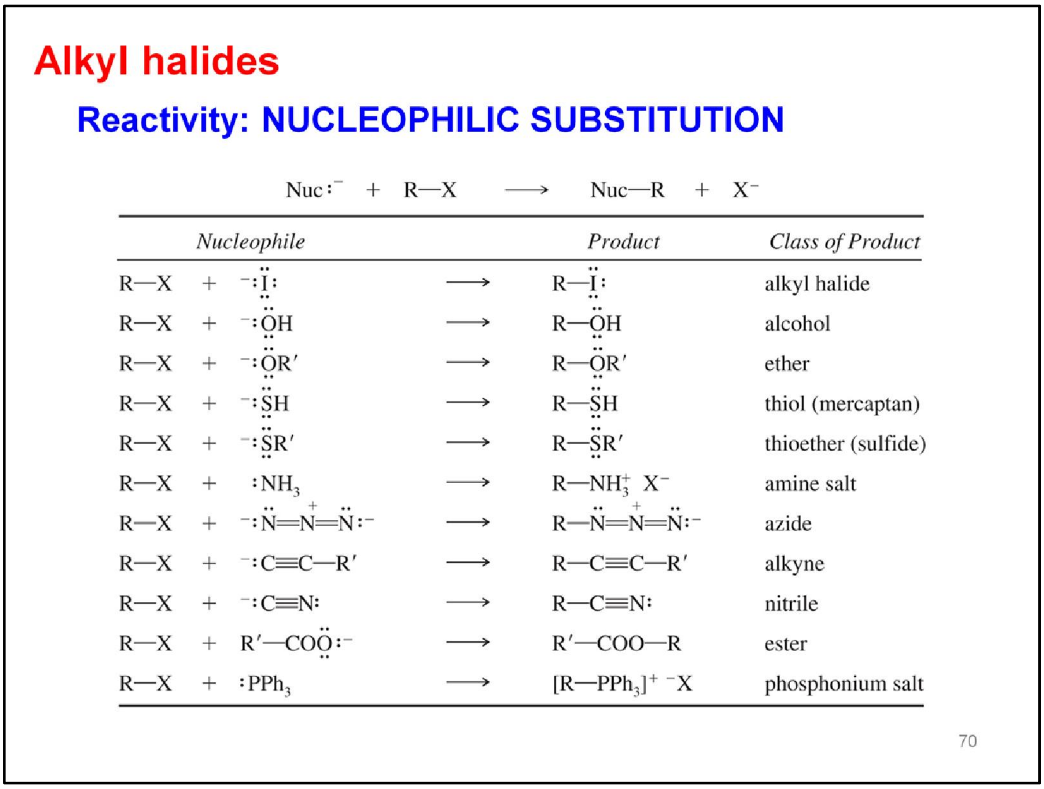
- The halogen atom on the alkyl halide is replaced with a nucleophile (Nuc^-).
- Since the halogen is more electronegative than carbon, the C—X bond breaks heterolytically and X^- leaves.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alkyl halides

Reactivity: NUCLEOPHILIC SUBSTITUTION

$$\mathrm{Nuc}{:}^{-} + \mathrm{R{-}X} \longrightarrow \mathrm{Nuc{-}R} + \mathrm{X}^{-}$$

Nucleophile				Product	Class of Product
R—X	+	$^{-}{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{I}}}{:}$	$\longrightarrow$	$\mathrm{R{-}}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{I}}}{:}$	alkyl halide
R—X	+	$^{-}{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{O}}}\mathrm{H}$	$\longrightarrow$	$\mathrm{R{-}}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{O}}}\mathrm{H}$	alcohol
R—X	+	$^{-}{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{O}}}\mathrm{R'}$	$\longrightarrow$	$\mathrm{R{-}}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{O}}}\mathrm{R'}$	ether
R—X	+	$^{-}{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{S}}}\mathrm{H}$	$\longrightarrow$	$\mathrm{R{-}}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{S}}}\mathrm{H}$	thiol (mercaptan)
R—X	+	$^{-}{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{S}}}\mathrm{R'}$	$\longrightarrow$	$\mathrm{R{-}}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{S}}}\mathrm{R'}$	thioether (sulfide)
R—X	+	${:}\mathrm{NH_3}$	$\longrightarrow$	$\mathrm{R{-}NH_3^{+}}\ \mathrm{X^{-}}$	amine salt
R—X	+	$^{-}{:}\overset{\cdot\cdot}{\mathrm{N}}{=}\overset{+}{\mathrm{N}}{=}\overset{\cdot\cdot}{\mathrm{N}}{:}^{-}$	$\longrightarrow$	$\mathrm{R{-}}\overset{\cdot\cdot}{\mathrm{N}}{=}\overset{+}{\mathrm{N}}{=}\overset{\cdot\cdot}{\mathrm{N}}{:}^{-}$	azide
R—X	+	$^{-}{:}\mathrm{C{\equiv}C{-}R'}$	$\longrightarrow$	$\mathrm{R{-}C{\equiv}C{-}R'}$	alkyne
R—X	+	$^{-}{:}\mathrm{C{\equiv}N}{:}$	$\longrightarrow$	$\mathrm{R{-}C{\equiv}N}{:}$	nitrile
R—X	+	$\mathrm{R'{-}CO}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{O}}}{:}^{-}$	$\longrightarrow$	$\mathrm{R'{-}COO{-}R}$	ester
R—X	+	${:}\mathrm{PPh_3}$	$\longrightarrow$	$[\mathrm{R{-}PPh_3}]^{+}\ {}^{-}\mathrm{X}$	phosphonium salt

Figure: 03_04.jpg

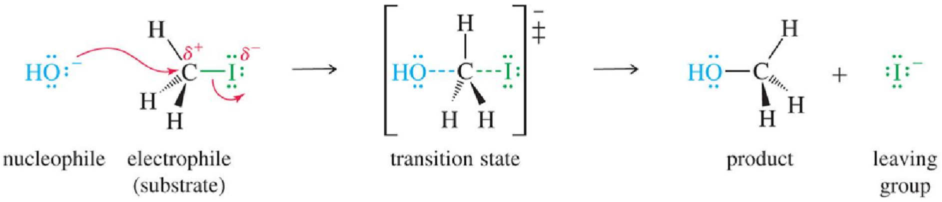
Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

Nucleophilic substitution

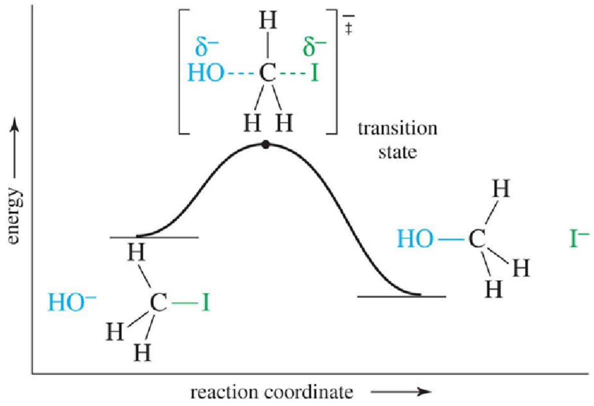
S_N2 Mechanism



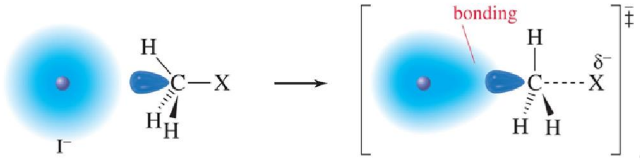
- Bimolecular nucleophilic substitution.
- Concerted reaction: new bond forming and old bond breaking at same time.
- Rate is first order in each reactant.

Nucleophilic substitution

S_N2 Energy diagram



- The S_N2 reaction is a one-step reaction.
- Transition state is highest in energy.

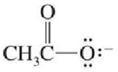


transition state

Nucleophilic substitution

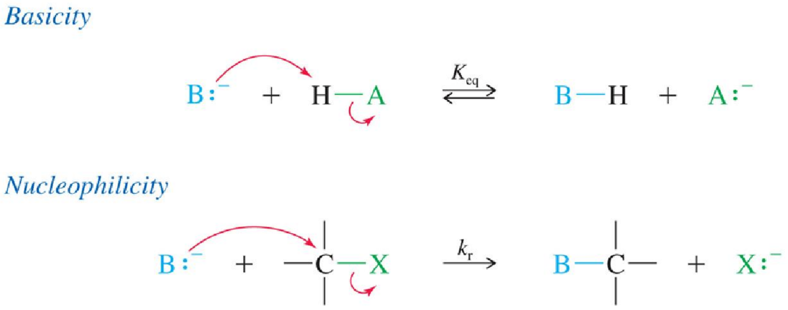
S_N2: Nucleophilic strength

- Stronger nucleophiles react faster.
- Strong bases are strong nucleophiles, but not all strong nucleophiles are basic.

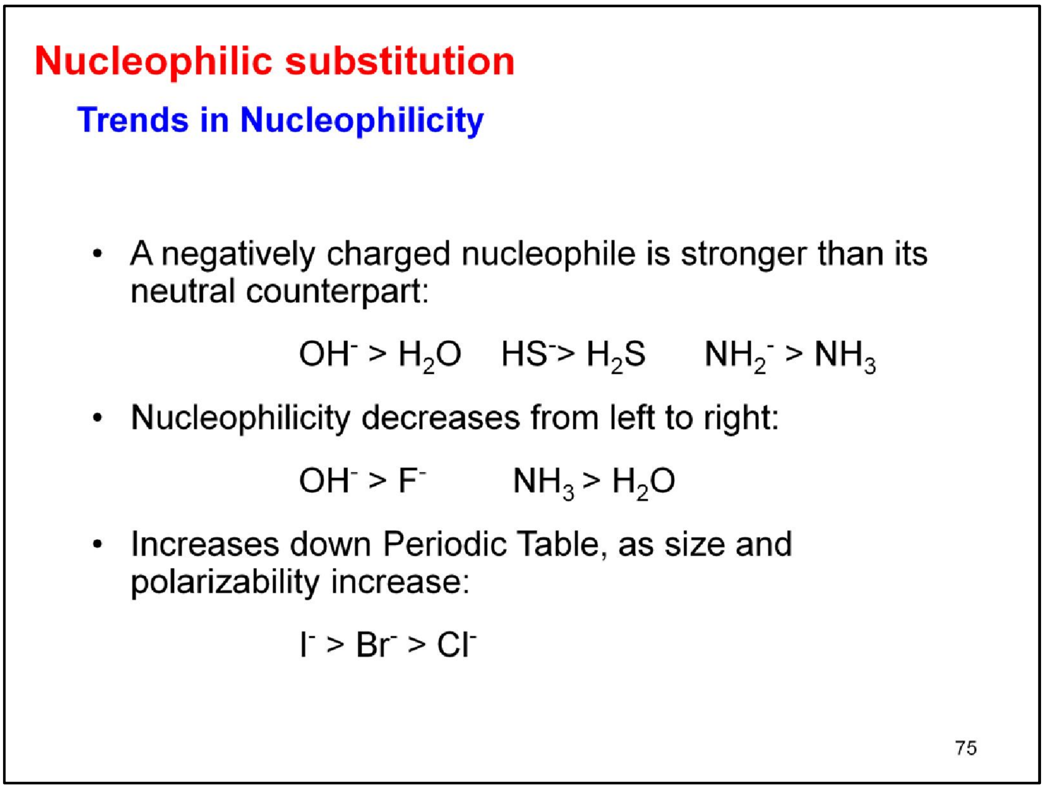
strong nucleophiles	$(CH_3CH_2)_3P:$ $^-:\ddot{S}-H$ $:\ddot{I}:^-$ $(CH_3CH_2)_2\ddot{N}H$ $^-:C\equiv N$ $(CH_3CH_2)_3N:$ $H-\ddot{O}:^-$ $CH_3-\ddot{O}:^-$	moderate nucleophiles	$:\ddot{Br}:^-$ $:NH_3$ $CH_3-\ddot{S}-CH_3$ $:\ddot{Cl}:^-$  $CH_3\overset{O}{\overset{\|}{C}}-\ddot{O}:^-$
		weak nucleophiles	$:\ddot{F}:^-$ $H-\ddot{O}-H$ $CH_3-\ddot{O}-H$

Nucleophilic substitution

Basicity vs Nucleophilicity



- Basicity is defined by the equilibrium constant for abstracting a proton.
- Nucleophilicity is defined by the rate of attack on the electrophilic carbon atom



Nucleophilic substitution

Trends in Nucleophilicity

- A negatively charged nucleophile is stronger than its neutral counterpart:

  $OH^- > H_2O$ $HS^- > H_2S$ $NH_2^- > NH_3$

- Nucleophilicity decreases from left to right:

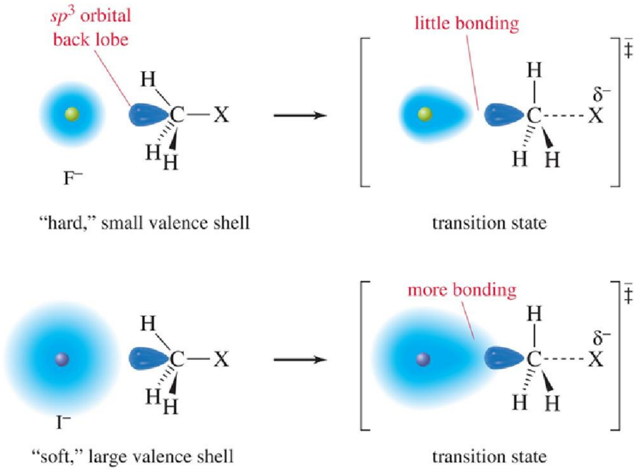
  $OH^- > F^-$ $NH_3 > H_2O$

- Increases down Periodic Table, as size and polarizability increase:

  $I^- > Br^- > Cl^-$

Nucleophilic substitution

Polarizability effect

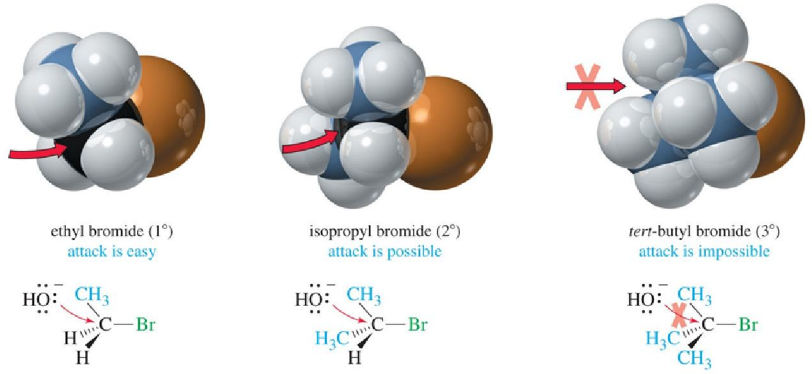


Bigger atoms have a soft shell which can start to overlap the carbon atom from a farther distance.

Nucleophilic substitution

S_N2: Structure of substrate

- Nucleophile approaches from the back side.
- It must overlap the back lobe of the C—X sp^3 orbital.


ethyl bromide (1°)
attack is easy

isopropyl bromide (2°)
attack is possible

tert-butyl bromide (3°)
attack is impossible

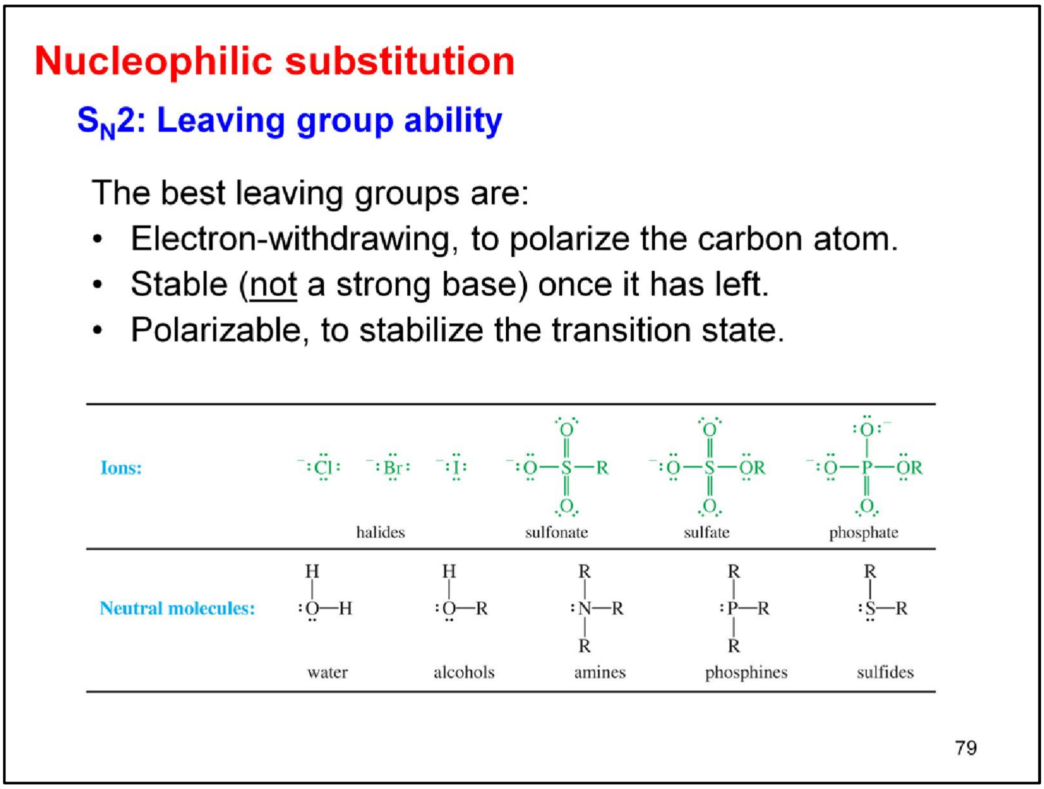
Nucleophilic substitution

S_N2: Structure of substrate

- Relative rates for S_N2:

  $CH_3X > 1° > 2° >> 3°$

- Tertiary halides do not react via the S_N2 mechanism, due to steric hindrance.



Nucleophilic substitution

S_N2: Leaving group ability

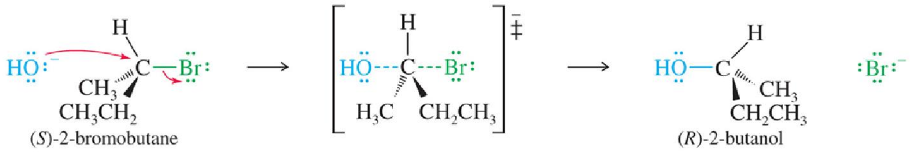
The best leaving groups are:

- Electron-withdrawing, to polarize the carbon atom.
- Stable (not a strong base) once it has left.
- Polarizable, to stabilize the transition state.

Nucleophilic substitution

S_N2: Stereochemistry

S_N2 reactions will result in an inversion of configuration.



Nucleophilic substitution

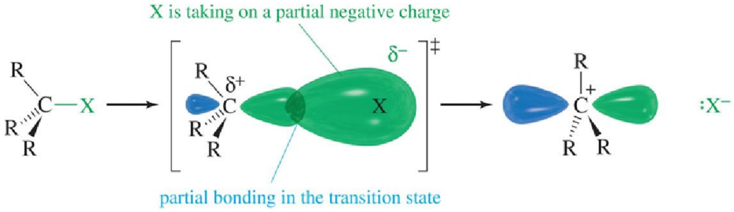
S_N1 Mechanism

- The S_N1 reaction is a unimolecular nucleophilic substitution.
- It is a two step reaction with a carbocation intermediate.
- Rate is first order in the alkyl halide, zero order in the nucleophile.
- Racemization occurs.

Nucleophilic substitution

S_N1 Mechanism

1. Formation of carbocation (rate determining step)



X is taking on a partial negative charge

partial bonding in the transition state

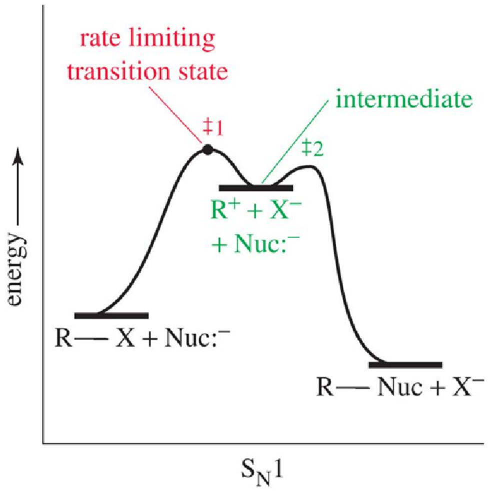
2. The nucleophile attacks the carbocation, forming the product. If the nucleophile was neutral, a third step (deprotonation) will be needed.

$$R^+ + Nuc:^- \longrightarrow R—Nuc$$

Nucleophilic substitution

S_N1 Energy diagram

- Forming the carbocation is an endothermic step.
- Step 2 is fast with a low activation energy.



Nucleophilic substitution

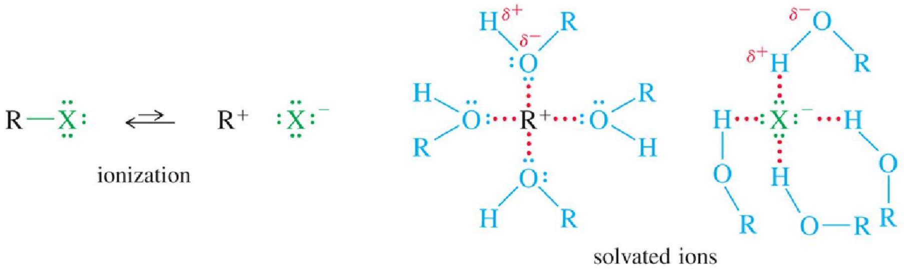
S_N1: Reaction rates

- Order of reactivity follows stability of carbocations (opposite to S_N2)
  - 3° > 2° > 1° >> CH_3X
  - More stable carbocation requires less energy to form.
- A better leaving group will increase the rate of the reaction.

Nucleophilic substitution

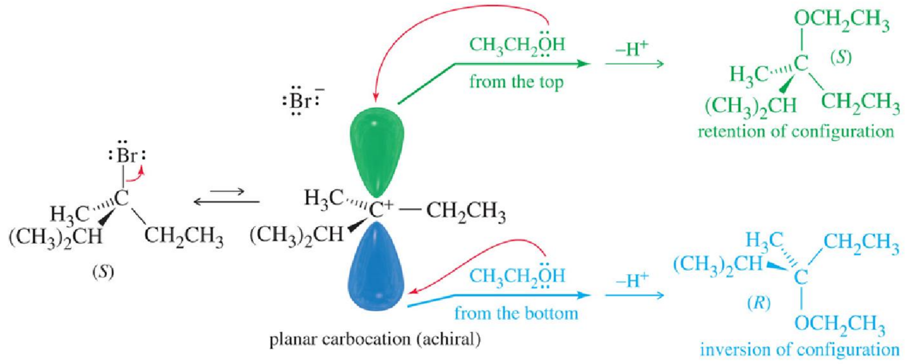
S_N1: Solvation effect

Polar <u>protic</u> solvent are the best choice because it can solvate both ions strongly through hydrogen bonding.



Nucleophilic substitution

S_N1: Stereochemistry

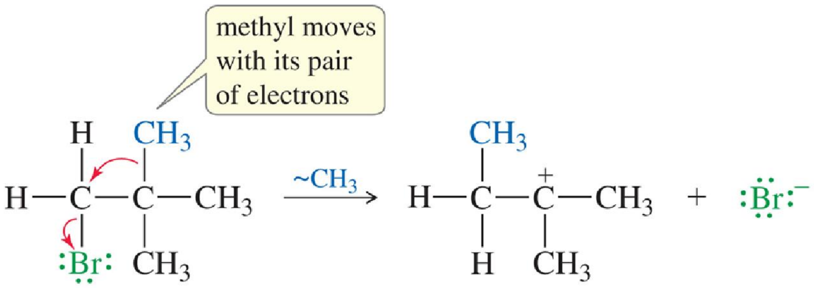


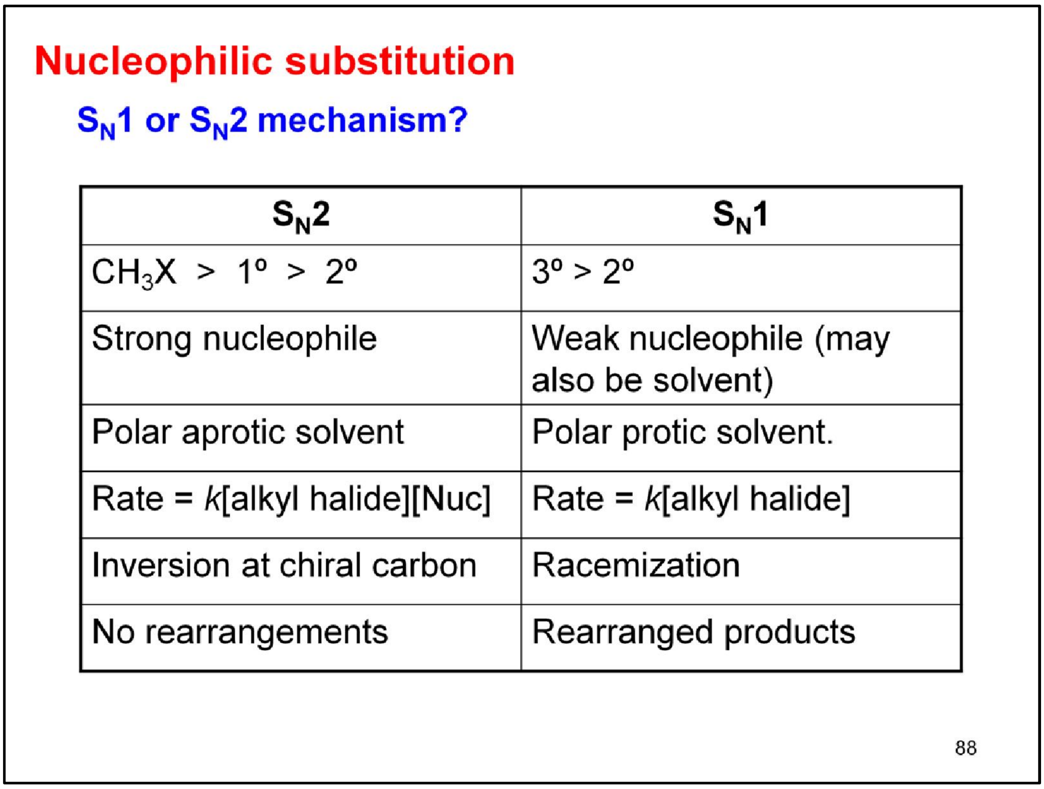
The S_N1 reaction produces mixtures of enantiomers. There is usually more inversion than retention of configuration.

Nucleophilic substitution

S_N1: Rearrangements

- Carbocations can rearrange to form a more stable carbocation.
- Hydride shift: H^- on adjacent carbon bonds with C^+.
- Methyl shift: CH_3^- moves from adjacent carbon <u>if</u> no hydrogens are available.

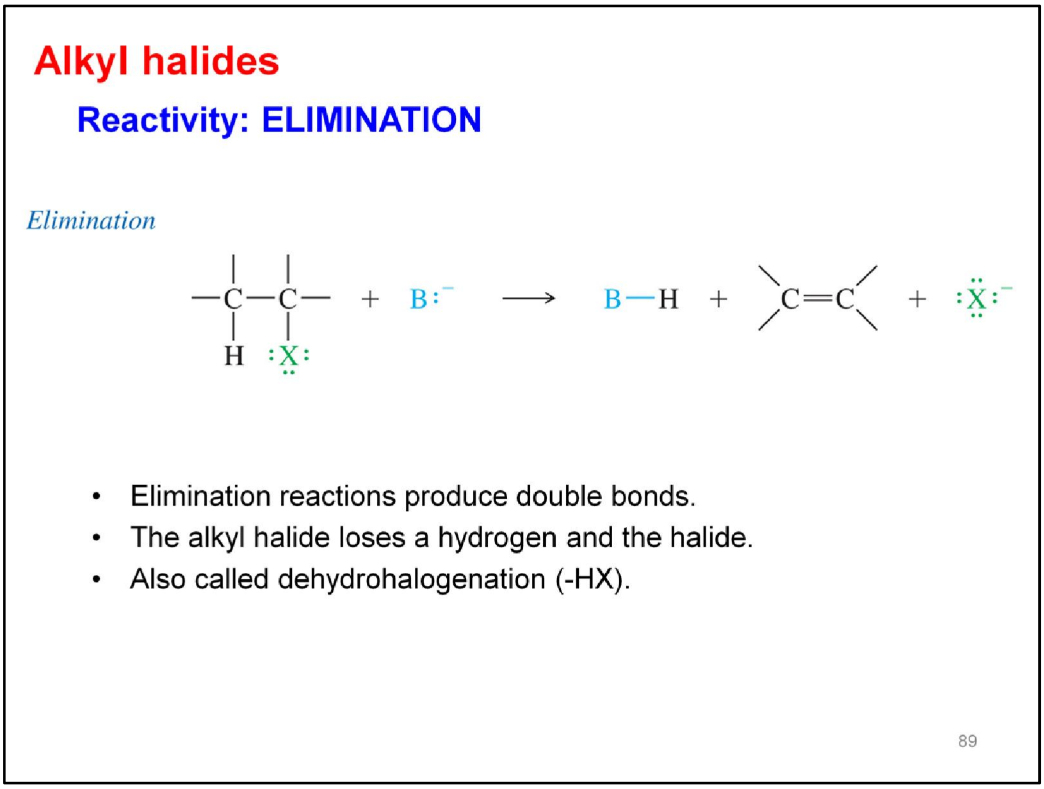

methyl moves with its pair of electrons



Nucleophilic substitution

S_N1 or S_N2 mechanism?

S_N2	S_N1
CH_3X > 1º > 2º	3º > 2º
Strong nucleophile	Weak nucleophile (may also be solvent)
Polar aprotic solvent	Polar protic solvent.
Rate = k[alkyl halide][Nuc]	Rate = k[alkyl halide]
Inversion at chiral carbon	Racemization
No rearrangements	Rearranged products



Alkyl halides

Reactivity: ELIMINATION

Elimination

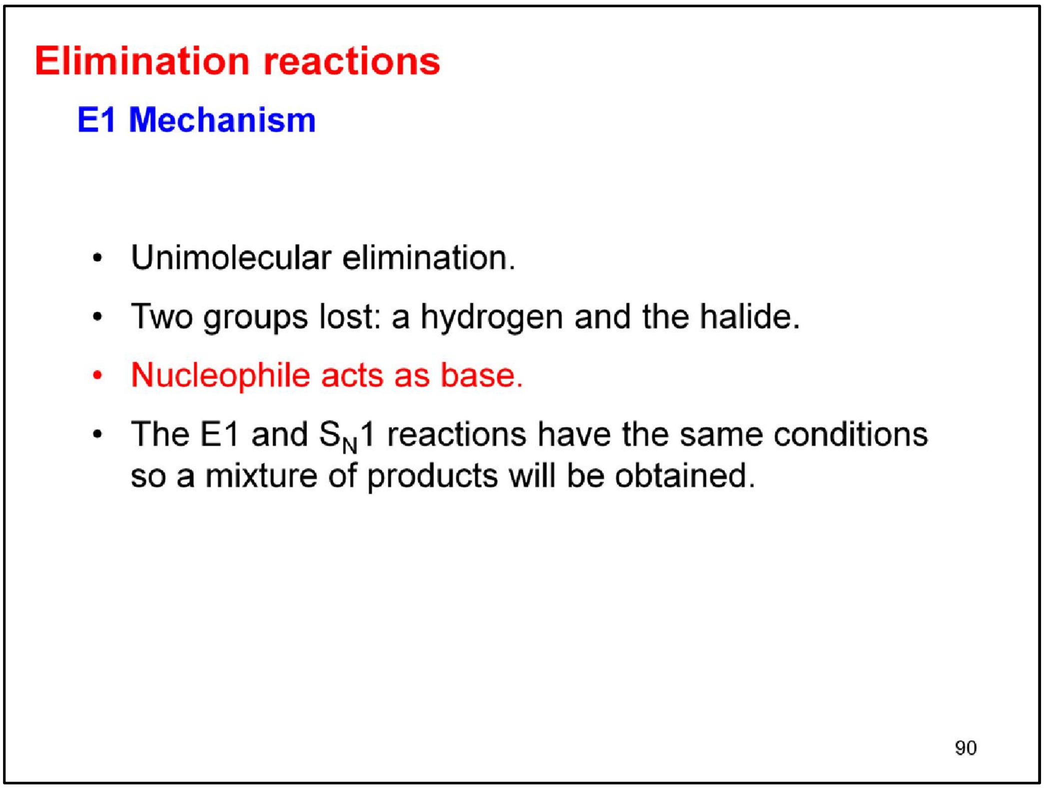
- Elimination reactions produce double bonds.
- The alkyl halide loses a hydrogen and the halide.
- Also called dehydrohalogenation (-HX).

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



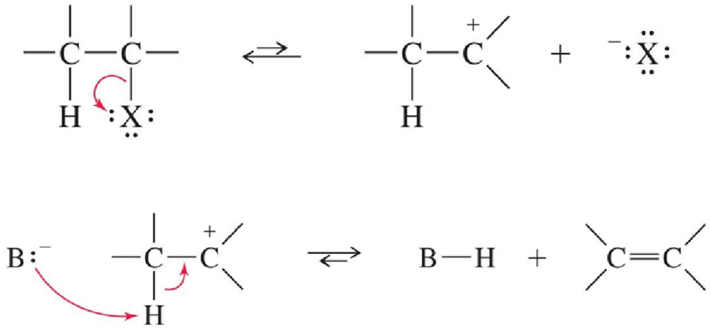
Elimination reactions

E1 Mechanism

- Unimolecular elimination.
- Two groups lost: a hydrogen and the halide.
- Nucleophile acts as base.
- The E1 and S_N1 reactions have the same conditions so a mixture of products will be obtained.

Elimination reactions

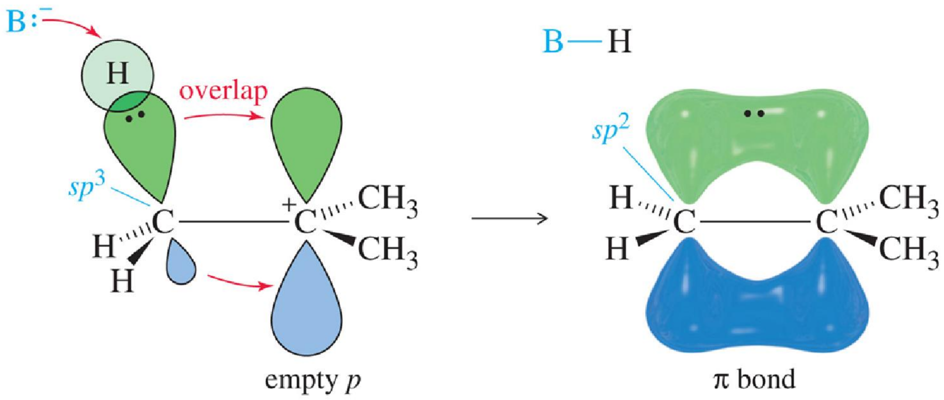
E1 Mechanism



- Step 1: halide ion leaves, forming a carbocation.
- Step 2: Base abstracts H^+ from adjacent carbon forming the double bond.

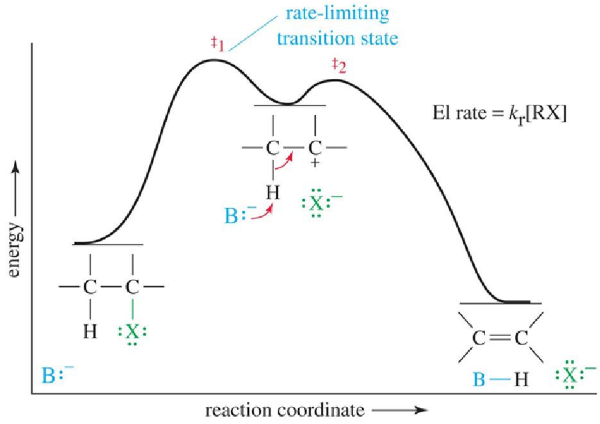
Elimination reactions

E1 Mechanism



Elimination reactions

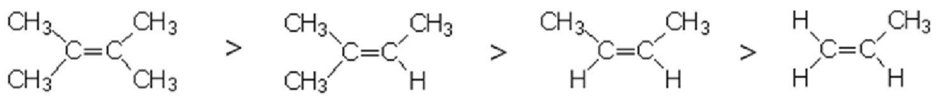
E1 Energy diagram



The E1 and the S_N1 reactions have the same first step: carbocation formation is the rate determining step for both mechanisms.

Elimination reactions

Double bond substitution patterns



tetrasubstituted trisubstituted disubstituted monosubstituted

- The more substituted double bond is more stable.
- If more than one elimination product is possible, the most-substituted alkene is the major product (most stable).

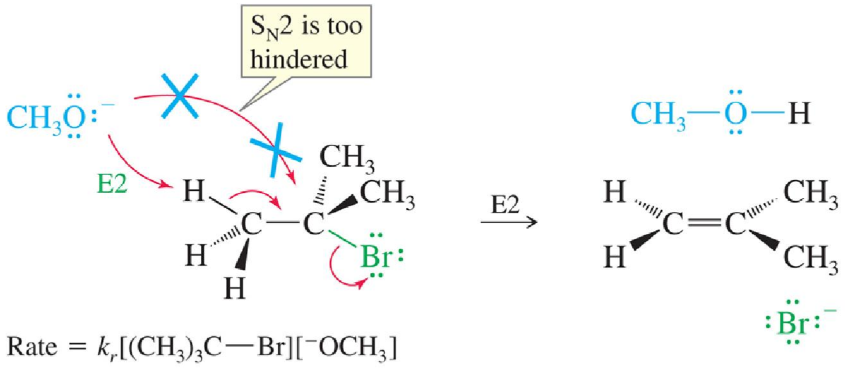
Elimination reactions

E2 Mechanism

- Elimination, bimolecular
- Requires a strong base
- This is a concerted reaction: the proton is abstracted, the double bond forms and the leaving group leaves, all in one step.

Elimination reactions

E2 Mechanism


S_N2 is too hindered

$$\text{Rate} = k_r[(CH_3)_3C—Br][^-OCH_3]$$

- Order of reactivity for alkyl halides:
  3° > 2 ° > 1°
- Mixture may form, but Zaitsev product predominates.

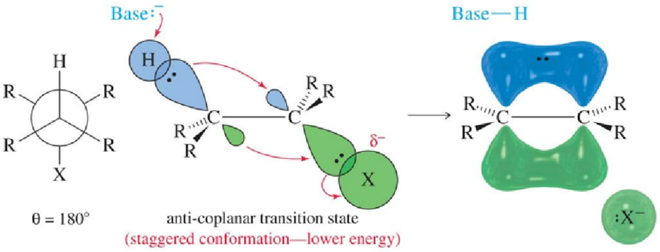
Elimination reactions

E2 stereochemistry

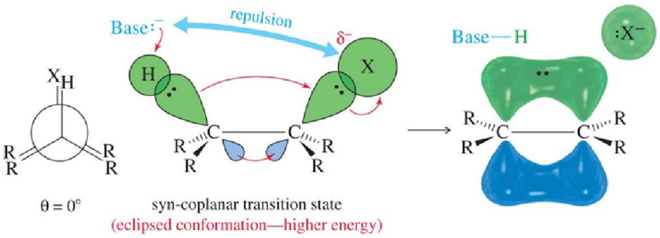
- The halide and the proton to be abstracted must be anti-coplanar (θ=180º) to each other for the elimination to occur.
- The orbitals of the hydrogen atom and the halide must be aligned so they can begin to form a pi bond in the transition state.
- The anti-coplanar arrangement minimizes any steric hindrance between the base and the leaving group.

Elimination reactions

E2 stereochemistry



anti-coplanar transition state
(staggered conformation—lower energy)



syn-coplanar transition state
(eclipsed conformation—higher energy)

Elimination reactions

E1 or E2 Mechanism?

Tertiary > Secondary	Tertiary > Secondary
Base strength unimportant (usually weak)	Strong base required
Good ionizing solvent	Solvent polarity not important.
Rate = *k*[alkyl halide]	Rate = *k*[alkylhalide][base]
More substituted product	More substituted product
No required geometry	Coplanar leaving groups (usually anti)
Rearranged products	No rearrangements

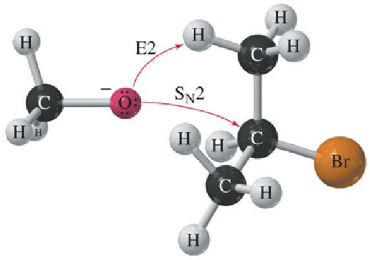
Elimination or substitution?

- Strength of the nucleophile determines order: Strong nucleophiles or bases promote bimolecular reactions.
- Primary halide usually undergo S_N2.
- Tertiary halide mixture of S_N1, E1 or E2. They cannot undergo S_N2.
- High temperature favors elimination.
- Bulky bases favor elimination.

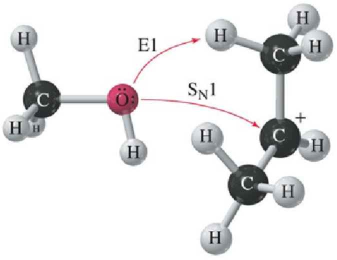
Elimination or substitution?

Secondary Alkyl Halides

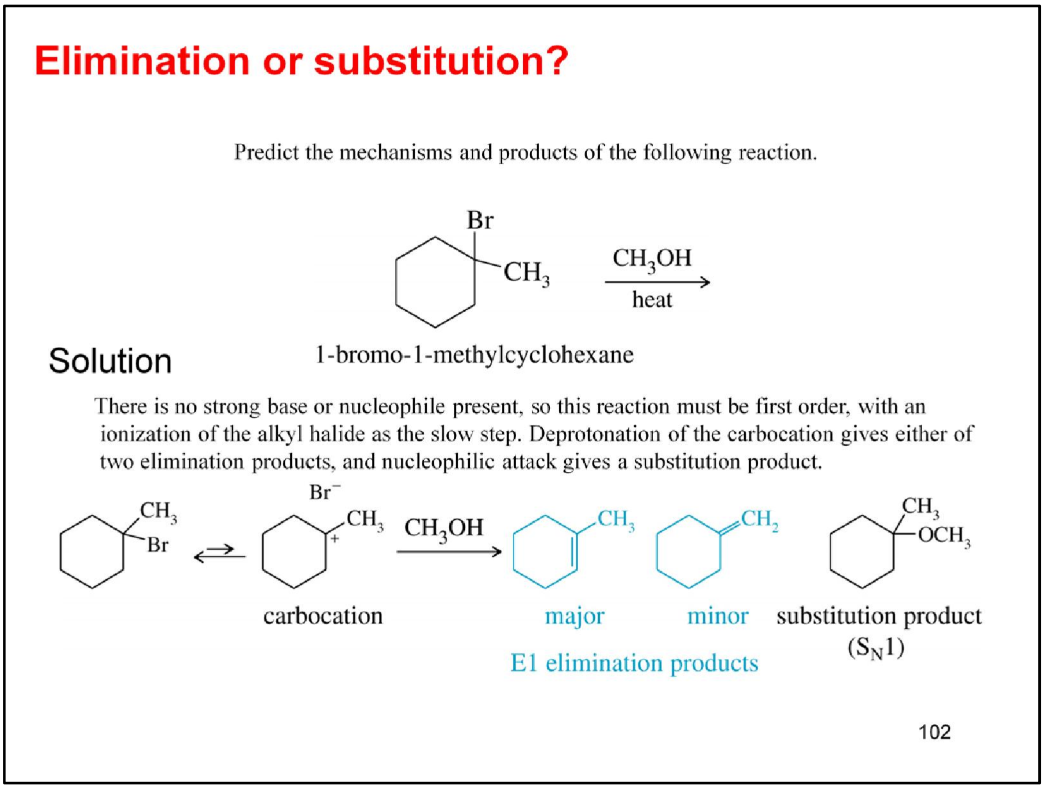
- Secondary alkyl halides are more challenging:
  - Strong nucleophiles will promote S_N2/E2
  - Weak nucleophiles promote S_N1/E1
- Strong nucleophiles with limited basicity favor S_N2. Bromide and iodide are good examples of these.



second-order conditions (strong base/nucleophile)



first-order conditions (weak base/nucleophile)



Elimination or substitution?

Predict the mechanisms and products of the following reaction.

1-bromo-1-methylcyclohexane

Solution

There is no strong base or nucleophile present, so this reaction must be first order, with an ionization of the alkyl halide as the slow step. Deprotonation of the carbocation gives either of two elimination products, and nucleophilic attack gives a substitution product.

carbocation

major

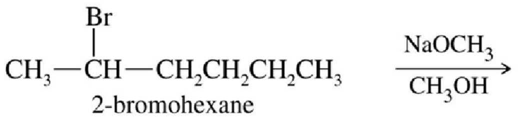
minor

E1 elimination products

substitution product (S_N1)

Elimination or substitution?

Predict the mechanisms and products of the following reaction.



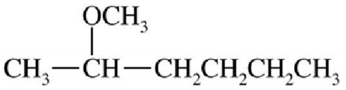
$$CH_3-\overset{\displaystyle Br}{\overset{|}{CH}}-CH_2CH_2CH_2CH_3 \xrightarrow[CH_3OH]{NaOCH_3}$$

2-bromohexane

Solution

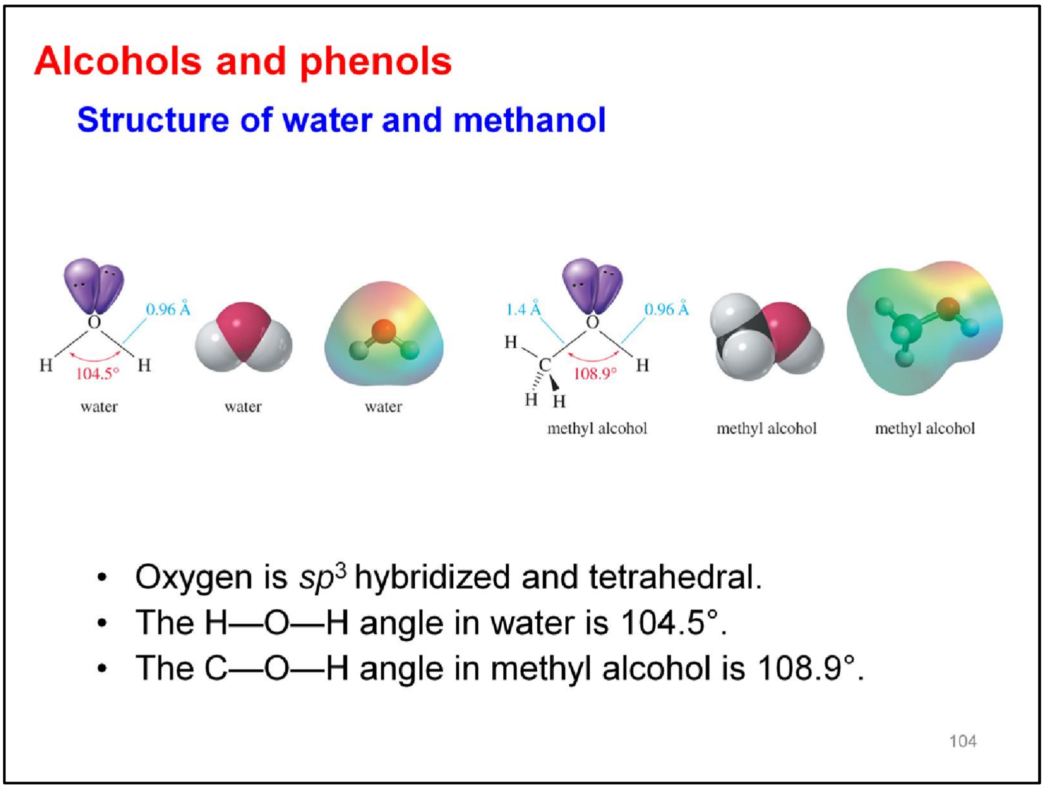
This reaction takes place with a strong base, so it is second order. This secondary halide can undergo both S_N2 substitution and E2 elimination. Both products will be formed, with the relative proportions of substitution and elimination depending on the reaction conditions.

$$\underbrace{\underset{\text{major}}{CH_3-CH{=}CH-CH_2CH_2CH_3} \quad \underset{\text{minor}}{CH_2{=}CH-CH_2CH_2CH_2CH_3}}_{\text{E2 products}}$$



$$CH_3-\overset{\displaystyle OCH_3}{\overset{|}{CH}}-CH_2CH_2CH_2CH_3$$

S_N2 product



Alcohols and phenols

Structure of water and methanol

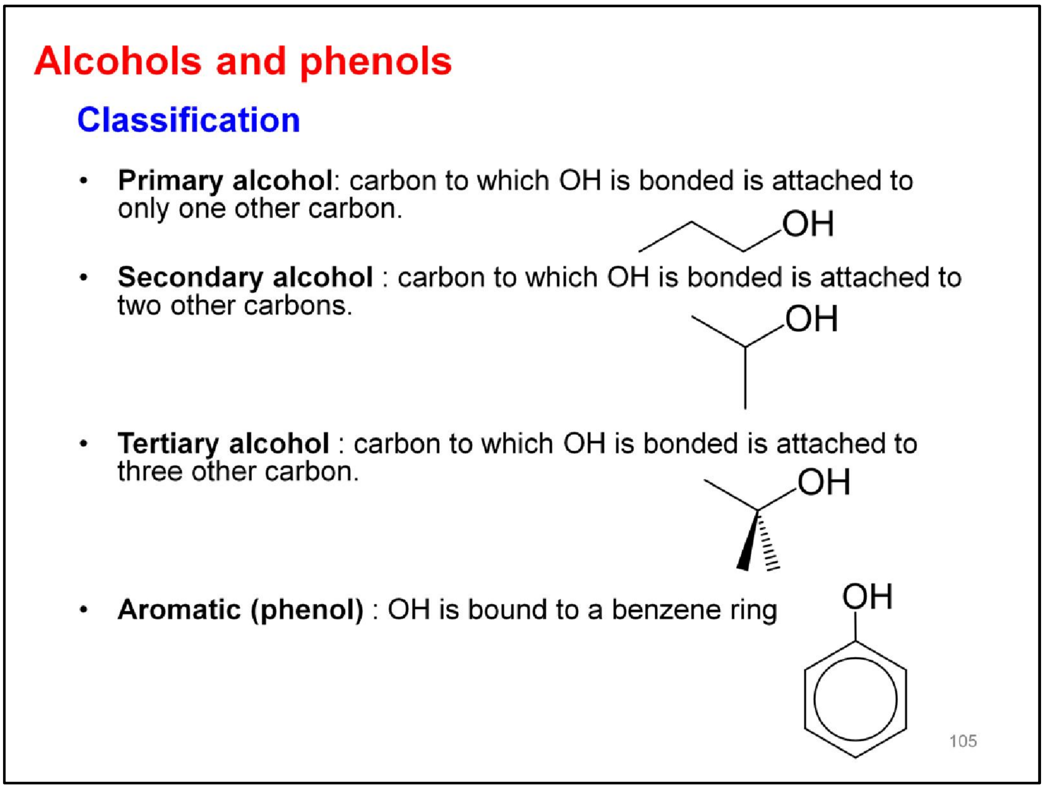
- Oxygen is *sp*^{3} hybridized and tetrahedral.
- The H—O—H angle in water is 104.5°.
- The C—O—H angle in methyl alcohol is 108.9°.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols and phenols

Classification

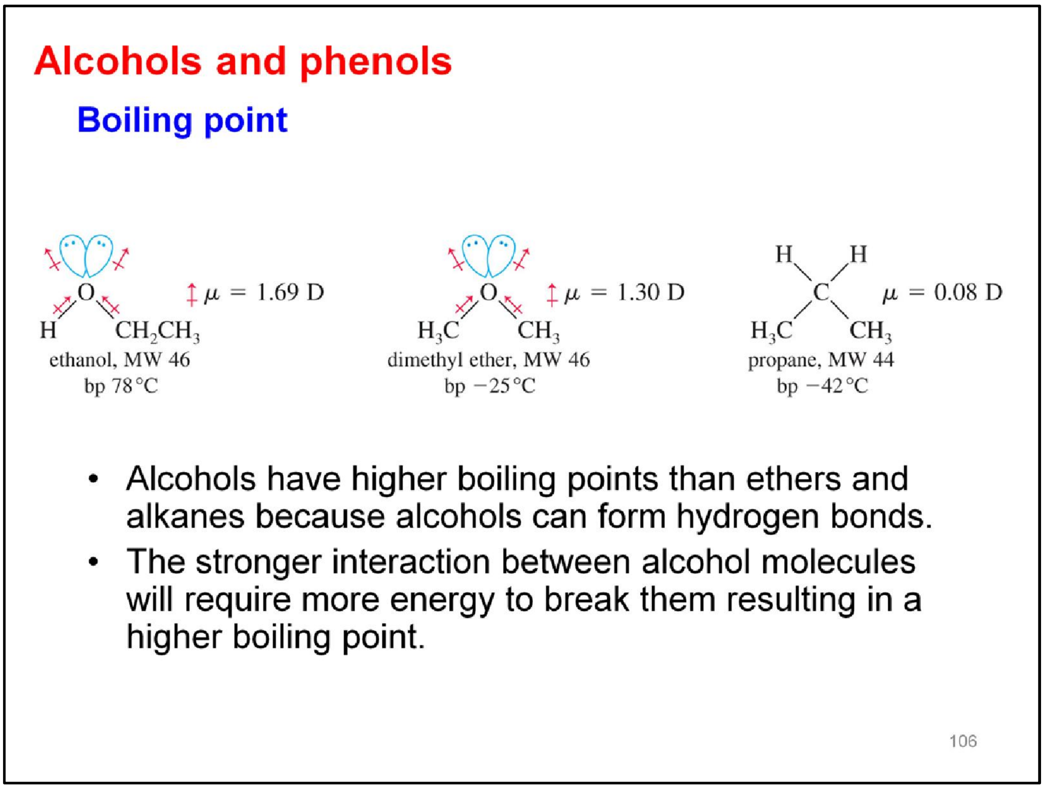
- **Primary alcohol**: carbon to which OH is bonded is attached to only one other carbon.
- **Secondary alcohol** : carbon to which OH is bonded is attached to two other carbons.
- **Tertiary alcohol** : carbon to which OH is bonded is attached to three other carbon.
- **Aromatic (phenol)** : OH is bound to a benzene ring

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols and phenols

Boiling point

ethanol, MW 46
bp 78 °C

dimethyl ether, MW 46
bp −25 °C

propane, MW 44
bp −42 °C

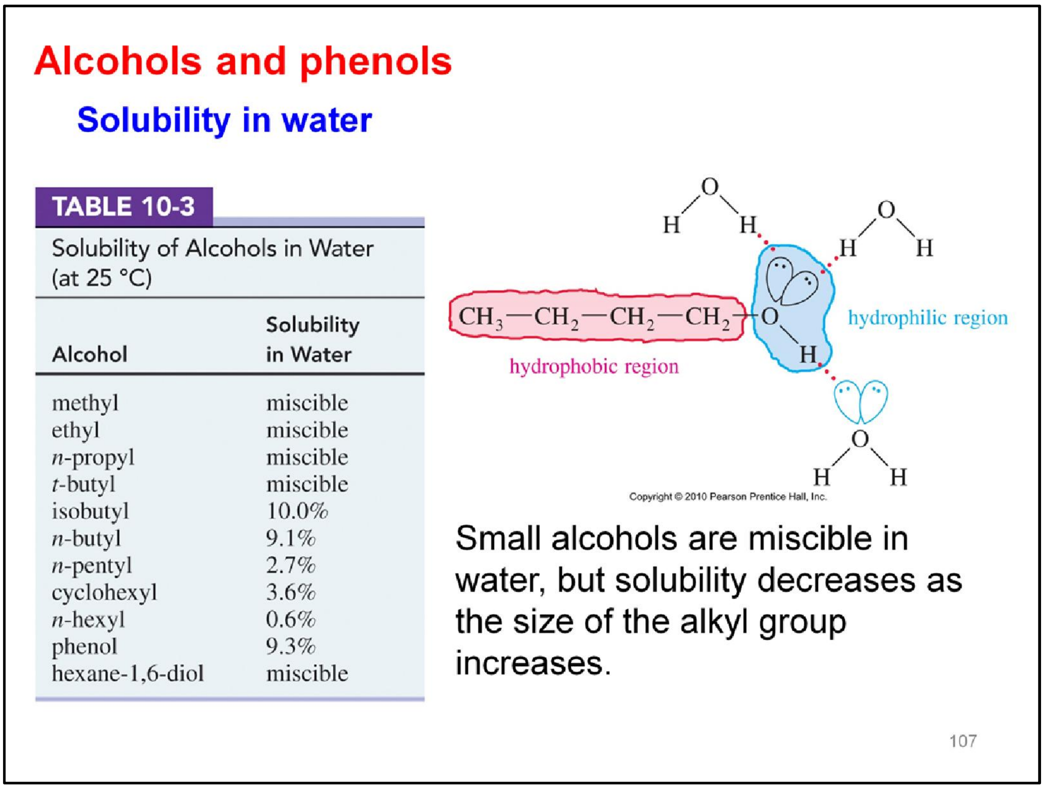
- Alcohols have higher boiling points than ethers and alkanes because alcohols can form hydrogen bonds.
- The stronger interaction between alcohol molecules will require more energy to break them resulting in a higher boiling point.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols and phenols

Solubility in water

TABLE 10-3

Solubility of Alcohols in Water (at 25 °C)

Alcohol	Solubility in Water
methyl	miscible
ethyl	miscible
n-propyl	miscible
t-butyl	miscible
isobutyl	10.0%
n-butyl	9.1%
n-pentyl	2.7%
cyclohexyl	3.6%
n-hexyl	0.6%
phenol	9.3%
hexane-1,6-diol	miscible

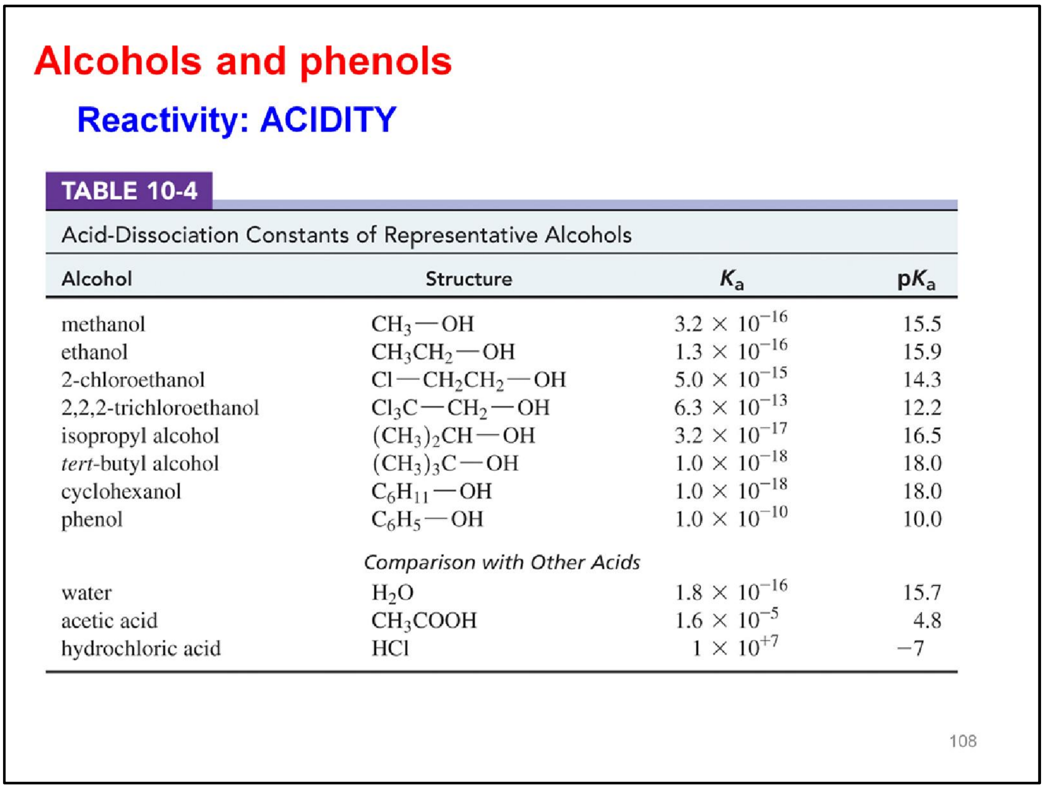
Small alcohols are miscible in water, but solubility decreases as the size of the alkyl group increases.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols and phenols

Reactivity: ACIDITY

TABLE 10-4

Acid-Dissociation Constants of Representative Alcohols

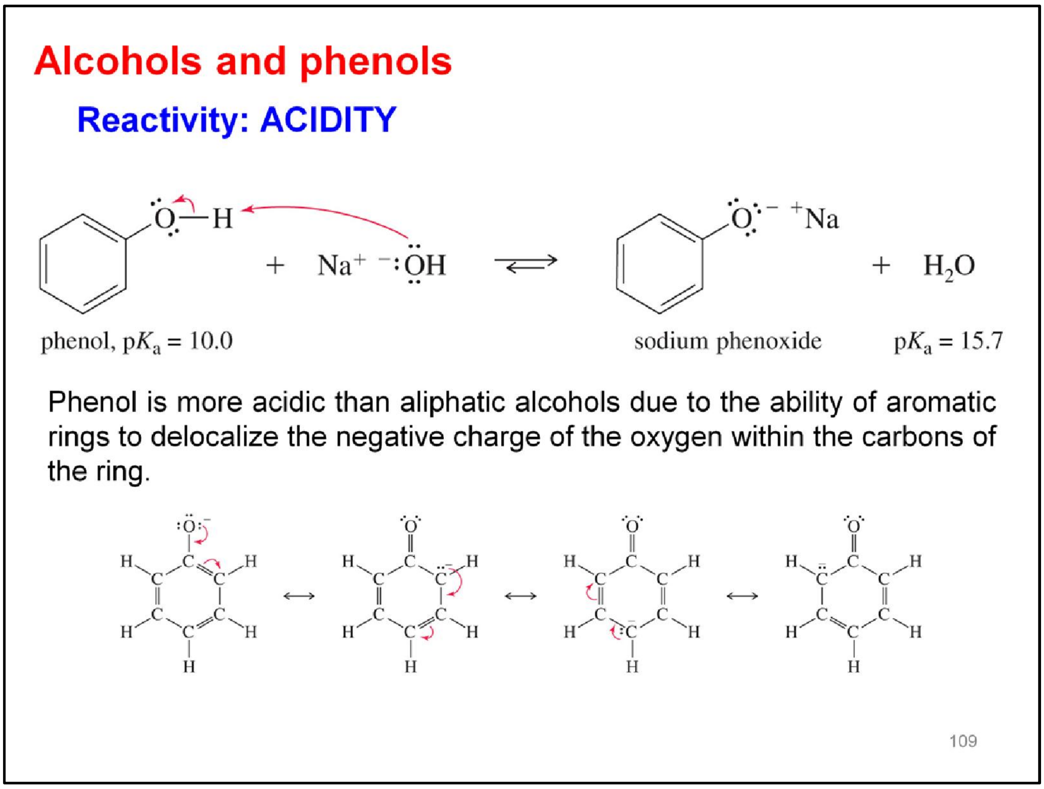
Alcohol	Structure	K_a	pK_a
methanol	$CH_3—OH$	3.2×10^{-16}	15.5
ethanol	$CH_3CH_2—OH$	1.3×10^{-16}	15.9
2-chloroethanol	$Cl—CH_2CH_2—OH$	5.0×10^{-15}	14.3
2,2,2-trichloroethanol	$Cl_3C—CH_2—OH$	6.3×10^{-13}	12.2
isopropyl alcohol	$(CH_3)_2CH—OH$	3.2×10^{-17}	16.5
tert-butyl alcohol	$(CH_3)_3C—OH$	1.0×10^{-18}	18.0
cyclohexanol	$C_6H_{11}—OH$	1.0×10^{-18}	18.0
phenol	$C_6H_5—OH$	1.0×10^{-10}	10.0
	Comparison with Other Acids		
water	H_2O	1.8×10^{-16}	15.7
acetic acid	CH_3COOH	1.6×10^{-5}	4.8
hydrochloric acid	HCl	$1 \times 10^{+7}$	−7

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols and phenols

Reactivity: ACIDITY

phenol, $pK_a = 10.0$

$+ \; Na^+ \; ^-{:}\ddot{O}H \rightleftharpoons$

sodium phenoxide $+ \; H_2O$ $pK_a = 15.7$

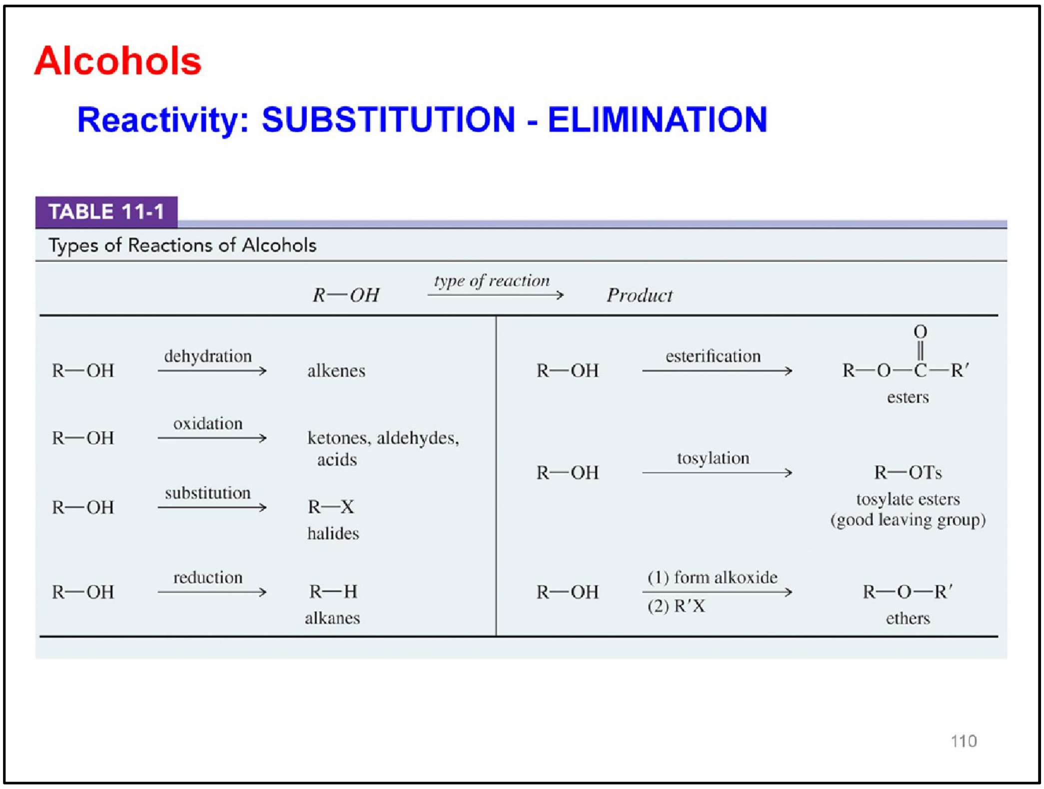
Phenol is more acidic than aliphatic alcohols due to the ability of aromatic rings to delocalize the negative charge of the oxygen within the carbons of the ring.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols

Reactivity: SUBSTITUTION - ELIMINATION

TABLE 11-1

Types of Reactions of Alcohols

$R{-}OH \xrightarrow{\text{type of reaction}} \text{Product}$

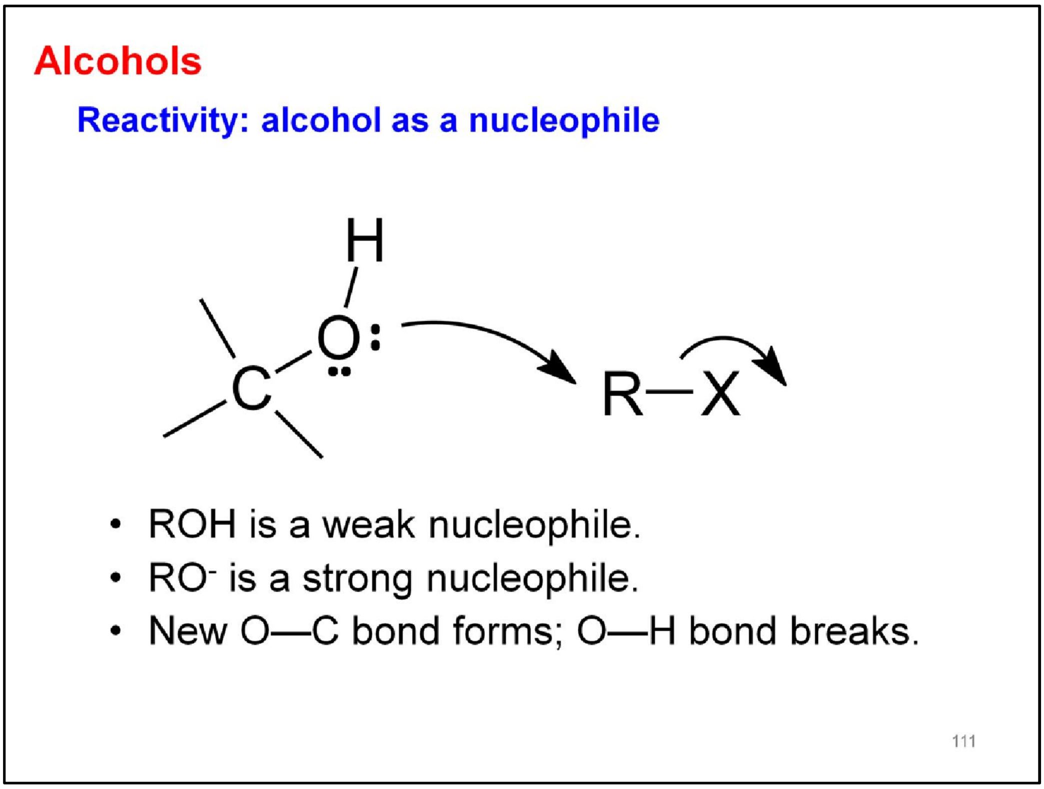
R—OH	$\xrightarrow{\text{dehydration}}$	alkenes	R—OH	$\xrightarrow{\text{esterification}}$	$R{-}O{-}\overset{\overset{O}{\|}}{C}{-}R'$ esters
R—OH	$\xrightarrow{\text{oxidation}}$	ketones, aldehydes, acids	R—OH	$\xrightarrow{\text{tosylation}}$	R—OTs tosylate esters (good leaving group)
R—OH	$\xrightarrow{\text{substitution}}$	R—X halides			
R—OH	$\xrightarrow{\text{reduction}}$	R—H alkanes	R—OH	$\xrightarrow[\text{(2) R}'\text{X}]{\text{(1) form alkoxide}}$	R—O—R′ ethers

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols

Reactivity: alcohol as a nucleophile

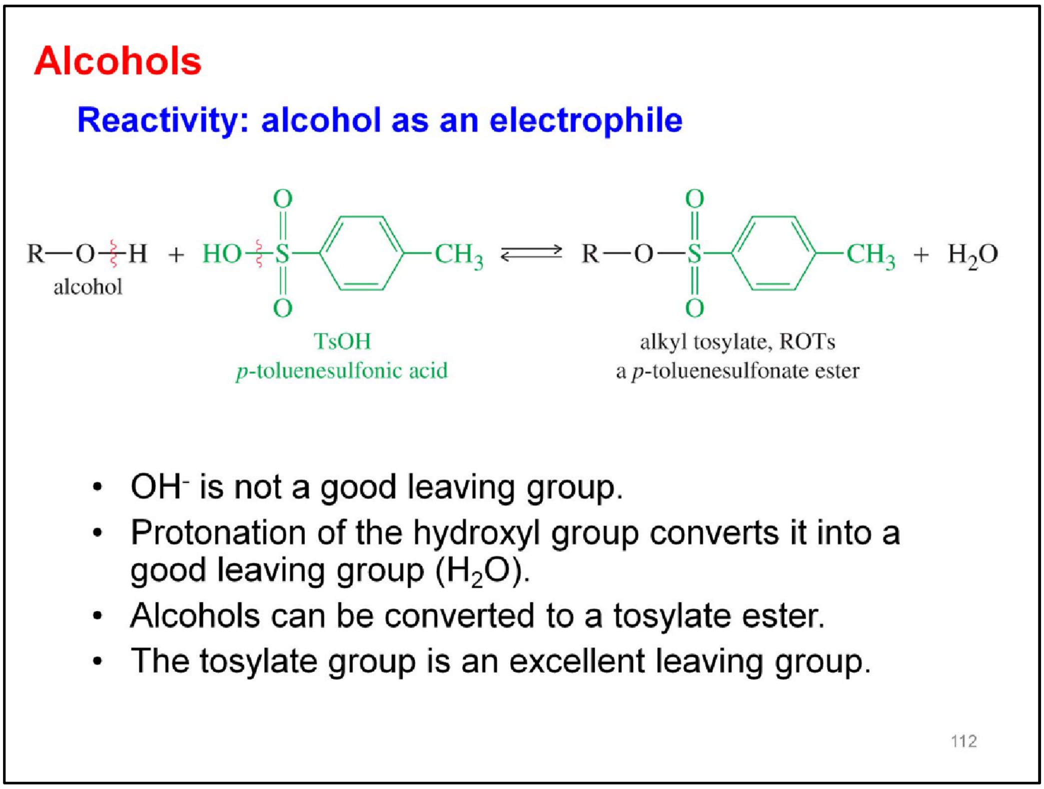
- ROH is a weak nucleophile.
- RO^- is a strong nucleophile.
- New O—C bond forms; O—H bond breaks.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols

Reactivity: alcohol as an electrophile

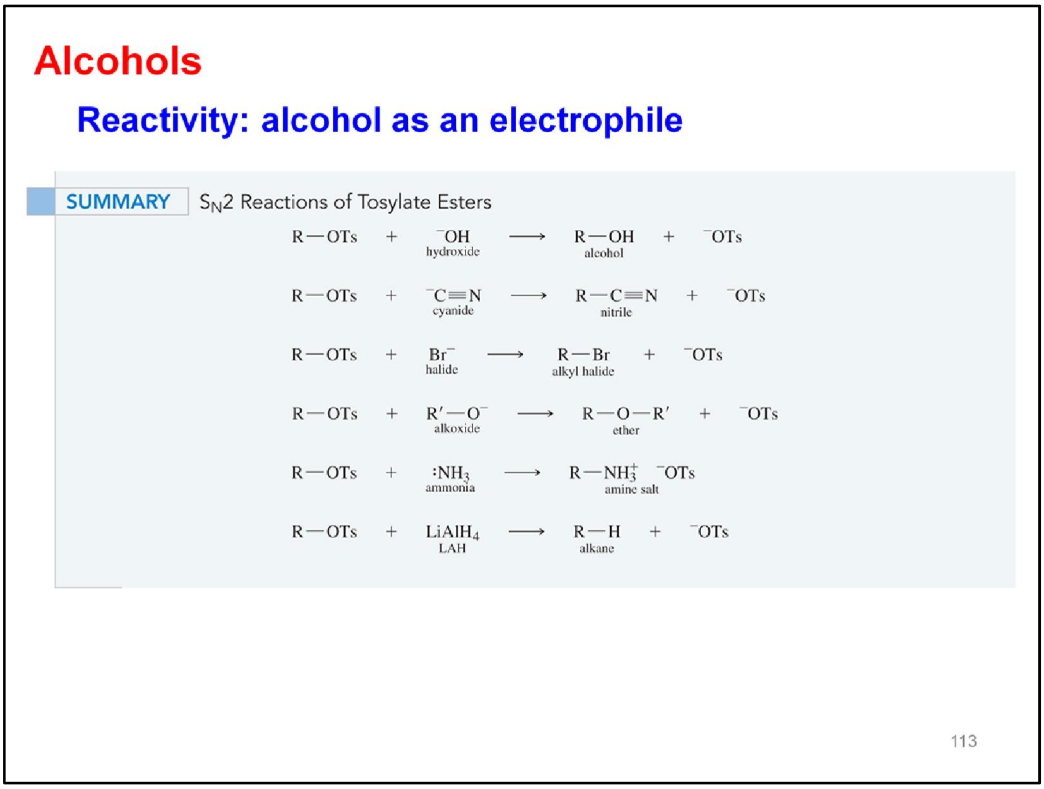
- OH^- is not a good leaving group.
- Protonation of the hydroxyl group converts it into a good leaving group (H_2O).
- Alcohols can be converted to a tosylate ester.
- The tosylate group is an excellent leaving group.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols

Reactivity: alcohol as an electrophile

SUMMARY S_N2 Reactions of Tosylate Esters

$$\mathrm{R{-}OTs} + \underset{\text{hydroxide}}{{}^{-}\mathrm{OH}} \longrightarrow \underset{\text{alcohol}}{\mathrm{R{-}OH}} + {}^{-}\mathrm{OTs}$$

$$\mathrm{R{-}OTs} + \underset{\text{cyanide}}{{}^{-}\mathrm{C{\equiv}N}} \longrightarrow \underset{\text{nitrile}}{\mathrm{R{-}C{\equiv}N}} + {}^{-}\mathrm{OTs}$$

$$\mathrm{R{-}OTs} + \underset{\text{halide}}{\mathrm{Br}^{-}} \longrightarrow \underset{\text{alkyl halide}}{\mathrm{R{-}Br}} + {}^{-}\mathrm{OTs}$$

$$\mathrm{R{-}OTs} + \underset{\text{alkoxide}}{\mathrm{R'{-}O}^{-}} \longrightarrow \underset{\text{ether}}{\mathrm{R{-}O{-}R'}} + {}^{-}\mathrm{OTs}$$

$$\mathrm{R{-}OTs} + \underset{\text{ammonia}}{:\mathrm{NH}_3} \longrightarrow \underset{\text{amine salt}}{\mathrm{R{-}NH}_3^{+}\ {}^{-}\mathrm{OTs}}$$

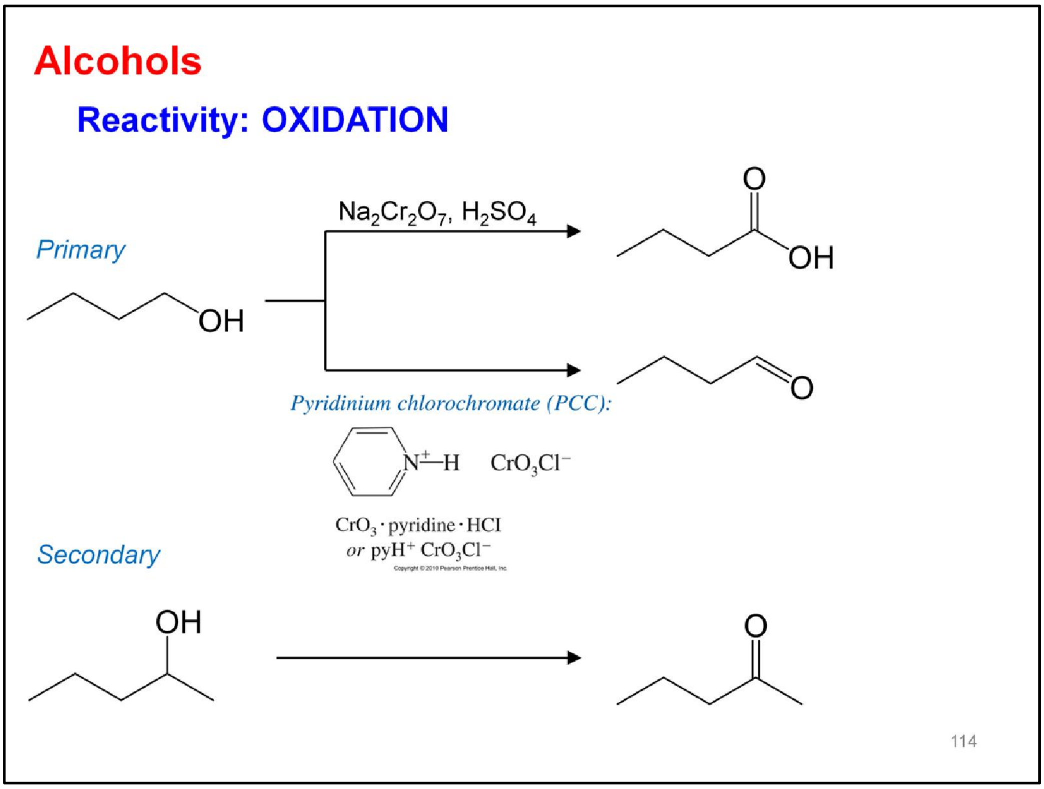
$$\mathrm{R{-}OTs} + \underset{\text{LAH}}{\mathrm{LiAlH}_4} \longrightarrow \underset{\text{alkane}}{\mathrm{R{-}H}} + {}^{-}\mathrm{OTs}$$

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Alcohols

Reactivity: OXIDATION

Primary

$Na_2Cr_2O_7$, H_2SO_4

Pyridinium chlorochromate (PCC):

CrO_3Cl^-

$CrO_3 \cdot$ pyridine $\cdot$ HCl
or $pyH^+ CrO_3Cl^-$

Copyright © 2010 Pearson Prentice Hall, Inc.

Secondary

114

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

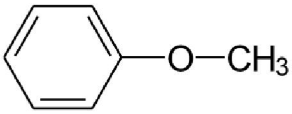
Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

Ethers

General formula

- Formula is R—O—R’ where R and R’ are alkyl or aryl.
- Symmetrical or unsymmetrical

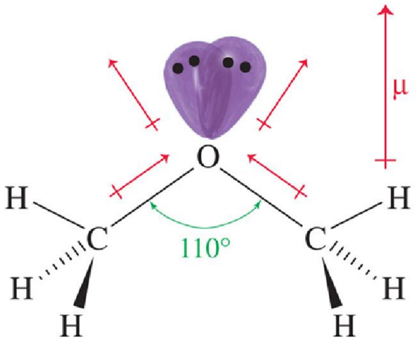
$CH_3—O—CH_3$



Ethers

Structure and polarity

- Oxygen is sp^3 hybridized.
- Bent molecular geometry.
- C—O—C angles is 110°.
- Polar C—O bonds.
- Dipole moment of 1.3 D.



Ethers

Boiling points

Similar to alkanes of comparable molecular weight.

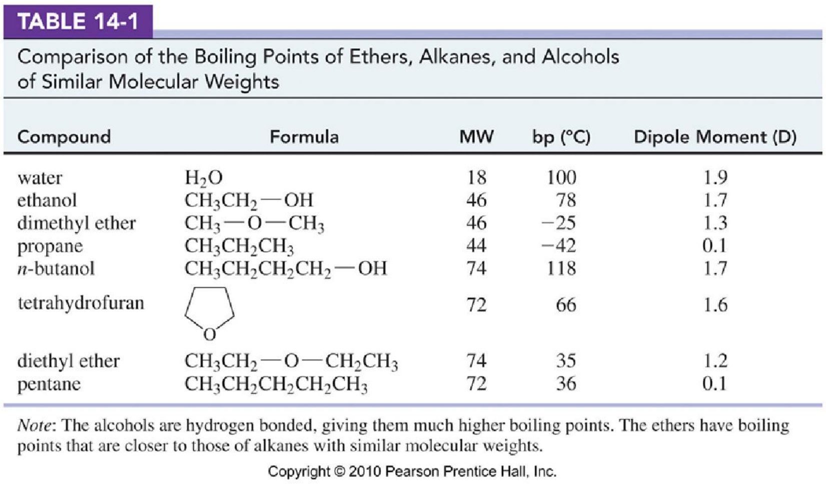


TABLE 14-1

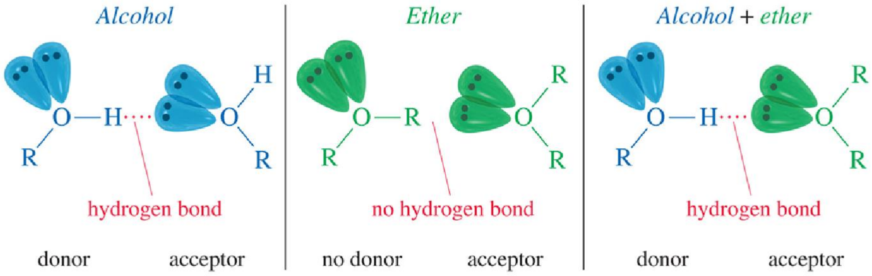
Comparison of the Boiling Points of Ethers, Alkanes, and Alcohols of Similar Molecular Weights

Compound	Formula	MW	bp (°C)	Dipole Moment (D)
water	H_2O	18	100	1.9
ethanol	$CH_3CH_2—OH$	46	78	1.7
dimethyl ether	$CH_3—O—CH_3$	46	−25	1.3
propane	$CH_3CH_2CH_3$	44	−42	0.1
n-butanol	$CH_3CH_2CH_2CH_2—OH$	74	118	1.7
tetrahydrofuran	O	72	66	1.6
diethyl ether	$CH_3CH_2—O—CH_2CH_3$	74	35	1.2
pentane	$CH_3CH_2CH_2CH_2CH_3$	72	36	0.1

Note: The alcohols are hydrogen bonded, giving them much higher boiling points. The ethers have boiling points that are closer to those of alkanes with similar molecular weights.

Ethers

Hydrogen bond acceptor



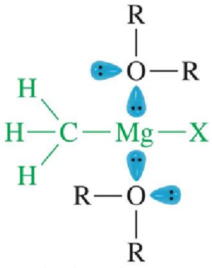
Copyright © 2010 Pearson Prentice Hall, Inc.

- Ethers cannot hydrogen-bond with other ether molecules.
- Molecules that cannot hydrogen-bond intermolecularly have a lower boiling point.
- Ether molecules can hydrogen-bond with water and alcohol molecules.

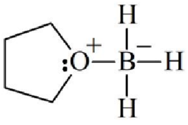
Ethers

Ether complexes

- Grignard reagents: Complexation of an ether with a Grignard reagent stabilizes the reagent and helps keep it in solution.



- Electrophiles: The ethers nonbonding electrons stabilize the borane (BH_3).



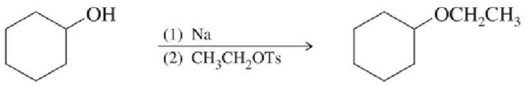
$BH_3 \cdot THF$

Ethers

Williamson synthesis

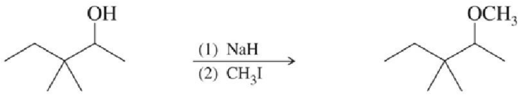
The alkoxide is commonly made by adding Na, K, or NaH to the alcohol (Section 11-14).

Examples



cyclohexanol

ethoxycyclohexane
(92%)

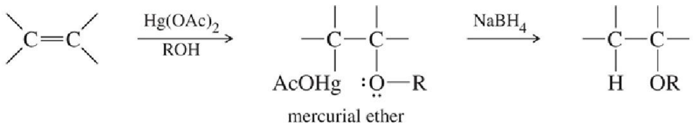


3,3-dimethyl-2-pentanol

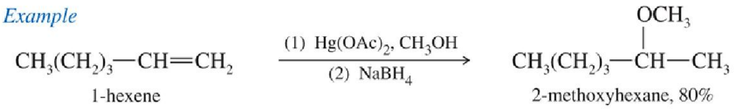
2-methoxy-3,3-dimethylpentane
(90%)

Ethers

Alkoxymercuration–Demercuration Reaction



Example



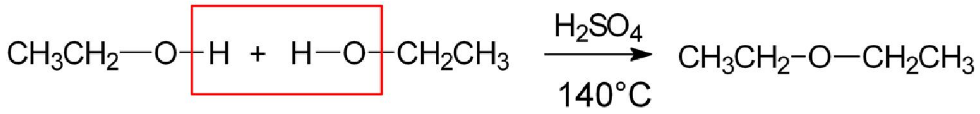
$$\mathrm{CH_3(CH_2)_3{-}CH{=}CH_2} \xrightarrow[\text{(2) NaBH}_4]{\text{(1) Hg(OAc)}_2\text{, CH}_3\text{OH}} \mathrm{CH_3(CH_2)_3{-}\underset{}{\overset{OCH_3}{CH}}{-}CH_3}$$

Use mercuric acetate with an alcohol. The alcohol will react with the intermediate mercurinium ion by attacking the more substituted carbon (Markovnikov’s rule).

Ethers

Industrial ether synthesis

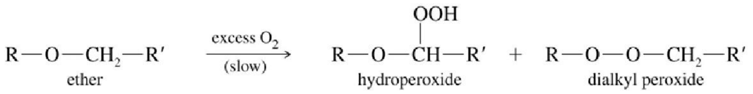
- Industrial method, not good lab synthesis.
- If temperature is too high, alkene forms.



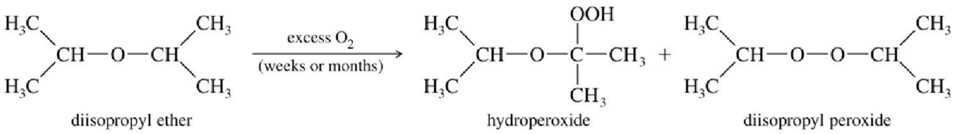
$$CH_3CH_2{-}O\boxed{{-}H \;+\; H{-}O}{-}CH_2CH_3 \xrightarrow[140°C]{H_2SO_4} CH_3CH_2{-}O{-}CH_2CH_3$$

Ethers

Autoxidation of ethers



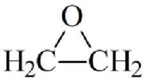
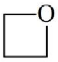
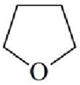
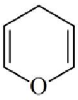
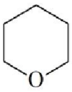
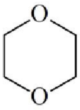
$$R{-}O{-}CH_2{-}R' \xrightarrow[\text{(slow)}]{\text{excess } O_2} R{-}O{-}\overset{OOH}{\overset{|}{C}H}{-}R' + R{-}O{-}O{-}CH_2{-}R'$$



- In the presence of atmospheric oxygen, ethers slowly oxidize to hydroperoxides and dialkyl peroxides. Both are highly explosive.
- Precautions:
  - Do not distill to dryness.
  - Store in full bottles with tight caps.

Epoxides

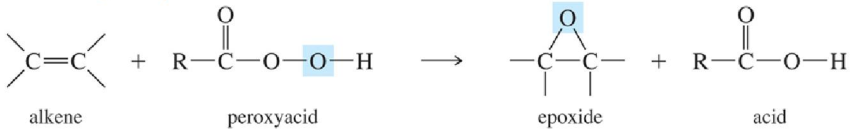
Cyclic ethers

- Epoxides (oxiranes) 
- Oxetanes 
- Furans  (Oxolanes )
- Pyrans  (Oxanes )
- Dioxanes 

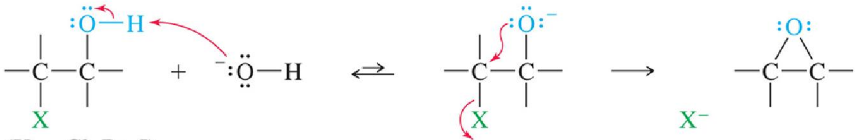
Epoxides

Synthesis

Reaction with peroxyacids



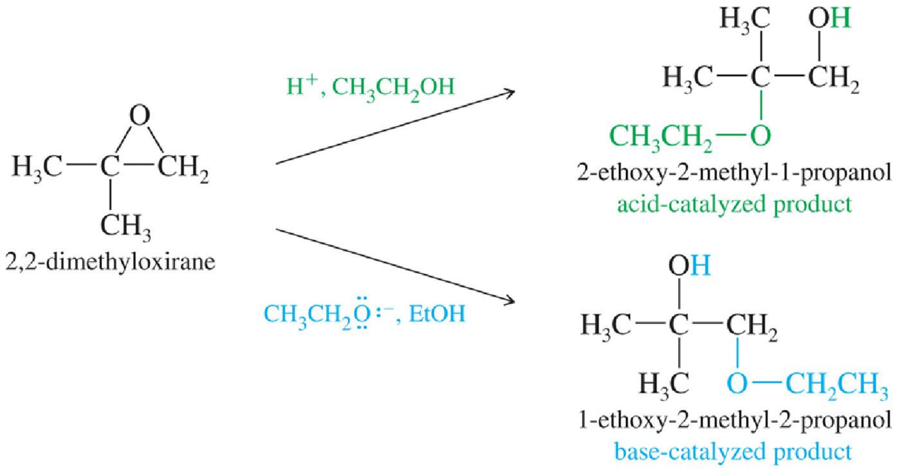
Halohydrin cyclization



(X = Cl, Br, I)

Epoxides

Ring opening

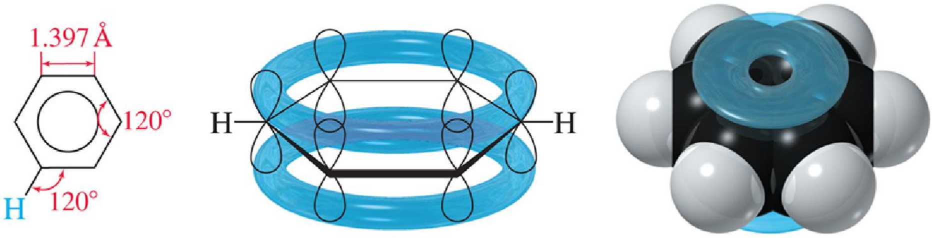


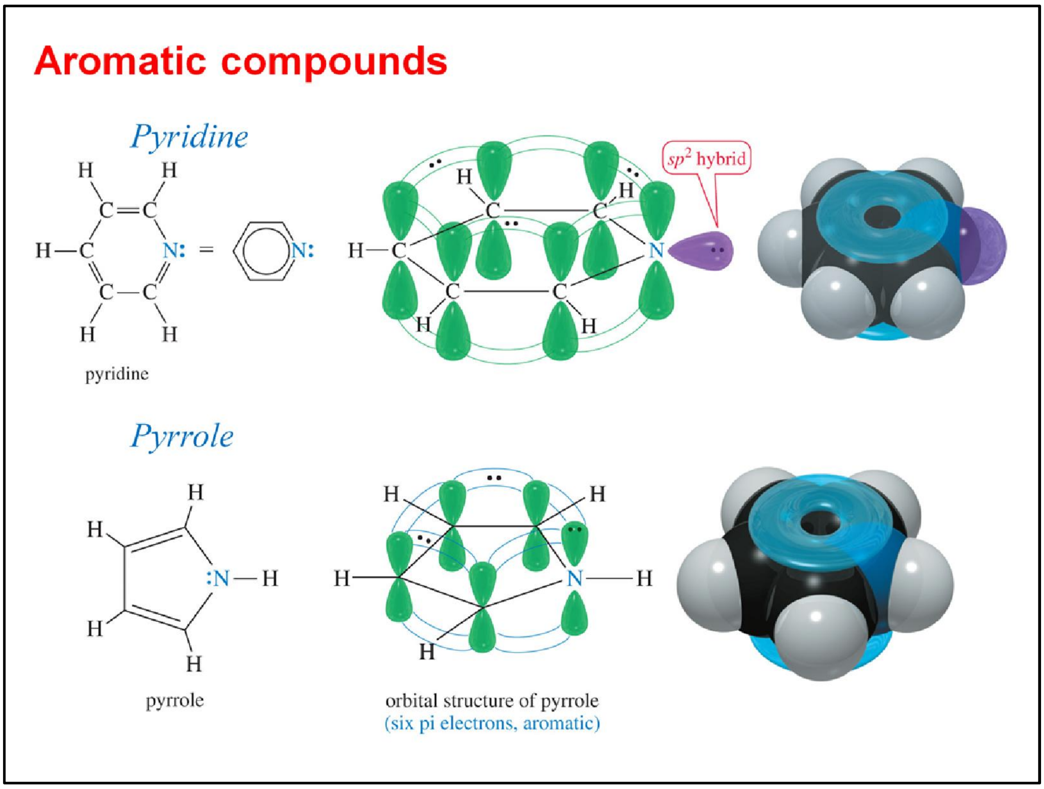
Aromatic compounds

Hückel's Rule

If the number of pi electrons is (4N + 2) the compound is aromatic (where N is an integer)

Benzene





Aromatic compounds

Pyridine

pyridine

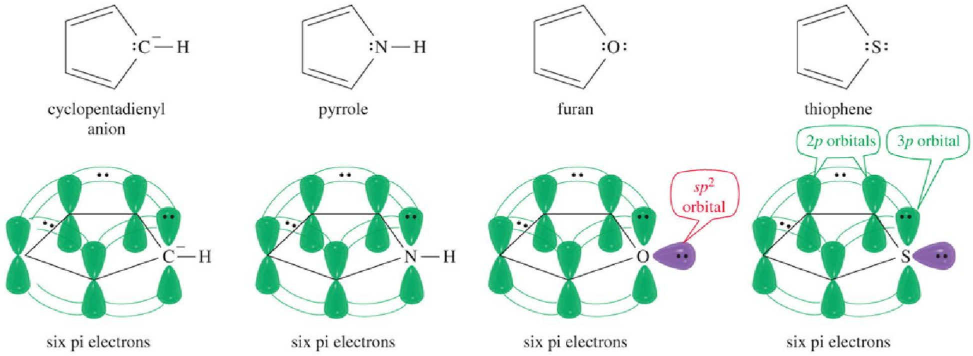
Pyrrole

pyrrole

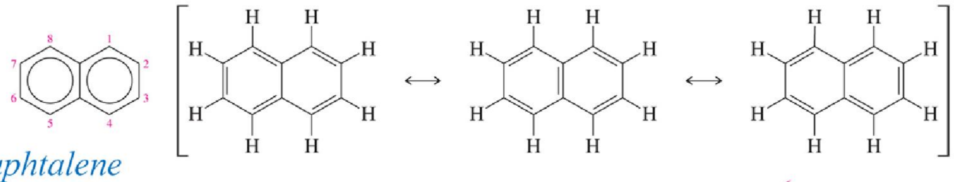
orbital structure of pyrrole
(six pi electrons, aromatic)

Aromatic compounds

Other heterocyclics

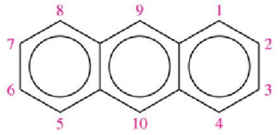


Aromatic compounds

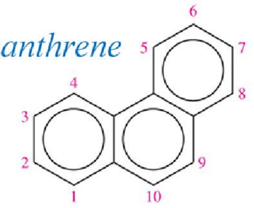


Naphtalene

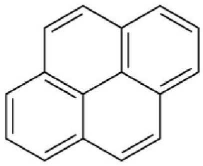
Anthracene



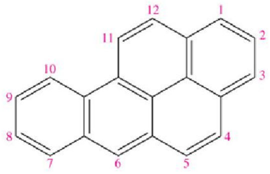
Phenanthrene



Pyrene



Benzo[a]pyrene



Many are carcinogenic

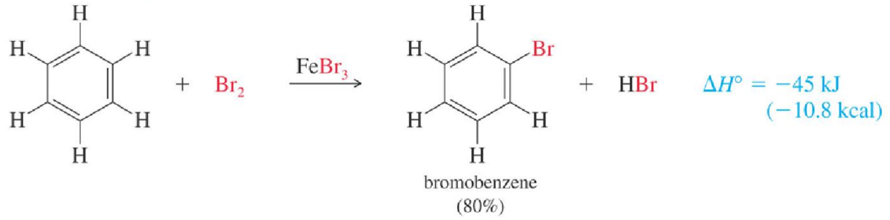
Aromatic compounds

Physical properties

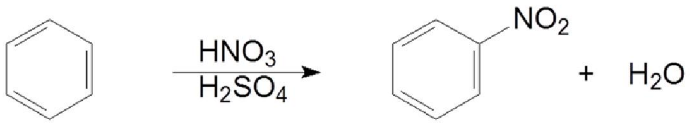
- Melting points: More symmetrical than corresponding alkane, pack better into crystals, so higher melting points.
- Boiling points: Dependent on dipole moment, so *ortho* > *meta* > *para*, for disubstituted benzenes.
- Density: More dense than non-aromatics, less dense than water.
- Solubility: Generally insoluble in water.

Aromatic compounds

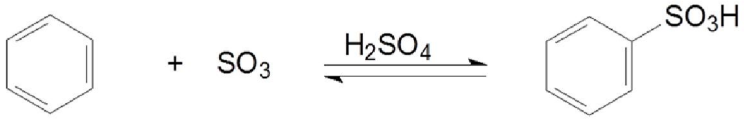
Reactivity: HALOGENATION



NITRATION

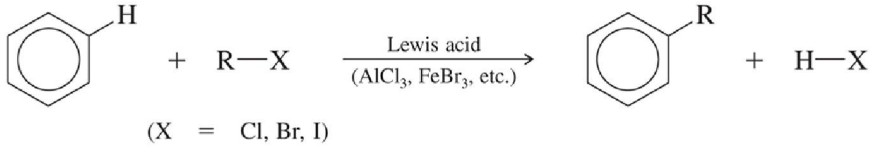


SULFONATION

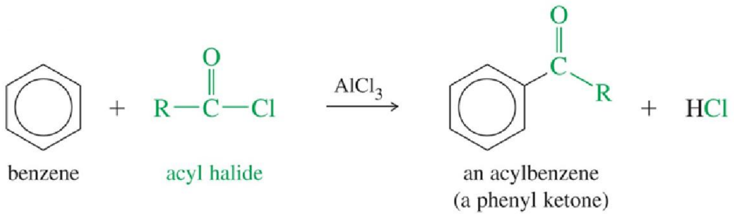


Aromatic compounds

Reactivity: FRIEDEL-CRAFTS ALKYLATION

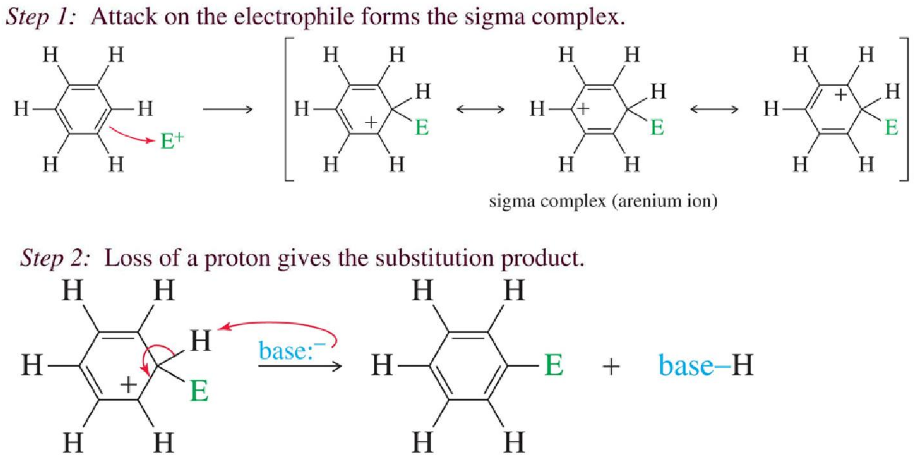


FRIEDEL-CRAFTS ACYLATION



Electrophilic aromatic substitution

General mechanism



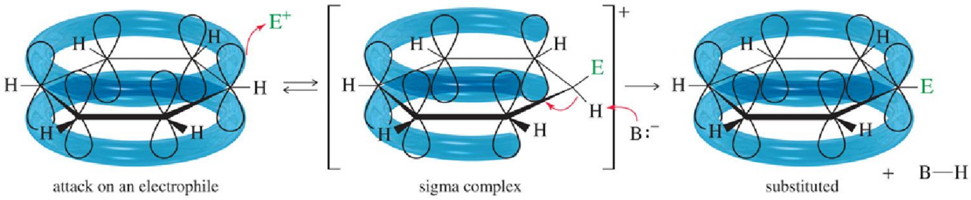
Step 1: Attack on the electrophile forms the sigma complex.

sigma complex (arenium ion)

Step 2: Loss of a proton gives the substitution product.

Aromatic compounds

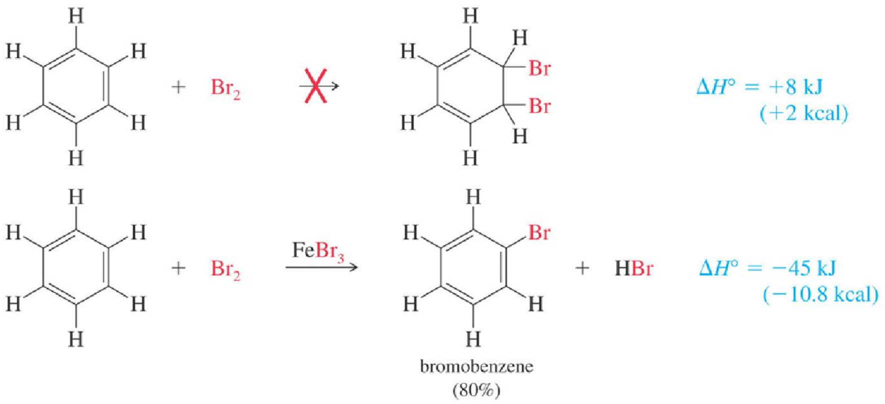
Reactivity: ELECTROPHYLIC SUBSTITUTION



- Although benzene’s pi electrons are in a stable aromatic system, they are available to attack a strong electrophile to give a carbocation.
- This resonance-stabilized carbocation is called a ***sigma complex*** because the electrophile is joined to the benzene ring by a new sigma bond.
- Aromaticity is regained by loss of a proton.

Electrophilic aromatic substitution

Bromination of benzene



$\Delta H^\circ = +8$ kJ
(+2 kcal)

$\Delta H^\circ = -45$ kJ
(−10.8 kcal)

bromobenzene
(80%)

Electrophilic aromatic substitution

Bromination of benzene: Step 1

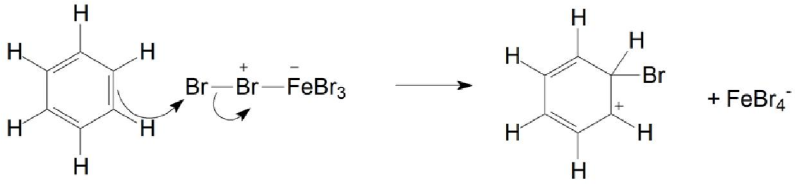
(stronger electrophile than Br_2)

- Before the electrophilic aromatic substitution can take place, the electrophile must be activated.
- A strong Lewis acid catalyst, such as $FeBr_3$, should be used.

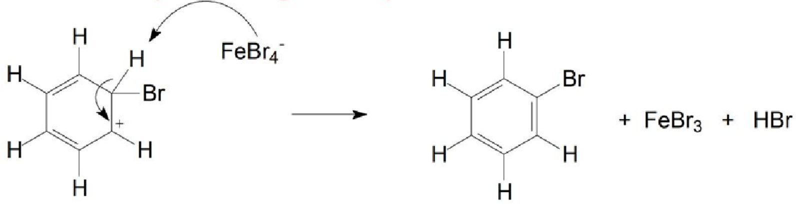
Electrophilic aromatic substitution

Bromination of benzene: Steps 2 & 3

Step 2: Electrophilic attack and formation of the sigma complex.

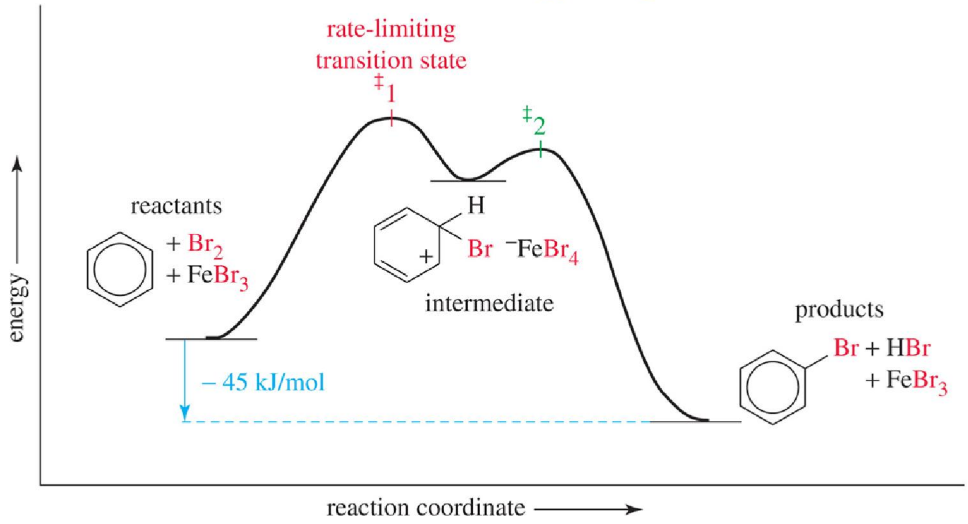


Step 3: Loss of a proton to give the products.



Electrophilic aromatic substitution

Bromination of benzene: Energy diagram



Electrophilic aromatic substitution

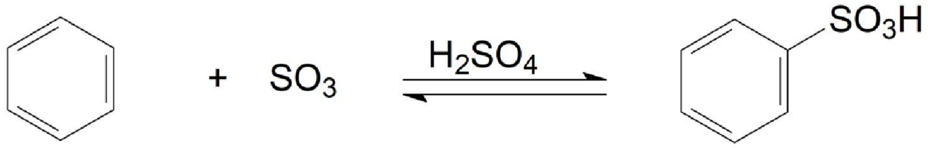
Chlorination and Iodination

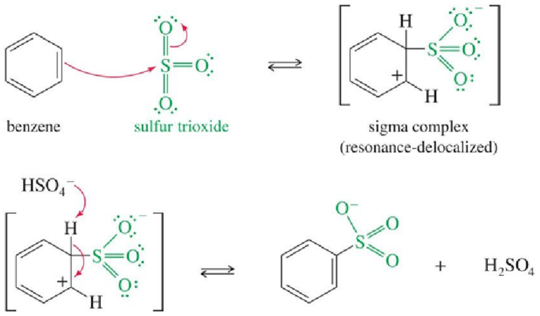
- Chlorination is similar to bromination. $AlCl_3$ is most often used as catalyst, but $FeCl_3$ will also work.
- Iodination requires an acidic oxidizing agent, like nitric acid, to produce iodide cation.

$$H^+ + HNO_3 + \tfrac{1}{2} I_2 \longrightarrow I^+ + NO_2 + H_2O$$

Electrophilic aromatic substitution

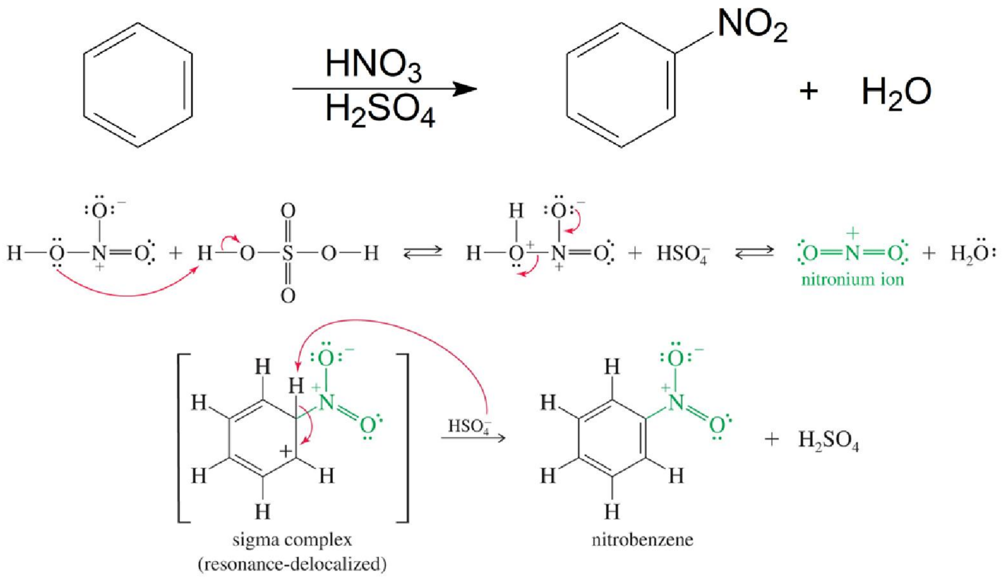
Sulfonation of benzene





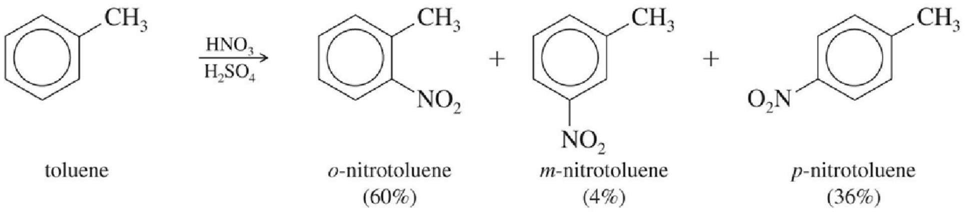
Electrophilic aromatic substitution

Nitration of benzene



Electrophilic aromatic substitution

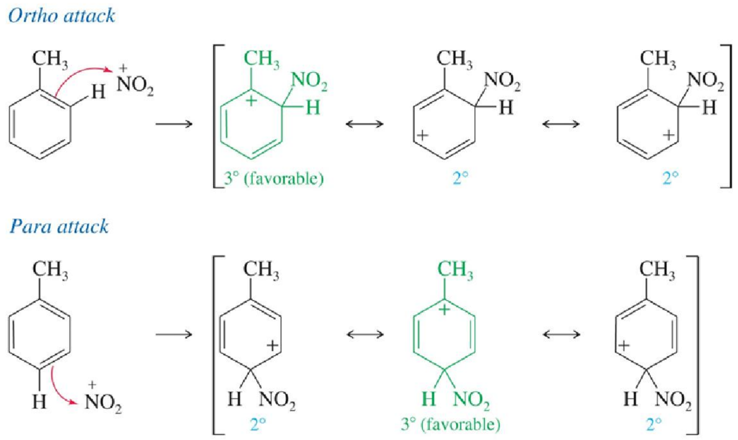
Nitration of toluene



- Toluene reacts 25 times faster than benzene.
- The methyl group is an activator.
- The product mix contains mostly *ortho* and *para* substituted molecules.

Electrophilic aromatic substitution

Ortho and Para Substitution

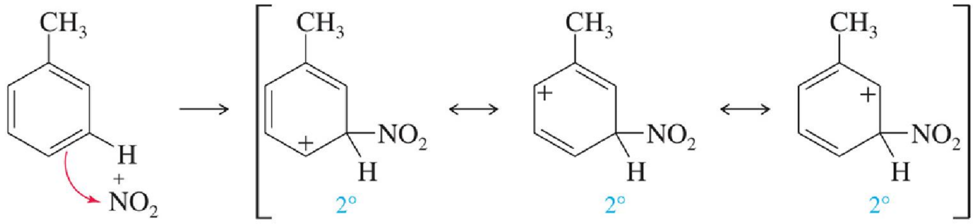


Ortho and *para* attacks are preferred because their resonance structures include one tertiary carbocation.

Electrophilic aromatic substitution

Meta Substitution

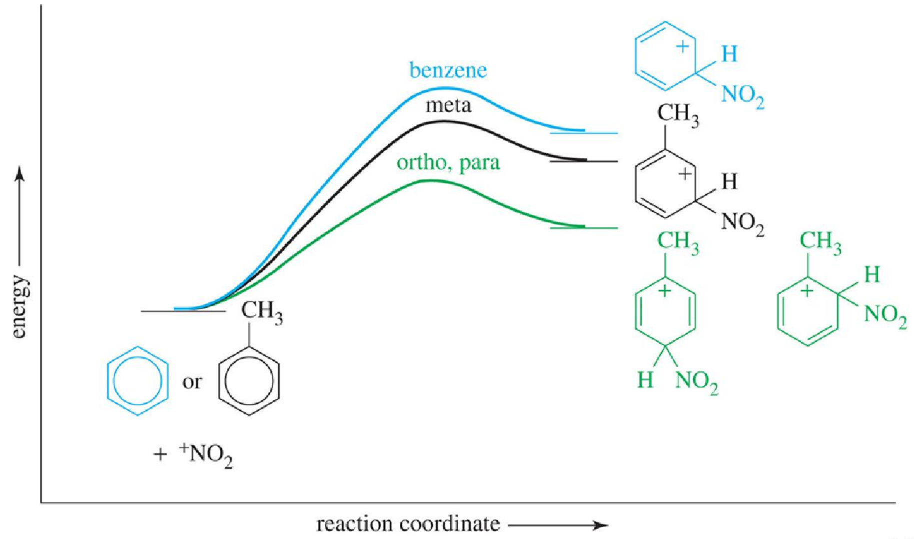
Meta attack



When substitution occurs at the meta position, the positive charge is not delocalized onto the tertiary carbon, and the methyl groups has a smaller effect on the stability of the sigma complex.

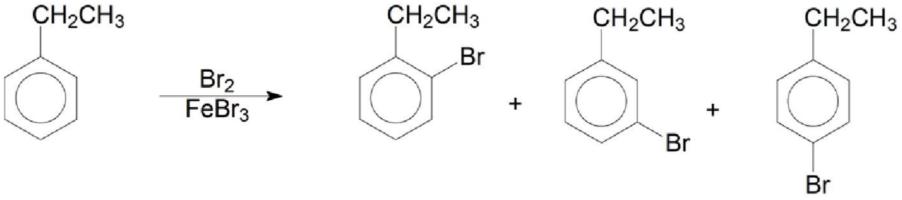
Electrophilic aromatic substitution

Energy diagram



Electrophilic aromatic substitution

Alkyl Group Stabilization

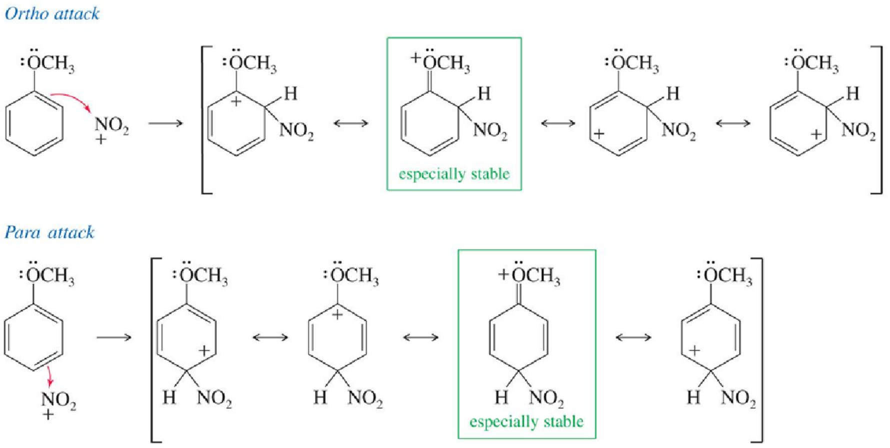


o-bromo (38%) | *m*-bromo (< 1%) | *p*-bromo (62%)

- Alkyl groups are **activating** substituents and ortho, para-directors.
- This effect is called the ***inductive effect*** because alkyl groups can donate electron density to the ring through the sigma bond, making them more active.

Electrophilic aromatic substitution

Substituents with Non Bonding Electrons

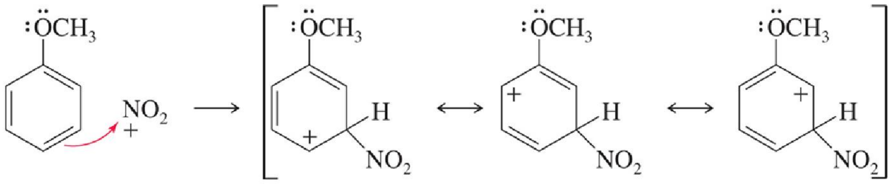


Resonance stabilization is provided by a pi bond between the —OCH_3 substituent and the ring.

Electrophilic aromatic substitution

Substituents with Non Bonding Electrons

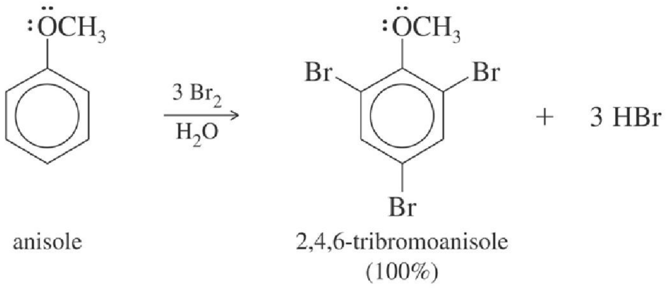
Meta attack



Resonance forms show that the methoxy group cannot stabilize the sigma complex in the meta substitution.

Electrophilic aromatic substitution

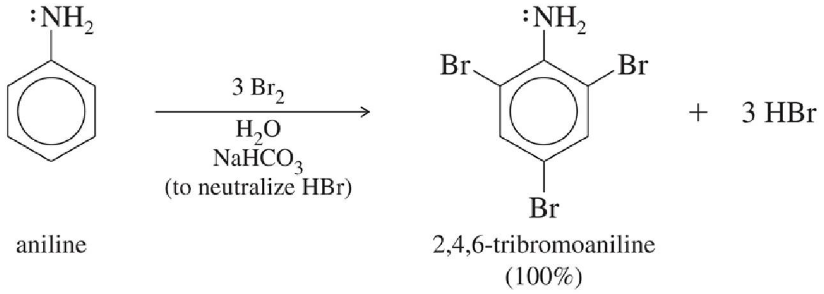
Bromination of anisole



A methoxy group is so strongly activating that anisole is quickly tribrominated without a catalyst.

Electrophilic aromatic substitution

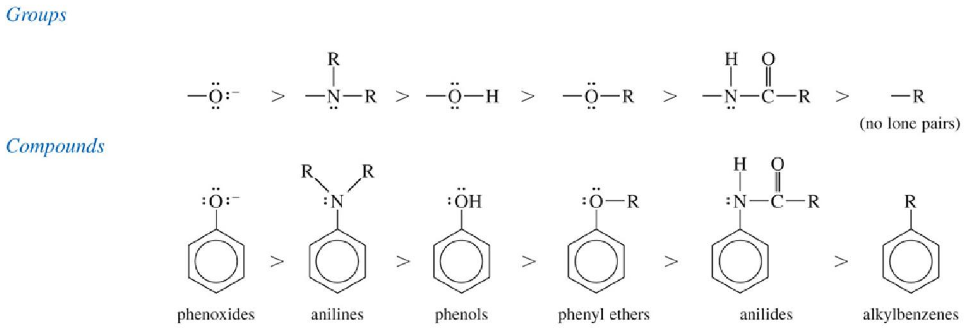
Bromination of aniline



- Aniline reacts with bromine water (without a catalyst) to yield the tribromoaniline.
- Sodium bicarbonate is added to neutralize the HBr that is also formed.

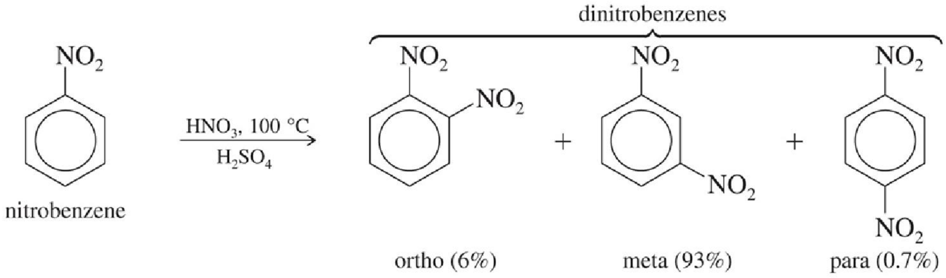
Electrophilic aromatic substitution

Summary of activators



Electrophilic aromatic substitution

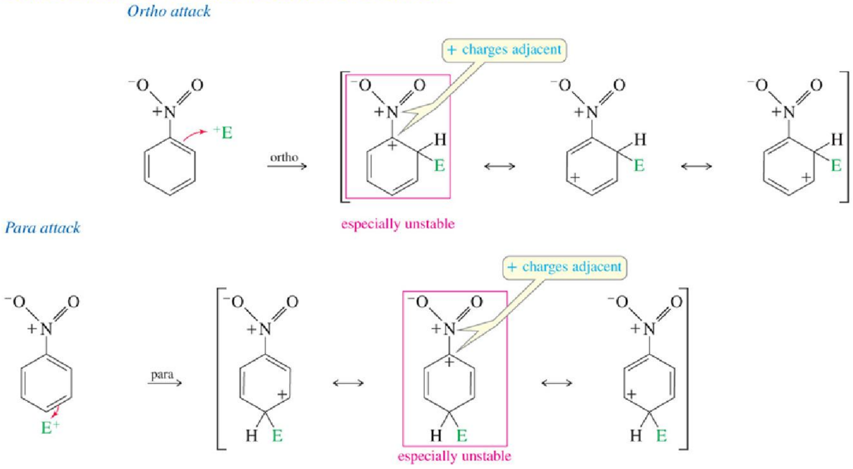
Nitration of nitrobenzene



- Electrophilic substitution reactions for nitrobenzene are 100,000 times slower than for benzene.
- The product mix contains mostly the meta isomer, only small amounts of the ortho and para isomers.

Electrophilic aromatic substitution

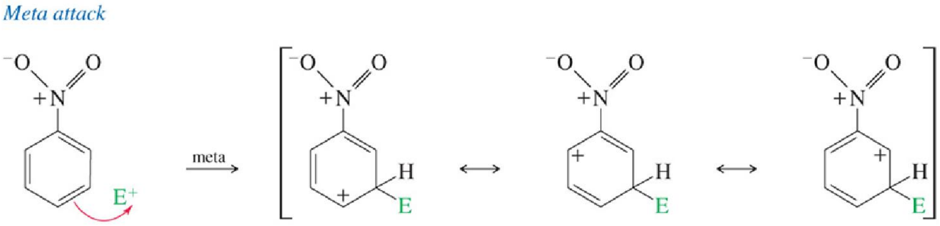
Ortho and Para Substitution



- The nitro group is a strongly deactivating group when considering its resonance forms. The nitrogen always has a formal positive charge.
- Ortho or para addition will create an especially unstable intermediate.

Electrophilic aromatic substitution

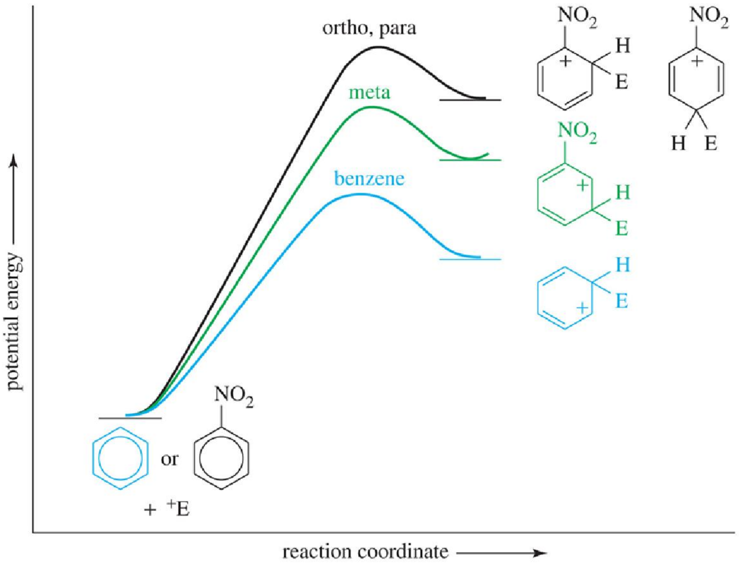
Meta Substitution



- Meta substitution will not put the positive charge on the same carbon that bears the nitro group.

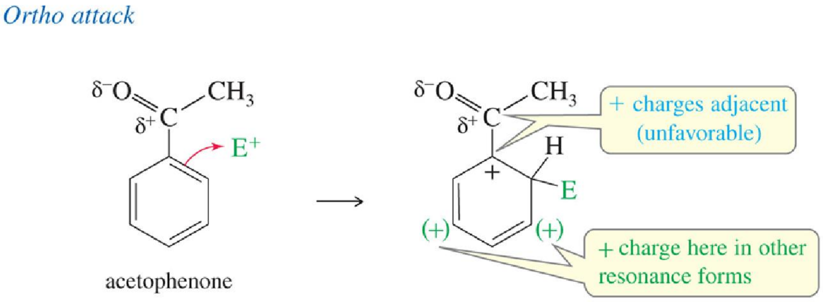
Electrophilic aromatic substitution

Energy Diagram



Electrophilic aromatic substitution

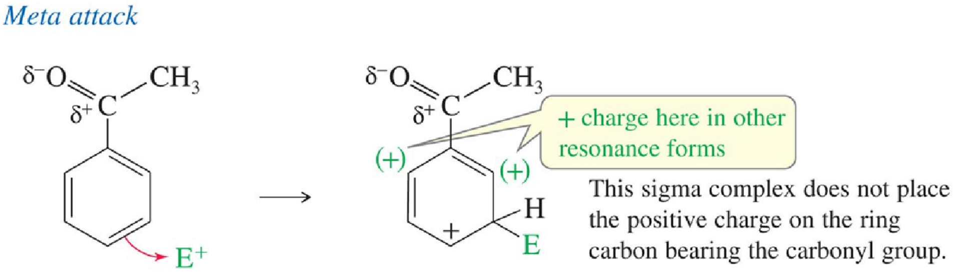
Ortho attack of acetophenone



- In ortho and para substitution of acetophenone, one of the carbon atoms bearing the positive charge is the carbon attached to the partial positive carbonyl carbon.
- Since like charges repel, this close proximity of the two positive charges is especially unstable.

Electrophilic aromatic substitution

Meta attack of acetophenone



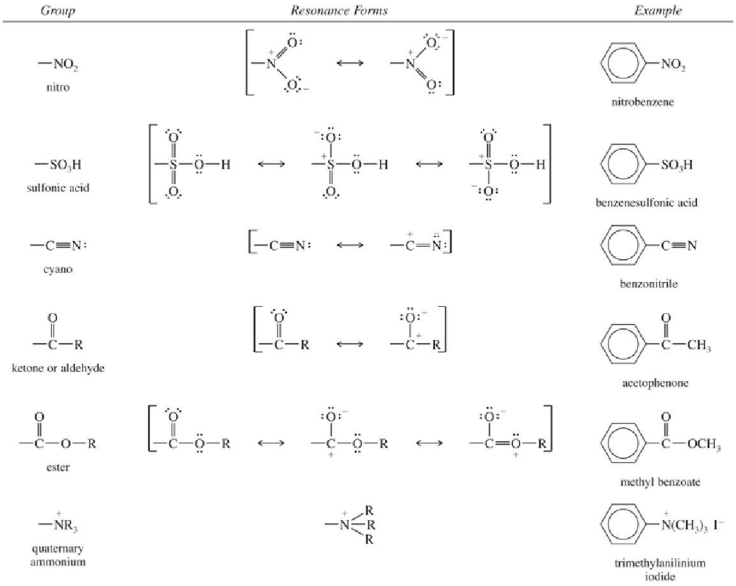
+ charge here in other resonance forms

This sigma complex does not place the positive charge on the ring carbon bearing the carbonyl group.

- The meta attack on acetophenone avoids bearing the positive charge on the carbon attached to the partial positive carbonyl.

Electrophilic aromatic substitution

Other deactivators



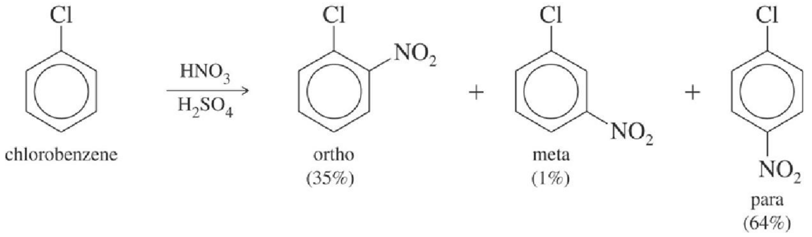
Electrophilic aromatic substitution

Deactivators and meta-directors

- Most electron withdrawing groups are deactivators and meta-directors.
- The atom attached to the aromatic ring has a positive or partial positive charge.
- Electron density is withdrawn inductively along the sigma bond, so the ring has less electron density than benzene and thus, it will be slower to react.

Electrophilic aromatic substitution

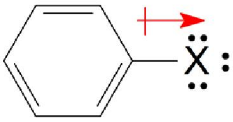
Nitration of chlorobenzene



- When chlorobenzene is nitrated the main substitution products are ortho and para. The meta substitution product is only obtained in 1% yield.

Electrophilic aromatic substitution

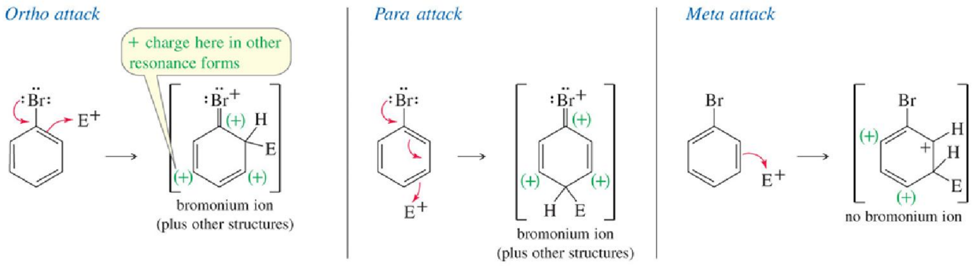
Halogens are deactivators



- ***Inductive Effect***: Halogens are deactivating because they are electronegative and can withdraw electron density from the ring along the sigma bond.

Electrophilic aromatic substitution

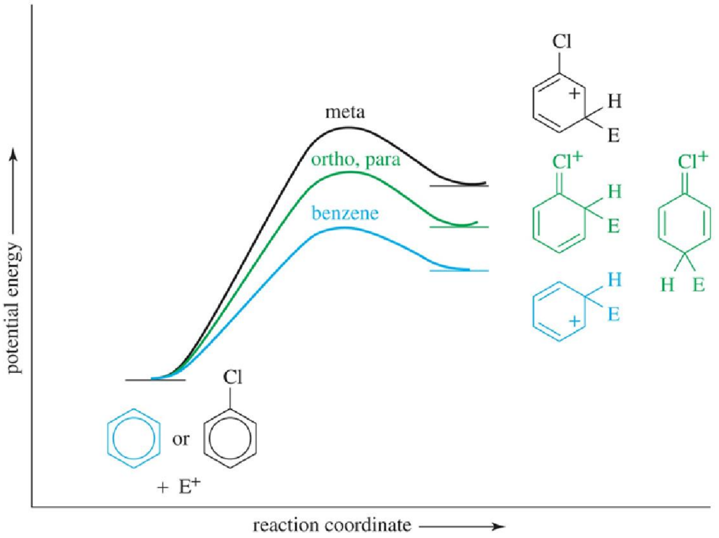
Halogens are ortho, para-directors



- ***Resonance Effect***: The lone pairs on the halogen can be used to stabilize the sigma complex by resonance.

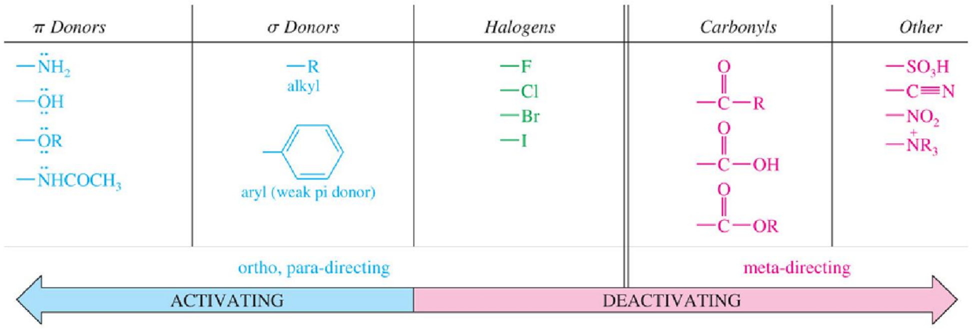
Electrophilic aromatic substitution

Energy diagram



Electrophilic aromatic substitution

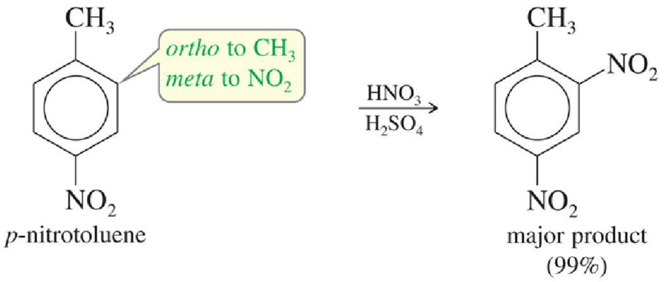
Summary od directing effects



π Donors	*σ Donors*	*Halogens*	*Carbonyls*	*Other*
$-\ddot{N}H_2$ $-\ddot{O}H$ $-\ddot{O}R$ $-\ddot{N}HCOCH_3$	$-R$ alkyl aryl (weak pi donor)	$-F$ $-Cl$ $-Br$ $-I$	$-\overset{O}{\overset{\|}{C}}-R$ $-\overset{O}{\overset{\|}{C}}-OH$ $-\overset{O}{\overset{\|}{C}}-OR$	$-SO_3H$ $-C\equiv N$ $-NO_2$ $-\overset{+}{N}R_3$

Electrophilic aromatic substitution

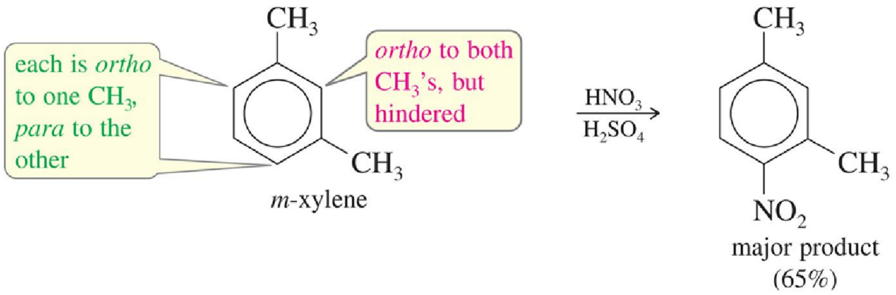
Effect of multiple substituents



The directing effect of the two (or more) groups may reinforce each other.

Electrophilic aromatic substitution

Effect of multiple substituents



each is *ortho* to one CH_3, *para* to the other

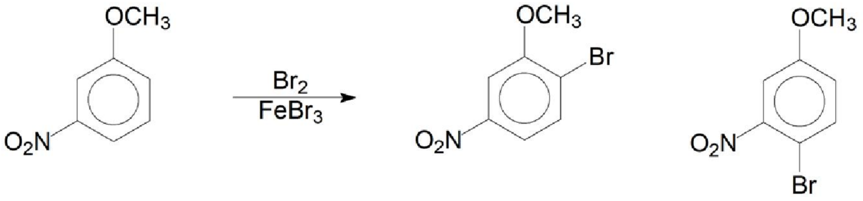
ortho to both CH_3's, but hindered

major product (65%)

The position in between two groups in Positions 1 and 3 is hindered for substitution, and it is less reactive.

Electrophilic aromatic substitution

Effect of multiple substituents



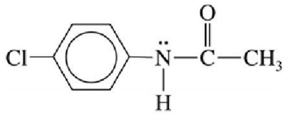
major products obtained

If directing effects oppose each other, the most powerful activating group has the dominant influence.

Electrophilic aromatic substitution

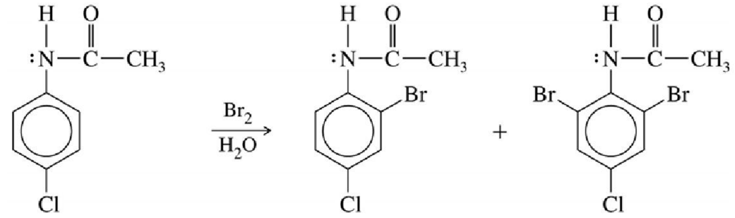
Problem 1

Predict the major product(s) of bromination of *p*-chloroacetanilide.



Solution

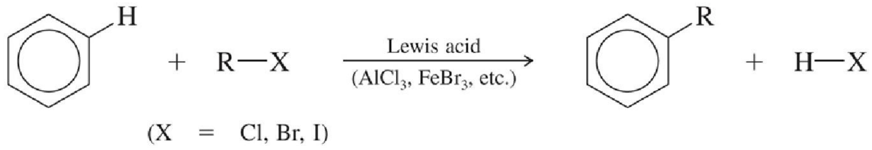
The amide group (–NHCOCH$_3$) is a strong activating and directing group because the nitrogen atom with its nonbonding pair of electrons is bonded to the aromatic ring. The amide group is a stronger director than the chlorine atom, and substitution occurs mostly at the positions ortho to the amide. Like an alkoxyl group, the amide is a particularly strong activating group, and the reaction gives some of the dibrominated product.



p-chloroacetanilide

Electrophilic aromatic substitution

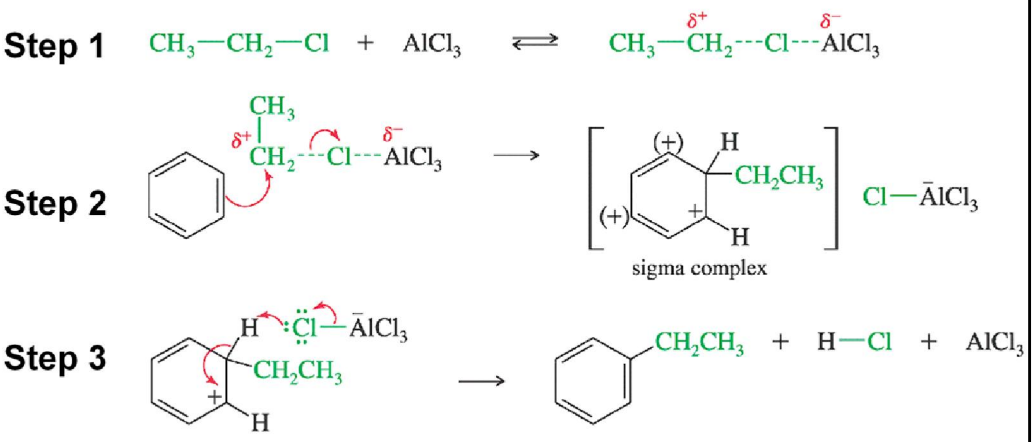
Friedel-Crafts alkylation



- Synthesis of alkyl benzenes from alkyl halides and a Lewis acid, usually $AlCl_3$.
- Reactions of alkyl halide with Lewis acid produces a carbocation, which is the electrophile.

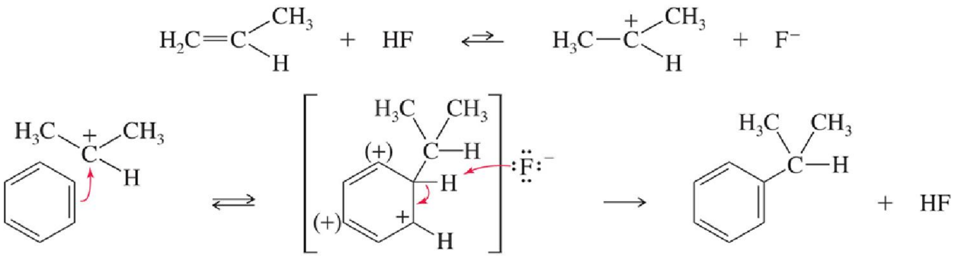
Electrophilic aromatic substitution

Mechanism of Friedel-Crafts alkylation



Electrophilic aromatic substitution

Friedel-Crafts alkylation: protonation of alkenes

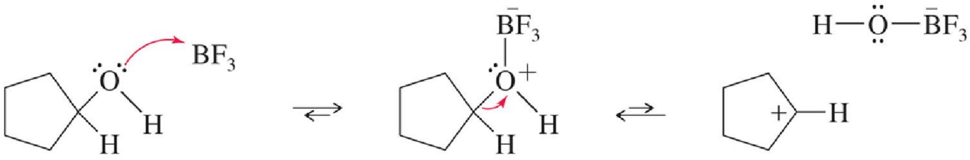


- An alkene can be protonated by HF.
- This weak acid is preferred because the fluoride ion is a weak nucleophile and will not attack the carbocation.

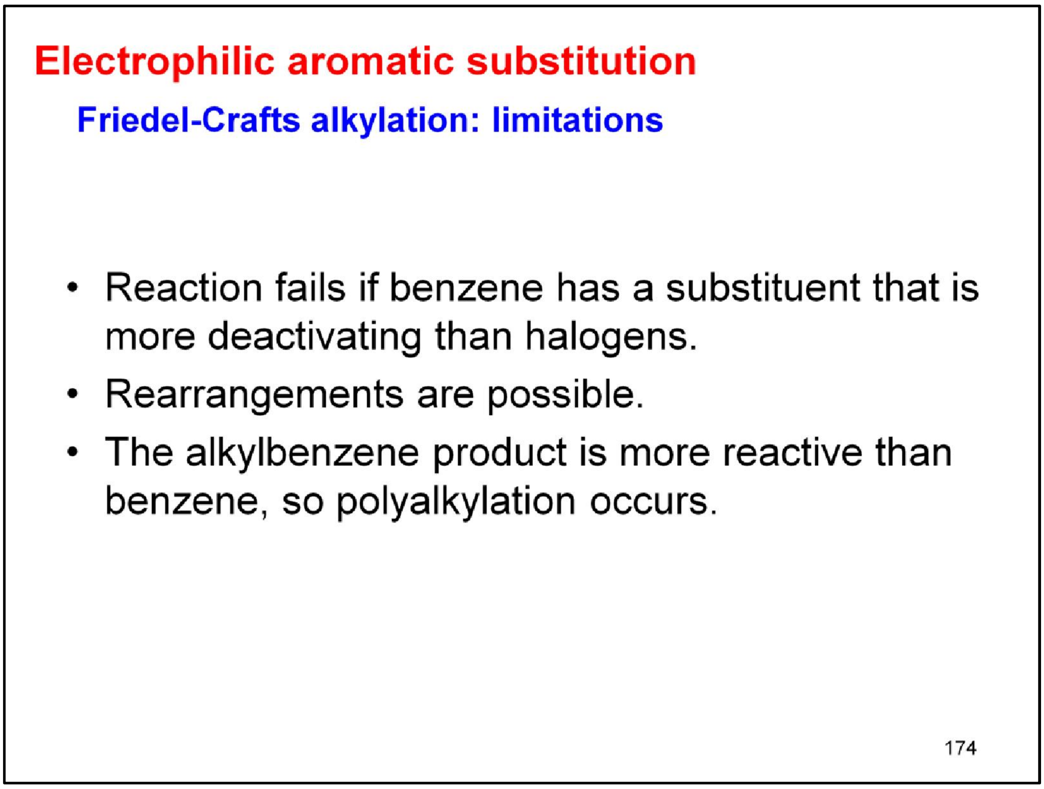
Electrophilic aromatic substitution

Friedel-Crafts alkylation: alcohols and Lewis acids

Formation of the cation



Alcohols can be treated with BF$_3$ to form the carbocation.



Electrophilic aromatic substitution

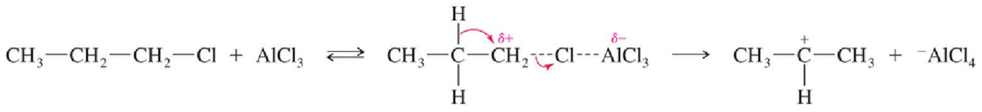
Friedel-Crafts alkylation: limitations

- Reaction fails if benzene has a substituent that is more deactivating than halogens.
- Rearrangements are possible.
- The alkylbenzene product is more reactive than benzene, so polyalkylation occurs.

Electrophilic aromatic substitution

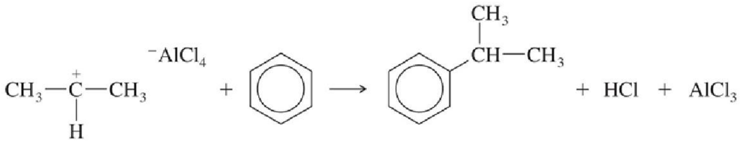
Friedel-Crafts alkylation: rearrangements

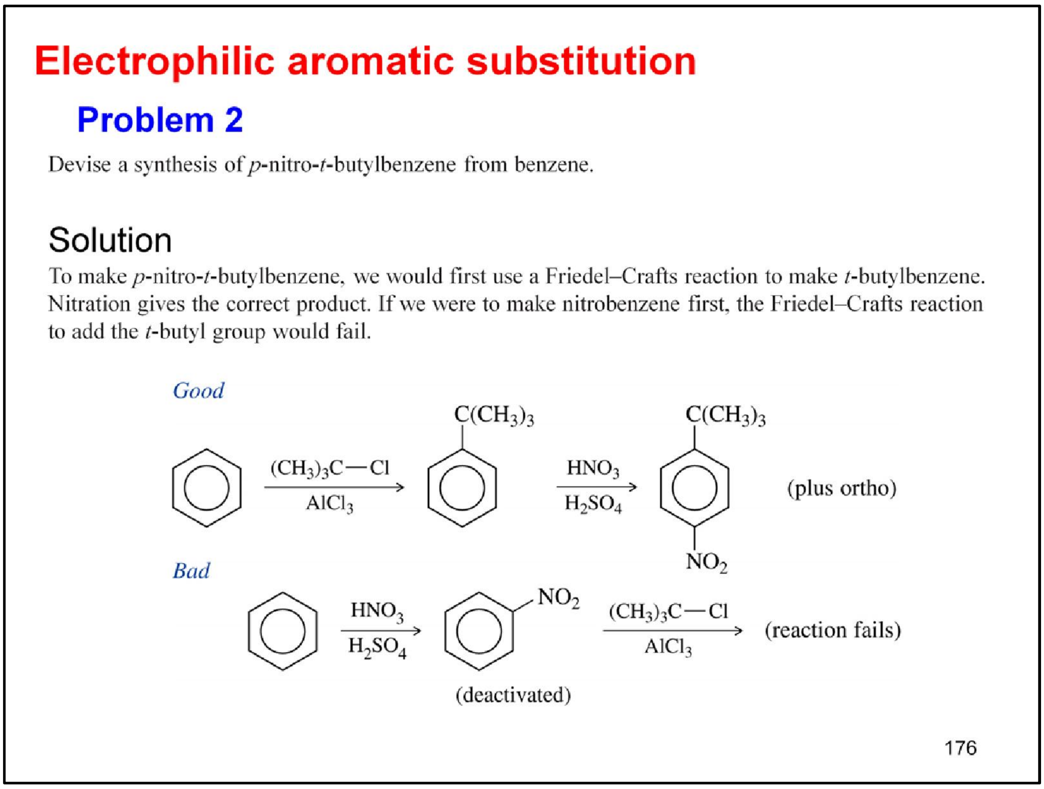
Ionization with rearrangement gives isopropyl cation



$$CH_3{-}CH_2{-}CH_2{-}Cl + AlCl_3 \rightleftharpoons CH_3{-}\underset{H}{\overset{H}{C}}{-}\overset{\delta+}{CH_2}\cdots Cl\cdots\overset{\delta-}{AlCl_3} \longrightarrow CH_3{-}\underset{H}{\overset{+}{C}}{-}CH_3 + {}^{-}AlCl_4$$

Reaction with benzene gives isopropylbenzene





Electrophilic aromatic substitution

Problem 2

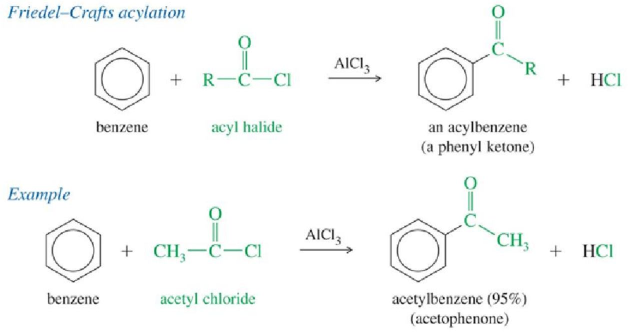
Devise a synthesis of *p*-nitro-*t*-butylbenzene from benzene.

Solution

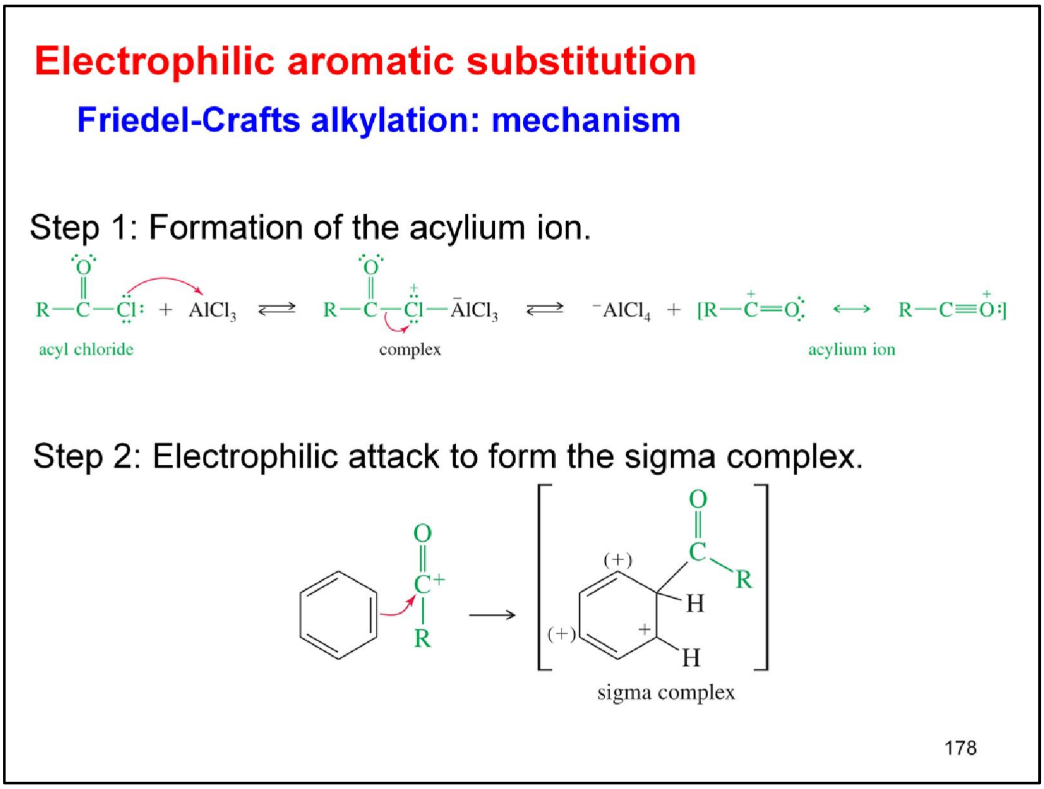
To make *p*-nitro-*t*-butylbenzene, we would first use a Friedel–Crafts reaction to make *t*-butylbenzene. Nitration gives the correct product. If we were to make nitrobenzene first, the Friedel–Crafts reaction to add the *t*-butyl group would fail.

Electrophilic aromatic substitution

Friedel-Crafts acylation



- Acyl chloride is used in place of alkyl chloride.
- The product is a phenyl ketone that is less reactive than benzene.

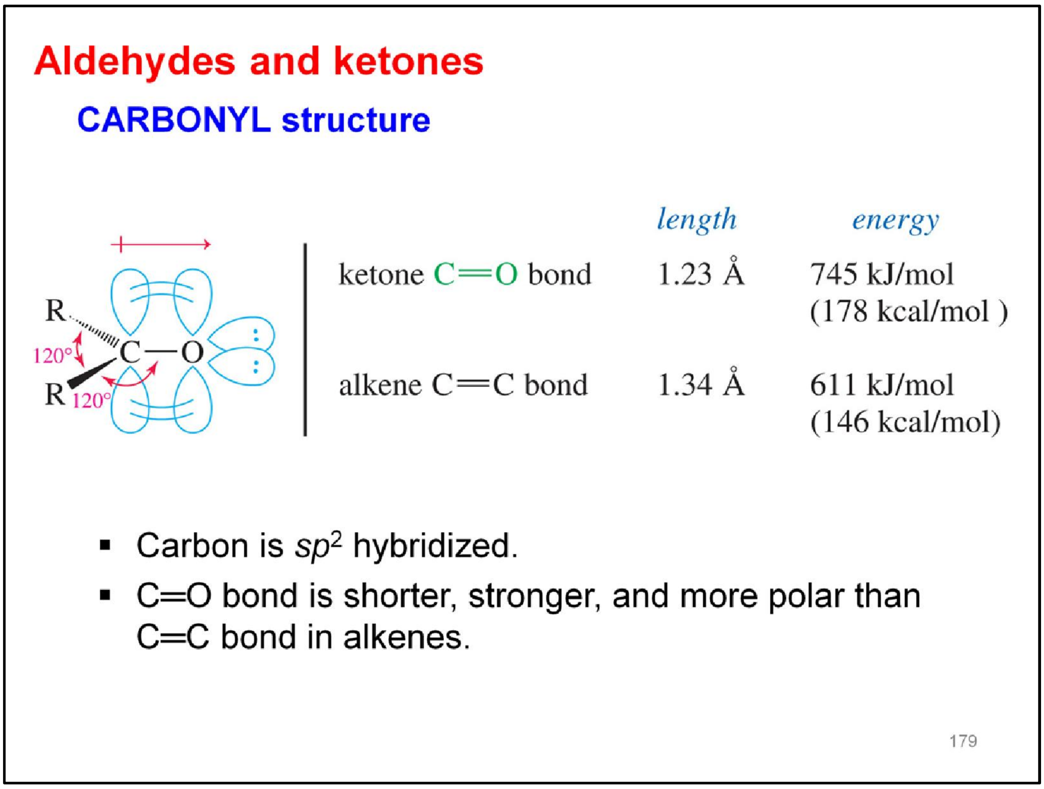


Electrophilic aromatic substitution

Friedel-Crafts alkylation: mechanism

Step 1: Formation of the acylium ion.

Step 2: Electrophilic attack to form the sigma complex.



Aldehydes and ketones

CARBONYL structure

	length	*energy*
ketone C=O bond	1.23 Å	745 kJ/mol (178 kcal/mol)
alkene C=C bond	1.34 Å	611 kJ/mol (146 kcal/mol)

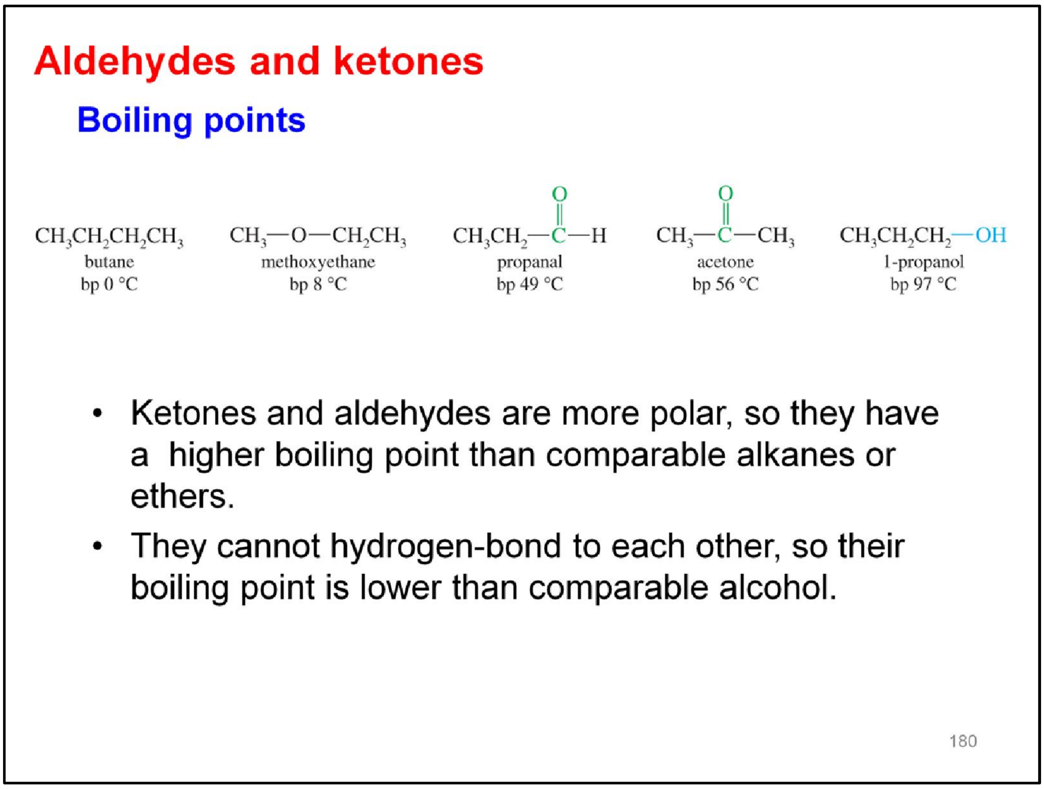
- Carbon is *sp*^{2} hybridized.
- C=O bond is shorter, stronger, and more polar than C=C bond in alkenes.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Boiling points

$CH_3CH_2CH_2CH_3$
butane
bp 0 °C

$CH_3{-}O{-}CH_2CH_3$
methoxyethane
bp 8 °C

$CH_3CH_2{-}\overset{\overset{O}{\|}}{C}{-}H$
propanal
bp 49 °C

$CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH_3$
acetone
bp 56 °C

$CH_3CH_2CH_2{-}OH$
1-propanol
bp 97 °C

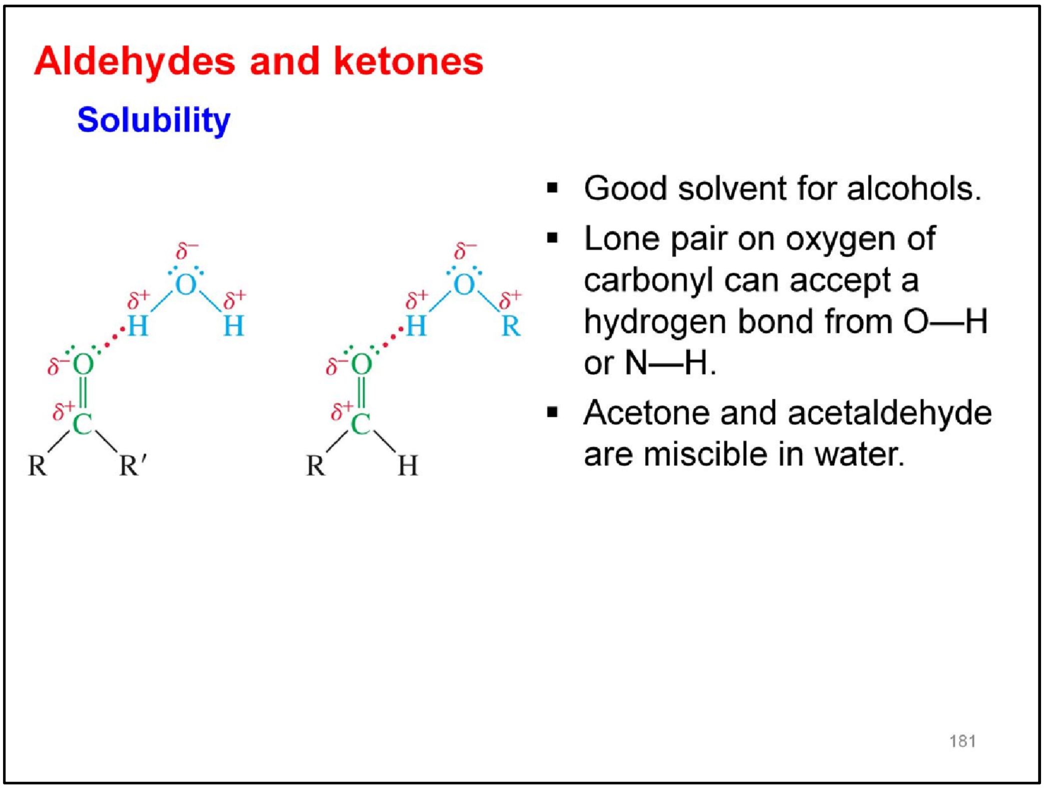
- Ketones and aldehydes are more polar, so they have a higher boiling point than comparable alkanes or ethers.
- They cannot hydrogen-bond to each other, so their boiling point is lower than comparable alcohol.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Solubility

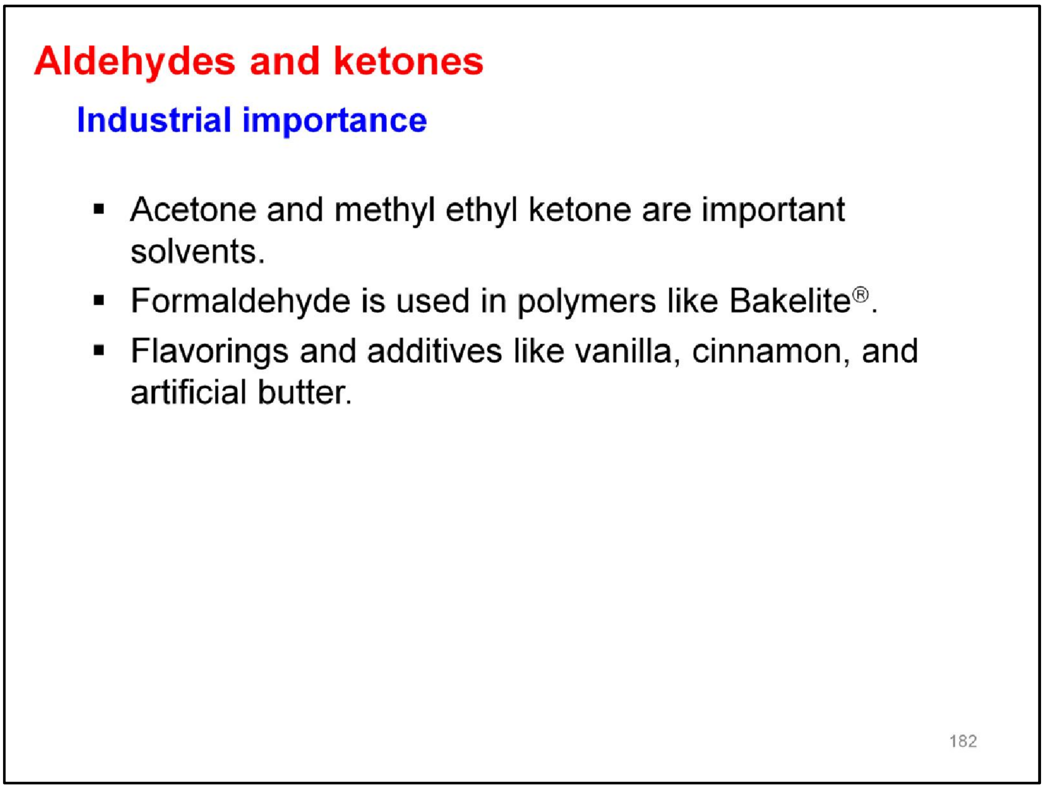
- Good solvent for alcohols.
- Lone pair on oxygen of carbonyl can accept a hydrogen bond from O—H or N—H.
- Acetone and acetaldehyde are miscible in water.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Industrial importance

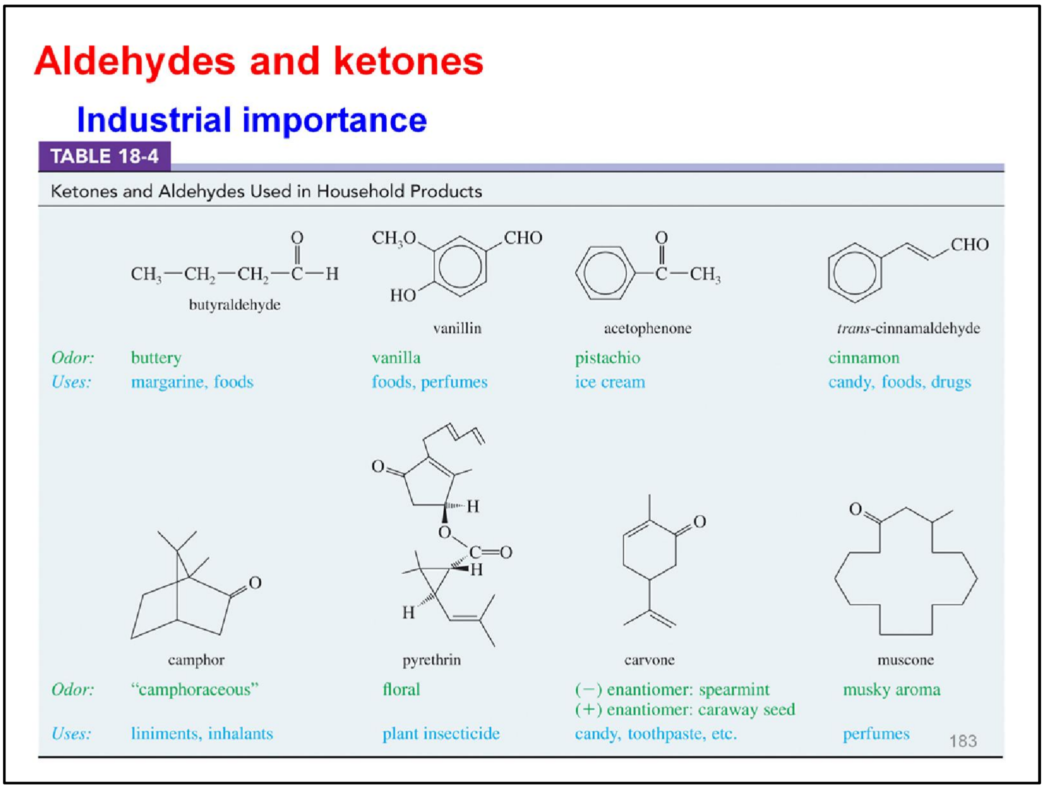
- Acetone and methyl ethyl ketone are important solvents.
- Formaldehyde is used in polymers like Bakelite®.
- Flavorings and additives like vanilla, cinnamon, and artificial butter.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Industrial importance

TABLE 18-4

Ketones and Aldehydes Used in Household Products

	butyraldehyde	vanillin	acetophenone	*trans*-cinnamaldehyde
Odor:	buttery	vanilla	pistachio	cinnamon
Uses:	margarine, foods	foods, perfumes	ice cream	candy, foods, drugs

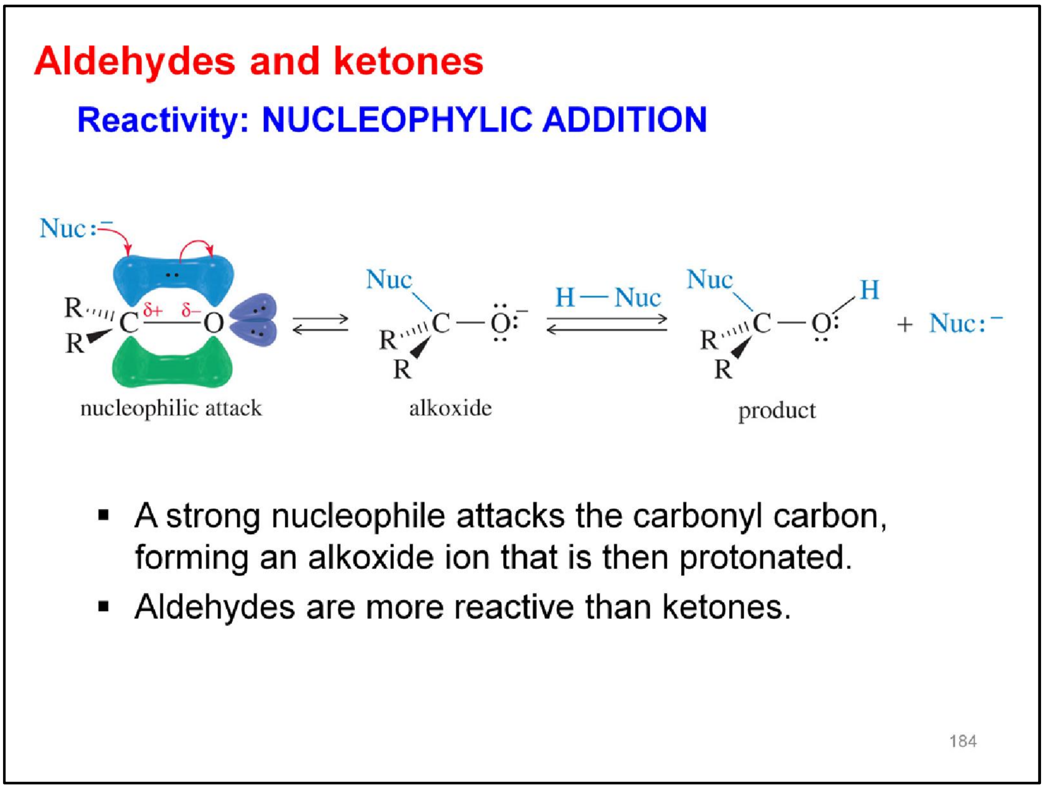
	camphor	pyrethrin	carvone	muscone
Odor:	"camphoraceous"	floral	(−) enantiomer: spearmint (+) enantiomer: caraway seed	musky aroma
Uses:	liniments, inhalants	plant insecticide	candy, toothpaste, etc.	perfumes

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: NUCLEOPHYLIC ADDITION

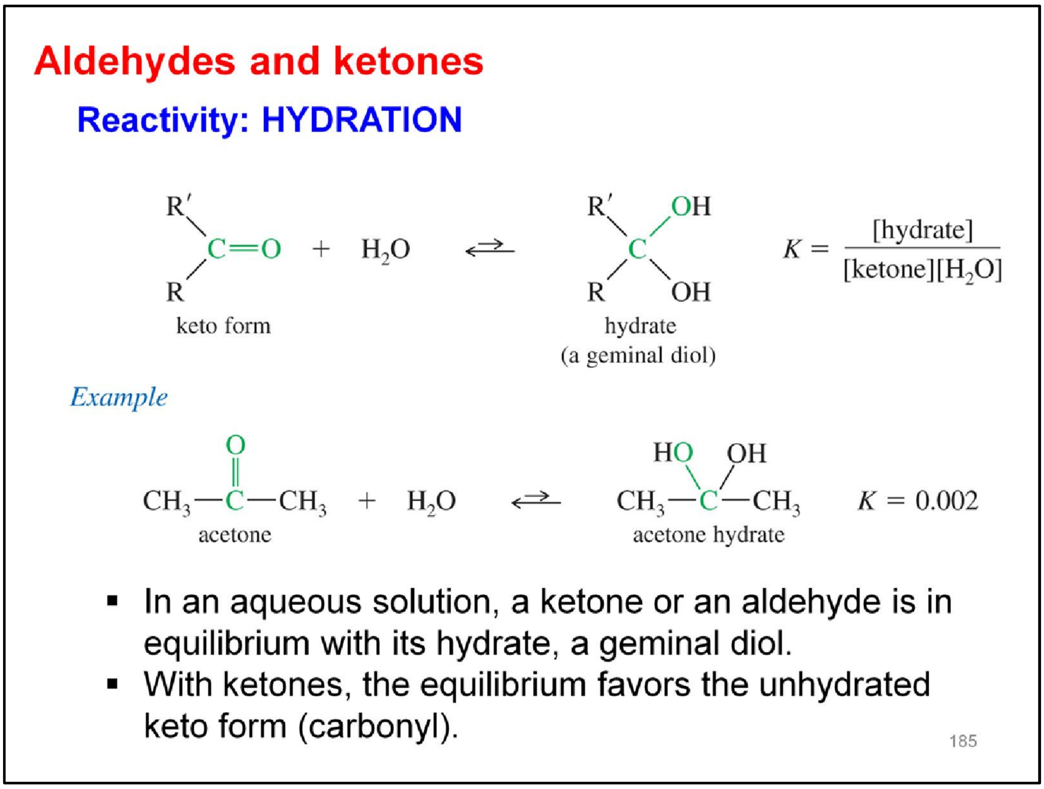
- A strong nucleophile attacks the carbonyl carbon, forming an alkoxide ion that is then protonated.
- Aldehydes are more reactive than ketones.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: HYDRATION

$$R'R\,C{=}O + H_2O \rightleftharpoons R'R\,C(OH)_2 \qquad K = \frac{[\text{hydrate}]}{[\text{ketone}][H_2O]}$$

keto form

hydrate
(a geminal diol)

Example

$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 + H_2O \rightleftharpoons CH_3-\overset{HO\quad OH}{C}-CH_3 \qquad K = 0.002$$

acetone

acetone hydrate

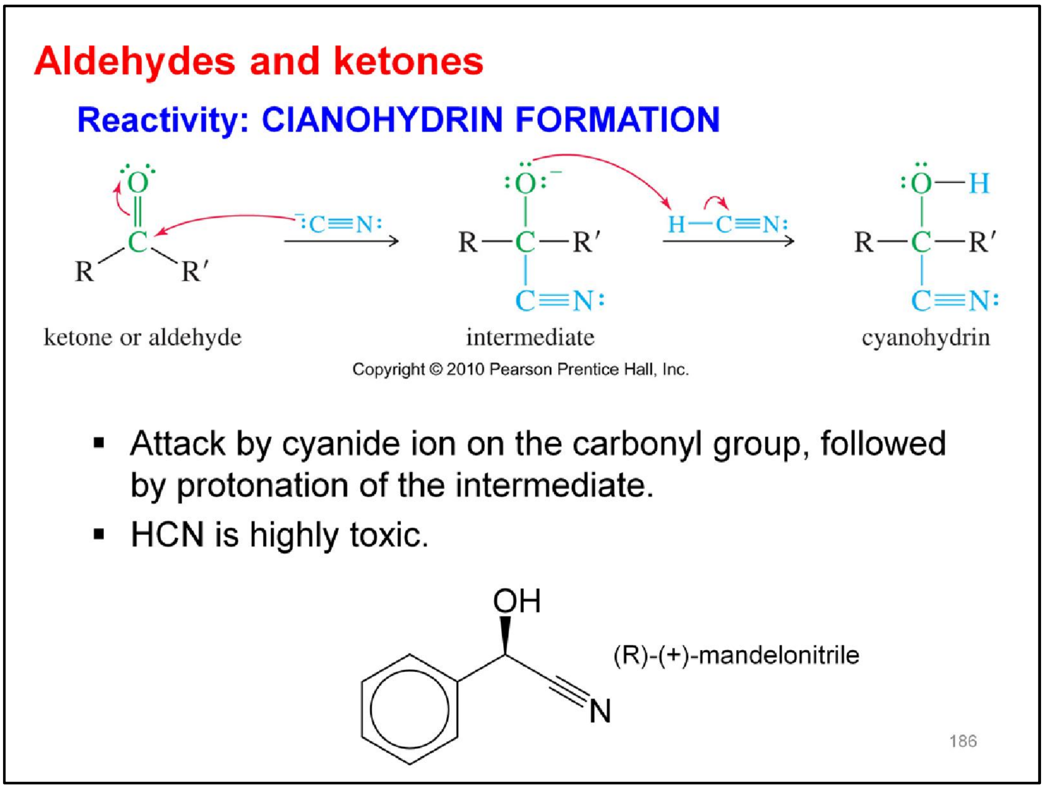
- In an aqueous solution, a ketone or an aldehyde is in equilibrium with its hydrate, a geminal diol.
- With ketones, the equilibrium favors the unhydrated keto form (carbonyl).

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: CIANOHYDRIN FORMATION

ketone or aldehyde

intermediate

cyanohydrin

- Attack by cyanide ion on the carbonyl group, followed by protonation of the intermediate.
- HCN is highly toxic.

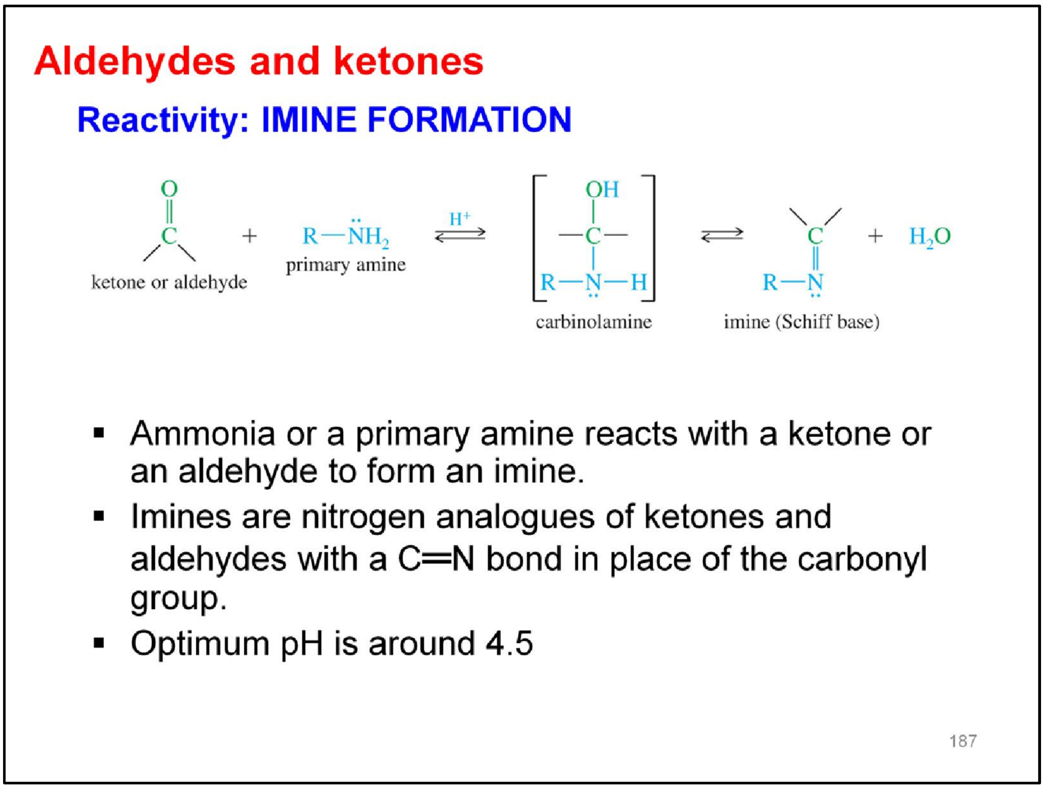
(R)-(+)-mandelonitrile

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: IMINE FORMATION

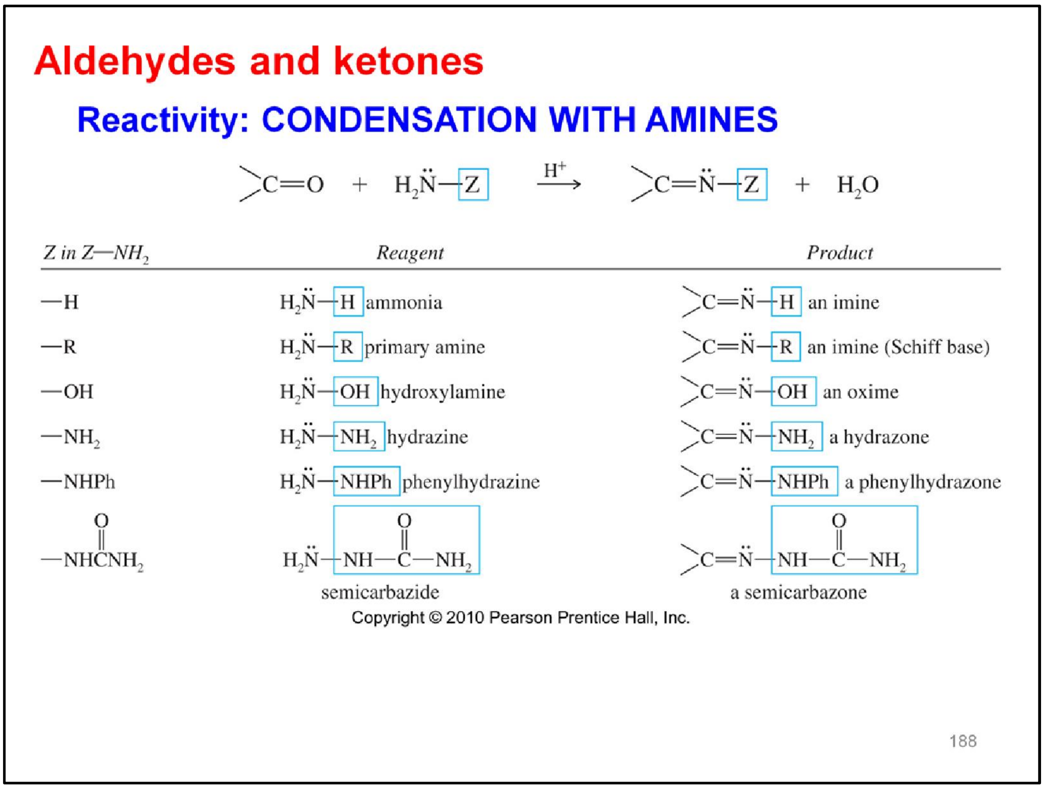
- Ammonia or a primary amine reacts with a ketone or an aldehyde to form an imine.
- Imines are nitrogen analogues of ketones and aldehydes with a C═N bond in place of the carbonyl group.
- Optimum pH is around 4.5

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: CONDENSATION WITH AMINES

$$>C=O \; + \; H_2\ddot{N}-\boxed{Z} \xrightarrow{H^+} >C=\ddot{N}-\boxed{Z} \; + \; H_2O$$

Z in Z—NH$_2$	*Reagent*	*Product*
—H	$H_2\ddot{N}-\boxed{H}$ ammonia	$>C=\ddot{N}-\boxed{H}$ an imine
—R	$H_2\ddot{N}-\boxed{R}$ primary amine	$>C=\ddot{N}-\boxed{R}$ an imine (Schiff base)
—OH	$H_2\ddot{N}-\boxed{OH}$ hydroxylamine	$>C=\ddot{N}-\boxed{OH}$ an oxime
—NH$_2$	$H_2\ddot{N}-\boxed{NH_2}$ hydrazine	$>C=\ddot{N}-\boxed{NH_2}$ a hydrazone
—NHPh	$H_2\ddot{N}-\boxed{NHPh}$ phenylhydrazine	$>C=\ddot{N}-\boxed{NHPh}$ a phenylhydrazone
$-NH\overset{\overset{O}{\|}}{C}NH_2$	$H_2\ddot{N}-\boxed{NH-\overset{\overset{O}{\|}}{C}-NH_2}$ semicarbazide	$>C=\ddot{N}-\boxed{NH-\overset{\overset{O}{\|}}{C}-NH_2}$ a semicarbazone

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

Aldehydes and ketones

Reactivity: FORMATION OF ACETAL

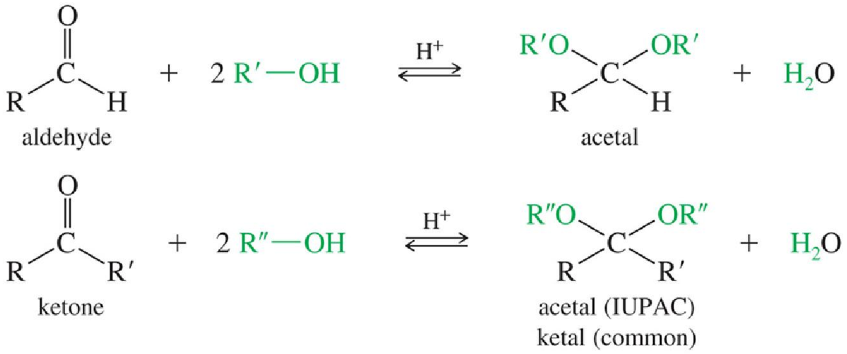
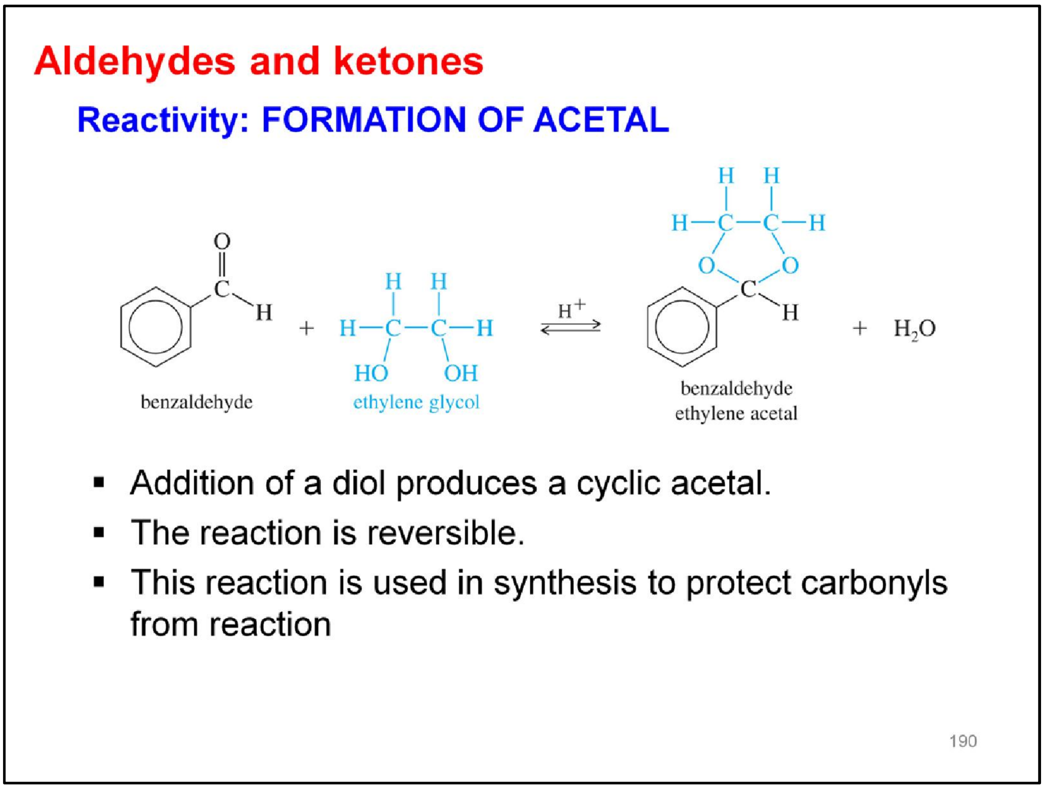


Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: FORMATION OF ACETAL

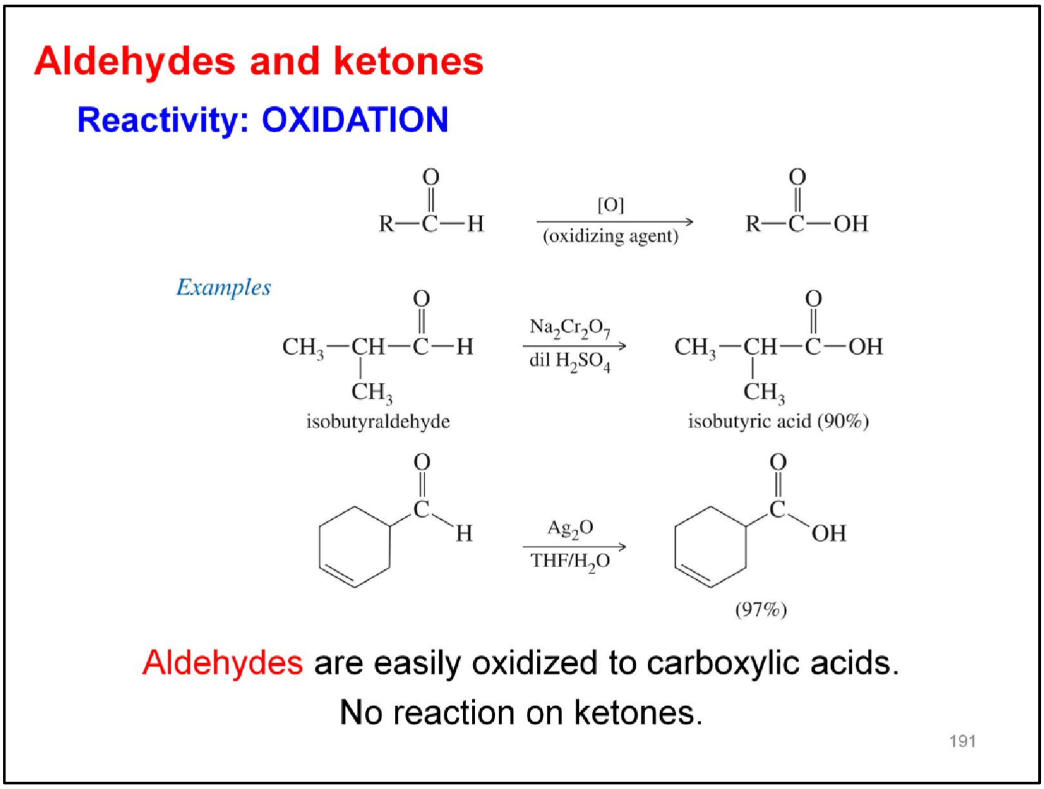
- Addition of a diol produces a cyclic acetal.
- The reaction is reversible.
- This reaction is used in synthesis to protect carbonyls from reaction

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: OXIDATION

$$R-\overset{O}{\overset{\|}{C}}-H \xrightarrow[\text{(oxidizing agent)}]{[O]} R-\overset{O}{\overset{\|}{C}}-OH$$

Examples

$$CH_3-\underset{CH_3}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-H \xrightarrow[\text{dil } H_2SO_4]{Na_2Cr_2O_7} CH_3-\underset{CH_3}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-OH$$

isobutyraldehyde

isobutyric acid (90%)

$$\xrightarrow[THF/H_2O]{Ag_2O}$$

(97%)

Aldehydes are easily oxidized to carboxylic acids.

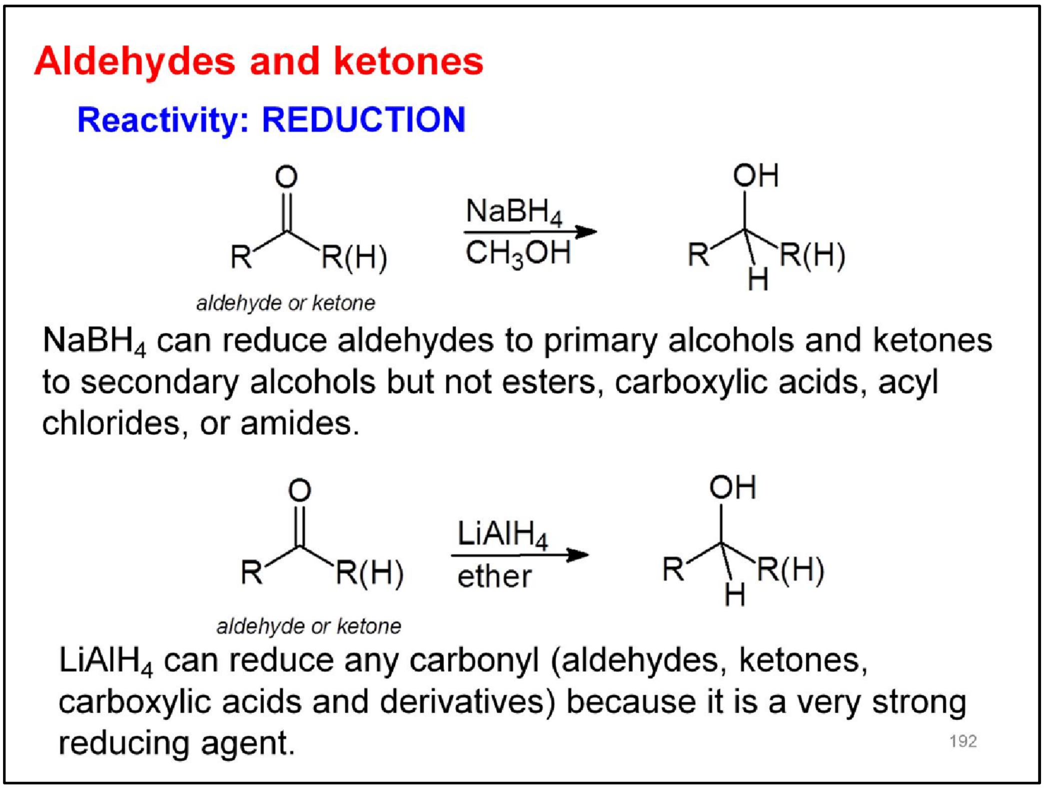
No reaction on ketones.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: REDUCTION

$NaBH_4$ can reduce aldehydes to primary alcohols and ketones to secondary alcohols but not esters, carboxylic acids, acyl chlorides, or amides.

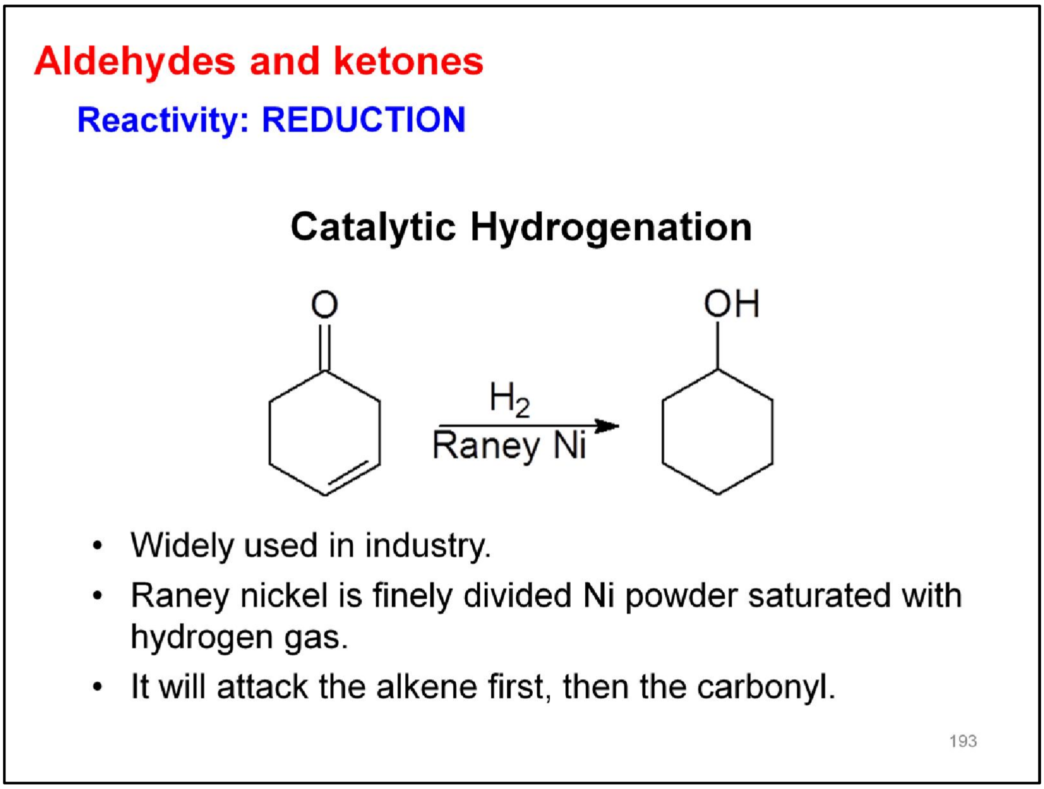
$LiAlH_4$ can reduce any carbonyl (aldehydes, ketones, carboxylic acids and derivatives) because it is a very strong reducing agent.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: REDUCTION

Catalytic Hydrogenation

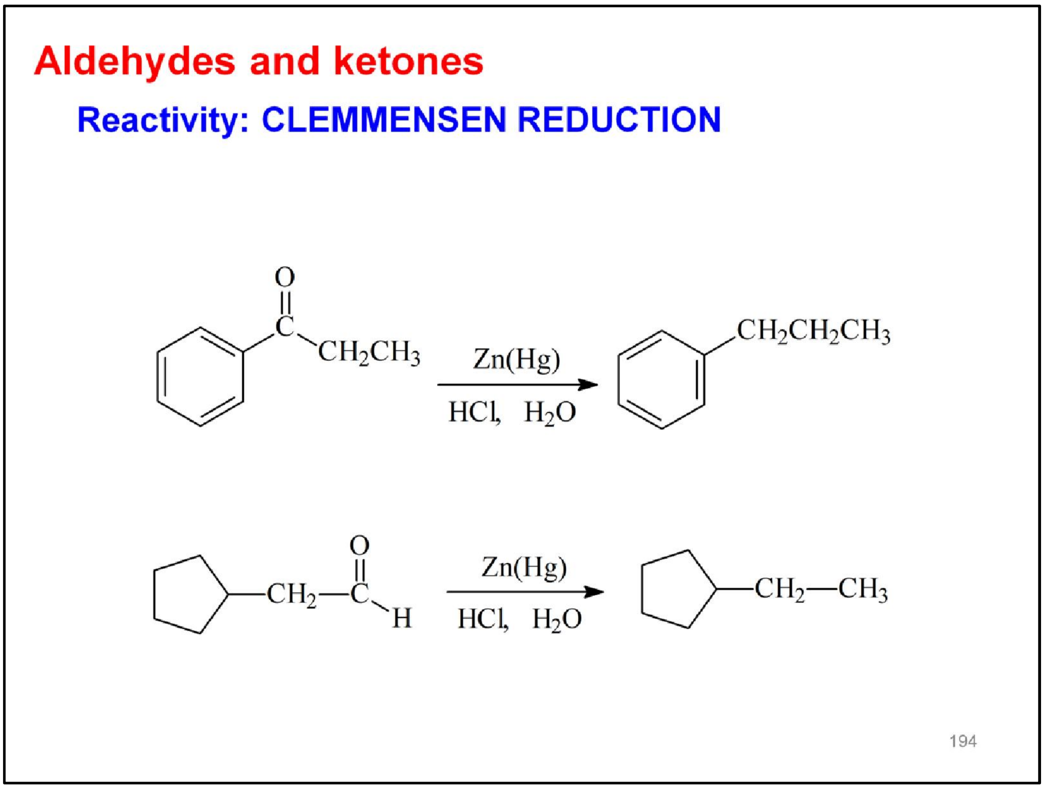
- Widely used in industry.
- Raney nickel is finely divided Ni powder saturated with hydrogen gas.
- It will attack the alkene first, then the carbonyl.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

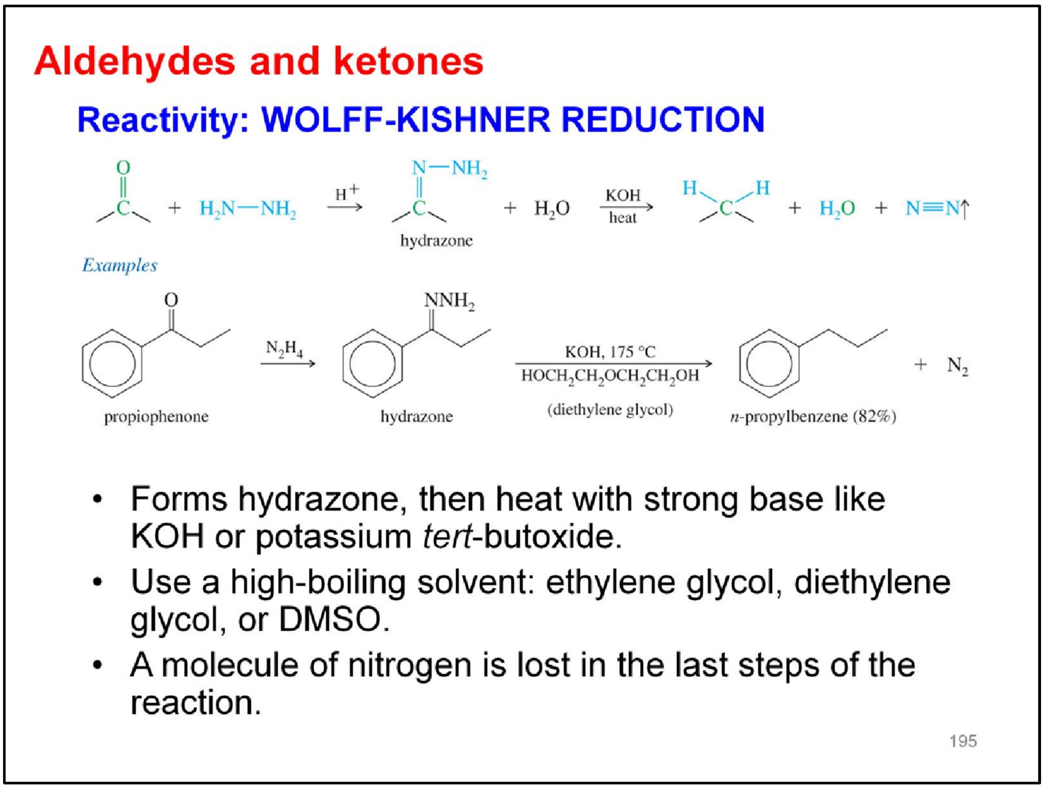
Reactivity: CLEMMENSEN REDUCTION

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.



Aldehydes and ketones

Reactivity: WOLFF-KISHNER REDUCTION

- Forms hydrazone, then heat with strong base like KOH or potassium *tert*-butoxide.
- Use a high-boiling solvent: ethylene glycol, diethylene glycol, or DMSO.
- A molecule of nitrogen is lost in the last steps of the reaction.

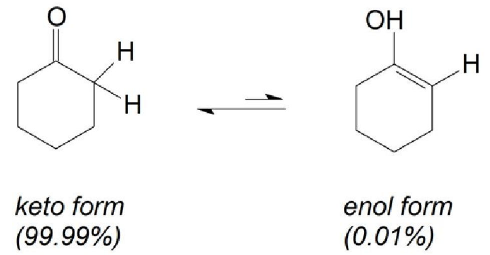
Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

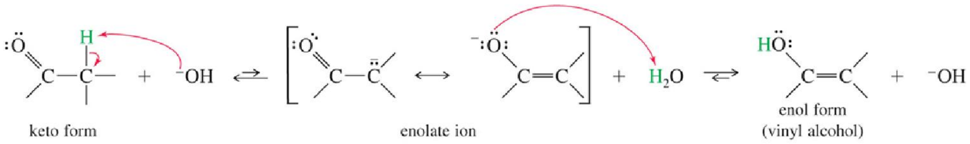
Keto-enol tautomerism



- Tautomerization is an interconversion of isomers that occur through the migration of a proton and the movement of a double bond.
- Tautomers are not resonance form.

Keto-enol tautomerism

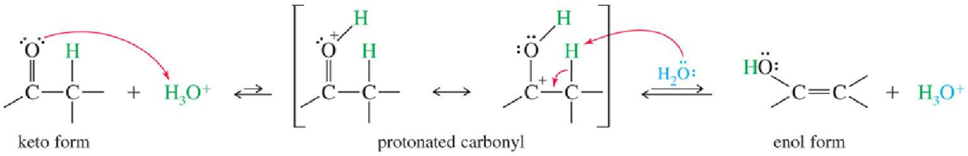
Base-catalyzed tautomerism



- In the presence of strong bases, ketones and aldehydes act as weak proton acids.
- A proton on the a carbon is abstracted to form a resonance-stabilized enolate ion with the negative charge spread over a carbon atom and an oxygen atom.
- The equilibrium favors the keto form over the enolate ion.

Keto-enol tautomerism

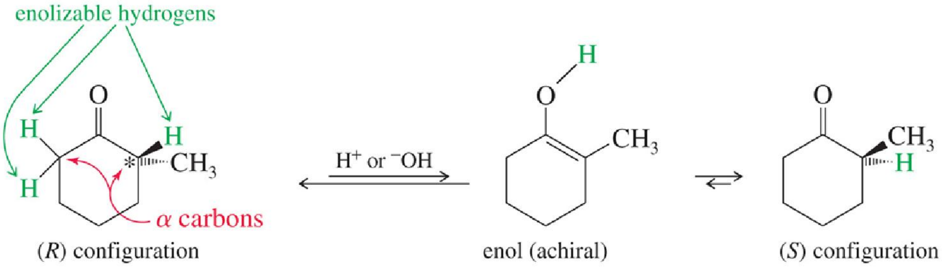
Base-catalyzed tautomerism



- In acid, a proton is moved from the α-carbon to oxygen by first protonating oxygen and then removing a proton from the carbon.

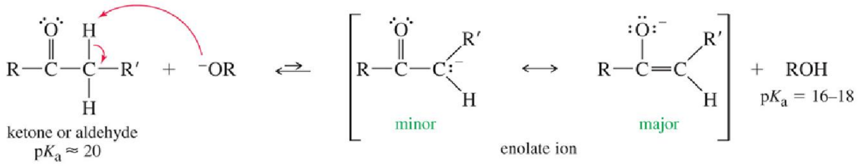
Keto-enol tautomerism

Racemization

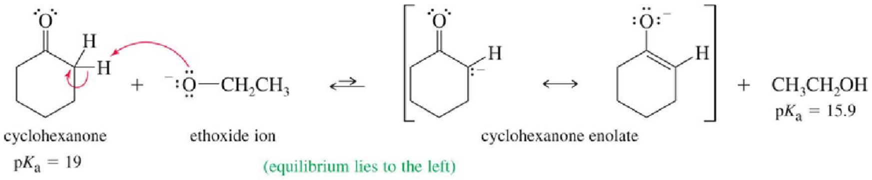


- For aldehydes and ketones, the keto form is greatly favored at equilibrium.
- If a chiral carbon has an enolizable hydrogen atom, a trace of acid or base allows that carbon to invert its configuration, with the enol serving as the intermediate. This is called ***racemization***.

Acidity of α Hydrogen



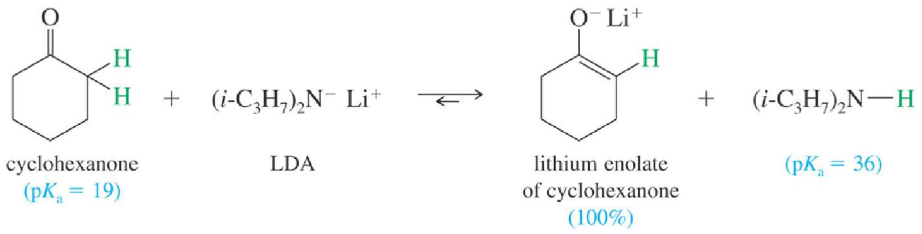
Example



The equilibrium mixture contains only a small fraction of the deprotonated, enolate form.

Acidity of α Hydrogen

Example



- When LDA reacts with a ketone, it abstracts the α-proton to form the lithium salt of the enolate.

Acidity of α Hydrogen

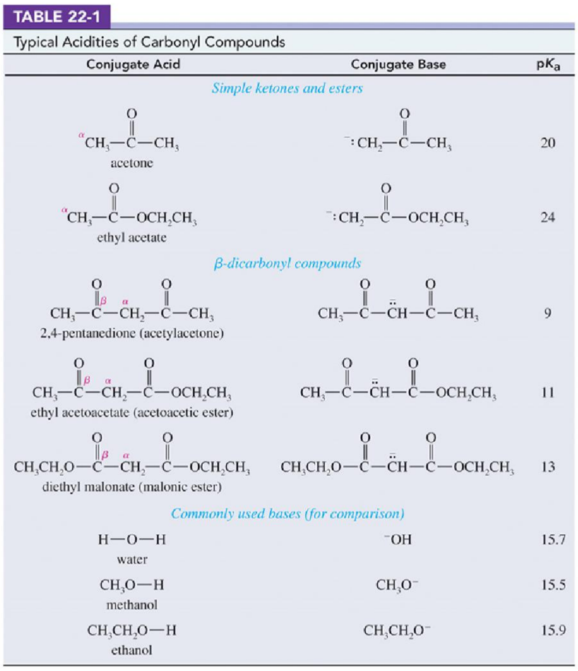
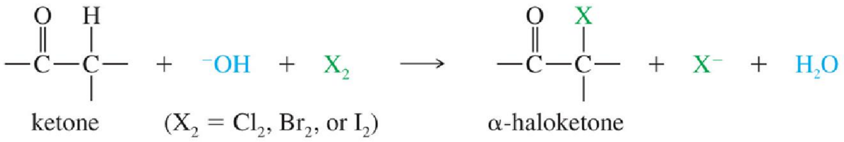


TABLE 22-1

Typical Acidities of Carbonyl Compounds

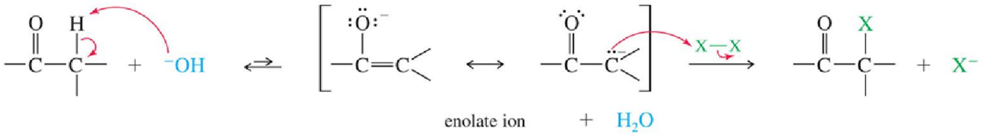
Conjugate Acid	Conjugate Base	pK_a
Simple ketones and esters		
$^{\alpha}CH_3-\overset{\overset{O}{\|}}{C}-CH_3$ acetone	$^{-}:CH_2-\overset{\overset{O}{\|}}{C}-CH_3$	20
$^{\alpha}CH_3-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$ ethyl acetate	$^{-}:CH_2-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$	24
β-dicarbonyl compounds		
$CH_3-\overset{\overset{O}{\|}}{C}^{\beta}-\overset{\alpha}{CH_2}-\overset{\overset{O}{\|}}{C}-CH_3$ 2,4-pentanedione (acetylacetone)	$CH_3-\overset{\overset{O}{\|}}{C}-\ddot{C}H-\overset{\overset{O}{\|}}{C}-CH_3$	9
$CH_3-\overset{\overset{O}{\|}}{C}^{\beta}-\overset{\alpha}{CH_2}-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$ ethyl acetoacetate (acetoacetic ester)	$CH_3-\overset{\overset{O}{\|}}{C}-\ddot{C}H-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$	11
$CH_3CH_2O-\overset{\overset{O}{\|}}{C}^{\beta}-\overset{\alpha}{CH_2}-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$ diethyl malonate (malonic ester)	$CH_3CH_2O-\overset{\overset{O}{\|}}{C}-\ddot{C}H-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$	13
Commonly used bases (for comparison)		
$H-O-H$ water	^{-}OH	15.7
CH_3O-H methanol	CH_3O^{-}	15.5
CH_3CH_2O-H ethanol	$CH_3CH_2O^{-}$	15.9

α Halogenation of ketones



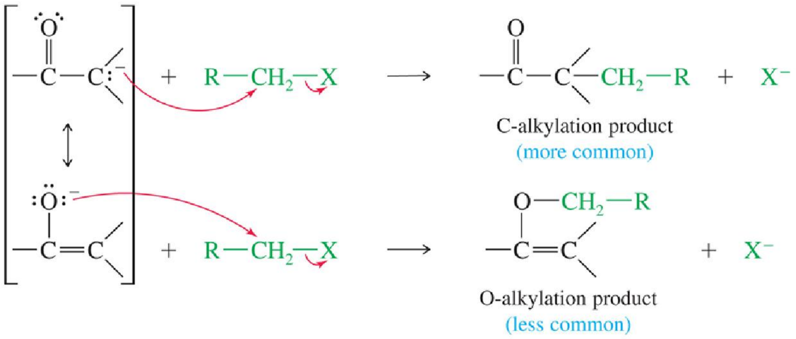
- When a ketone is treated with a halogen and a base, an α halogenation reaction occurs.
- The reaction is called ***base-promoted***, rather than base-catalyzed, because a full equivalent of the base is consumed in the reaction.

α Halogenation of ketones



- The base-promoted halogenation takes place by a nucleophilic attack of an enolate ion on the electrophilic halogen molecule.
- The products are the halogenated ketone and a halide ion.

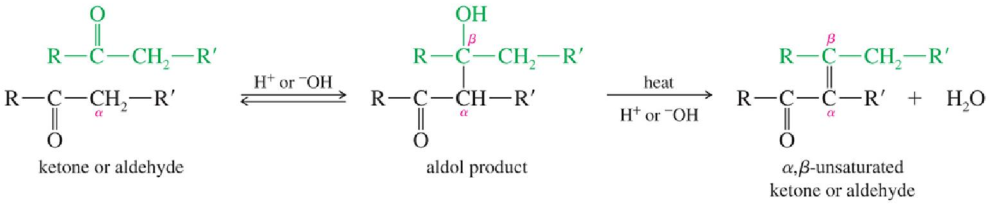
α Alkylation



- Because the enolate has two nucleophilic sites (the oxygen and the α carbon), it can react at either of these sites.
- The reaction usually takes place primarily at the α–carbon, forming a new C—C bond.

Aldol condensation

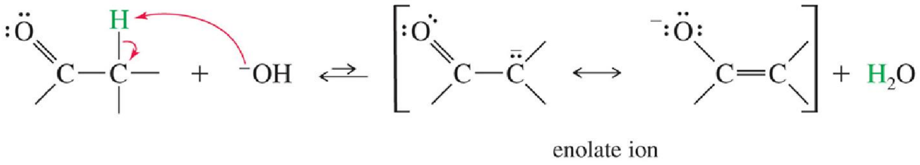
The aldol condensation



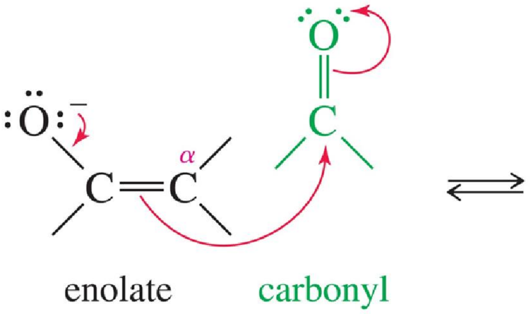
- Under basic conditions, the aldol condensation involves the nucleophilic addition of an enolate ion to another carbonyl group.
- When the reaction is carried out at low temperatures, the β-hydroxy carbonyl compound can be isolated.
- Heating will dehydrate the aldol product to the α–β unsaturated compound.

Aldol condensation

Step 1

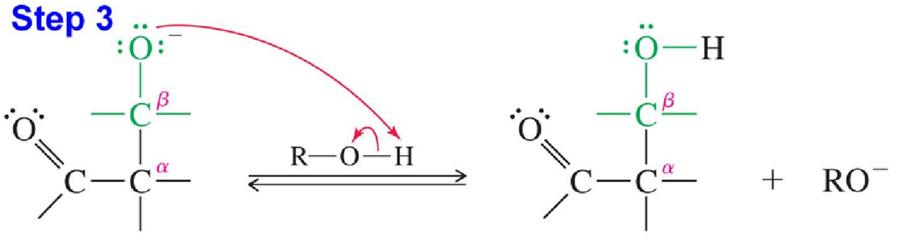


Step 2



Aldol condensation

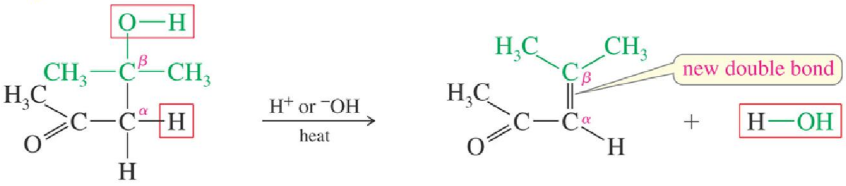
Step 3



alkoxide

aldol product

Step 4



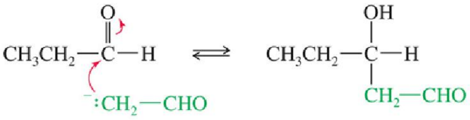
diacetone alcohol

4-methyl-3-penten-2-one
(mesityl oxide)

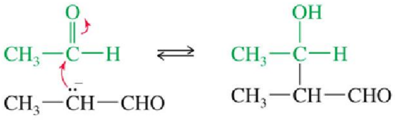
Aldol condensation

Crossed aldol condensation

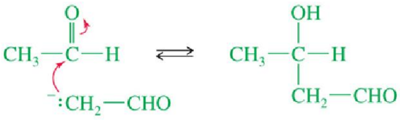
Enolate of ethanal adds to propanal



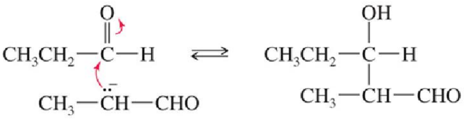
Enolate of propanal adds to ethanal



Self-condensation of ethanal

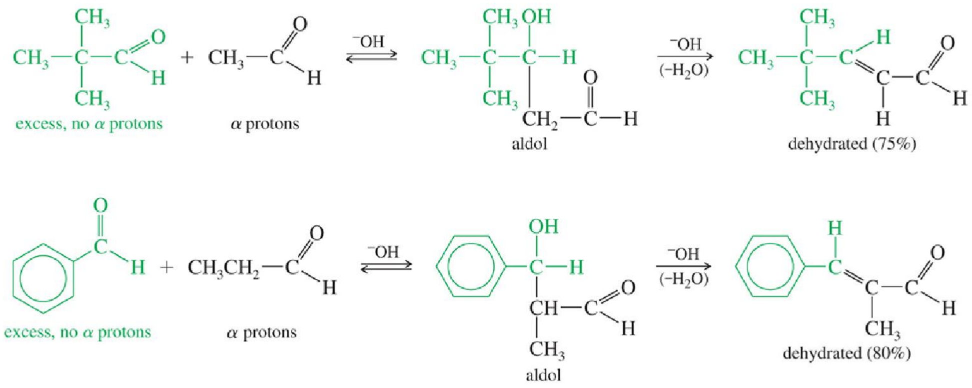


Self-condensation of propanal

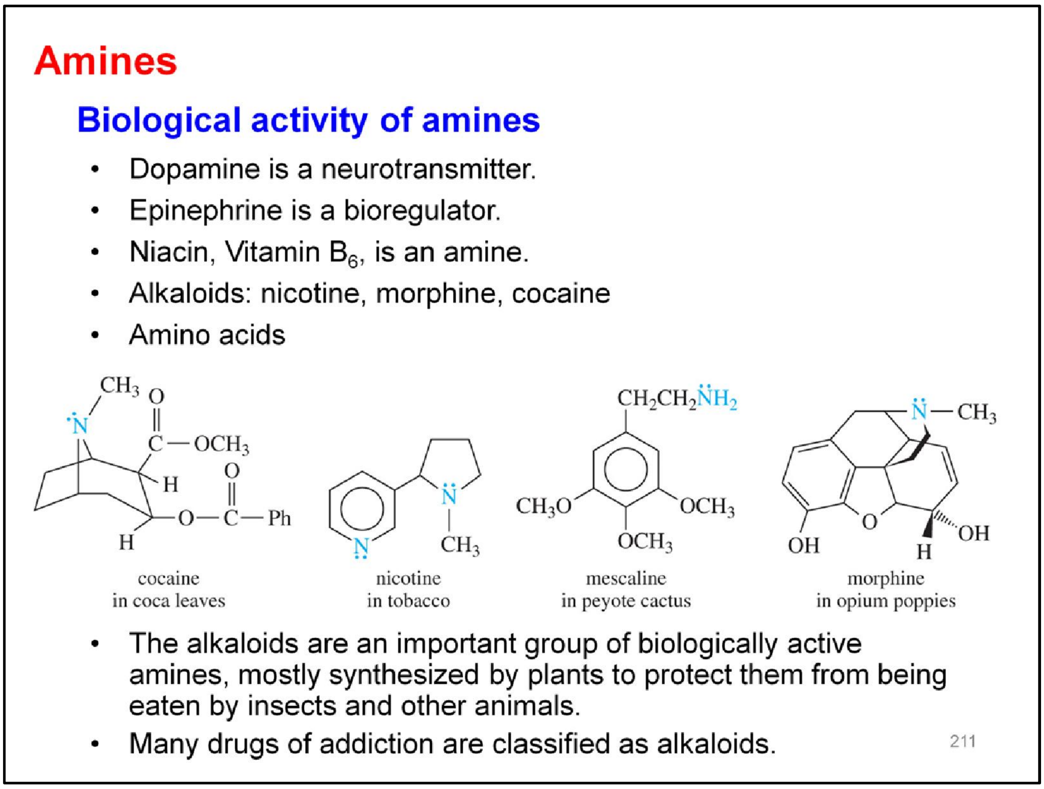


Aldol condensation

Successful aldol condensation



Successful only if one carbonylic compounds has no H in α position



Amines

Biological activity of amines

- Dopamine is a neurotransmitter.
- Epinephrine is a bioregulator.
- Niacin, Vitamin B$_6$, is an amine.
- Alkaloids: nicotine, morphine, cocaine
- Amino acids

cocaine
in coca leaves

nicotine
in tobacco

mescaline
in peyote cactus

morphine
in opium poppies

- The alkaloids are an important group of biologically active amines, mostly synthesized by plants to protect them from being eaten by insects and other animals.
- Many drugs of addiction are classified as alkaloids.

Figure: 03_04.jpg

Title:
Melting Points of Alkanes

Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

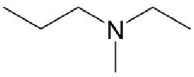
Amines

Classification

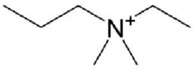
- ***Primary (1°)***: Has one alkyl group bonded to the nitrogen (RNH_2).

- ***Secondary (2°)***: Has two alkyl groups bonded to the nitrogen (R_2NH).

- ***Tertiary (3°)***: Has three alkyl groups bonded to the nitrogen (R_3N).

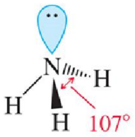


- ***Quaternary (4°)***: Has four alkyl groups bonded to the nitrogen and the nitrogen bears a positive charge (R_4N^+).

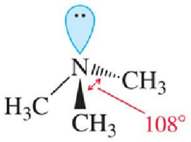


Amines

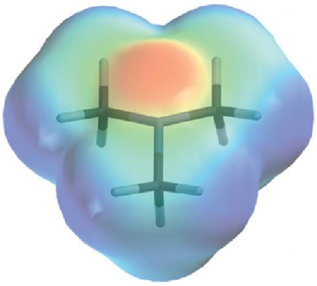
Structure of amines



ammonia



trimethylamine

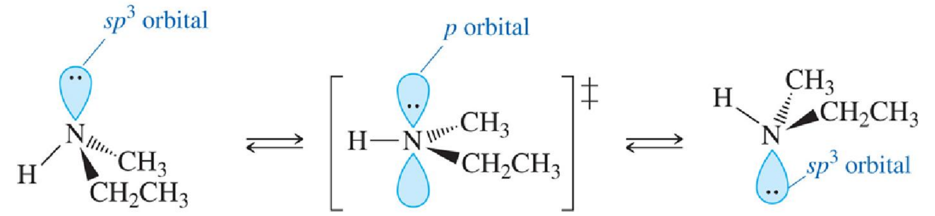


electrostatic potential
map for trimethylamine

- Nitrogen is *sp*^{3} hybridized with a lone pair of electrons.
- The angle is less than 109.5º.

Amines

Interconversion of chiral amines



(R)-ethylmethylamine

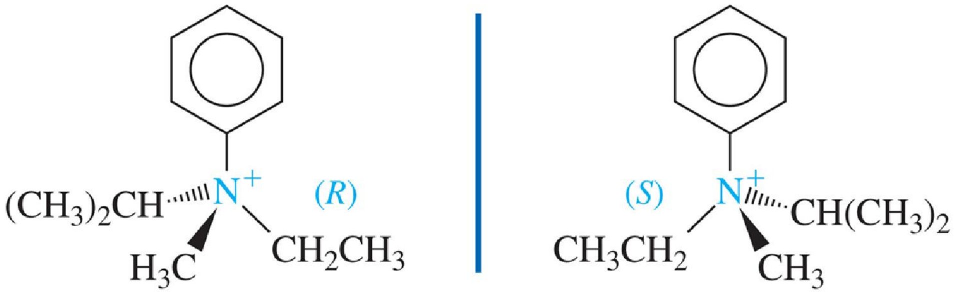
[transition state]

(S)-ethylmethylamine

Nitrogen may have three different groups and a lone pair, but enantiomers cannot be isolated due to inversion around N.

Amines

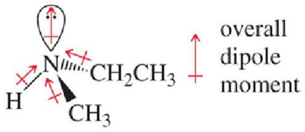
Chiral quaternary ammonium salts

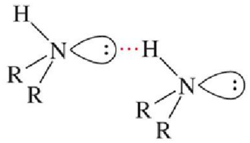


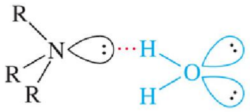
- Quaternary ammonium salts may have a chiral nitrogen atom if the four substituents are different.
- Inversion of configuration is not possible because there is no lone pair to undergo nitrogen inversion.

Amines

Boiling points




1° or 2° amine:
hydrogen bond donor and acceptor


3° amine:
hydrogen bond acceptor only

- N—H less polar than O—H.
- Weaker hydrogen bonds, so amines will have a lower boiling point than the corresponding alcohol.
- Tertiary amines cannot hydrogen-bond, so they have lower boiling points than primary and secondary amines.

Amines

Solubility and odor

- Small amines (< 6 Cs) are soluble in water.
- All amines accept hydrogen bonds from water and alcohol.
- Branching increases solubility.
- Most amines smell like rotting fish.

$NH_2CH_2CH_2CH_2CH_2CH_2NH_2$

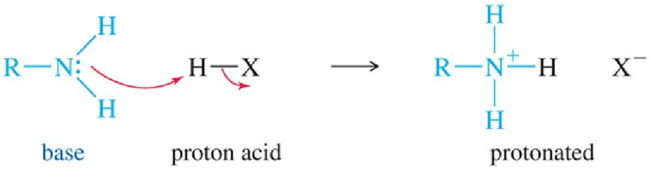
1,5-pentanediamine or cadaverine

Amines

Basicity of amines

- Lone pair of electrons on nitrogen can accept a proton from an acid.

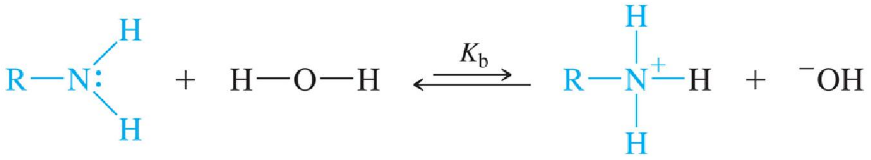
Reaction of an amine as a proton base



- Aqueous solutions are basic to litmus.
- Ammonia pK_b = 4.74
- Alkyl amines are usually stronger bases than ammonia.
- Increasing the number of alkyl groups decreases solvation of ion, so 2° and 3° amines are similar to 1° amines in basicity.

Amines

Base-dissociation constants

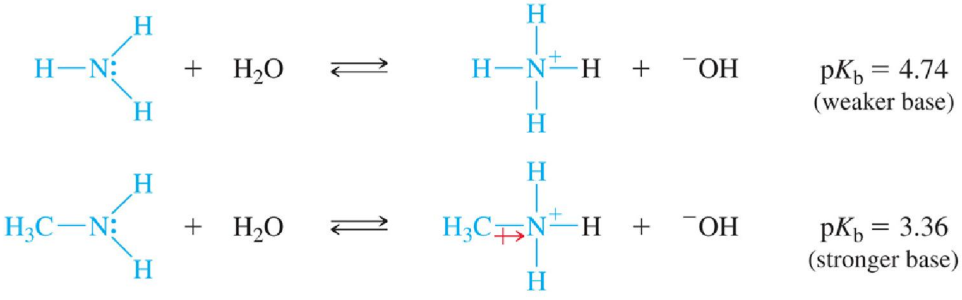


$$K_b = \frac{[RNH_3^+][^-OH]}{[RNH_2]} \qquad pK_b = -\log_{10} K_b$$

- An amine can abstract a proton from water, giving an ammonium ion and a hydroxide ion.
- The equilibrium constant for this reaction is called the ***base-dissociation constant*** for the amine, symbolized by K_b.

Amines

Alkyl groups stabilization of amines



$$H-\ddot{N}H_2 + H_2O \rightleftharpoons H-\overset{+}{N}H_3 + {}^-OH \qquad pK_b = 4.74$$

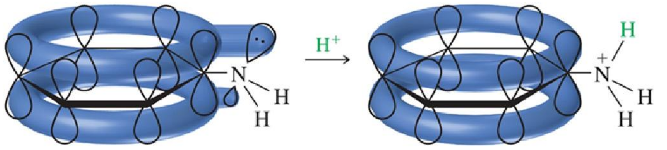
$$H_3C-\ddot{N}H_2 + H_2O \rightleftharpoons H_3C-\overset{+}{N}H_3 + {}^-OH \qquad pK_b = 3.36$$

stabilized by the alkyl group

Alkyl groups make the nitrogen a stronger base than ammonia.

Amines

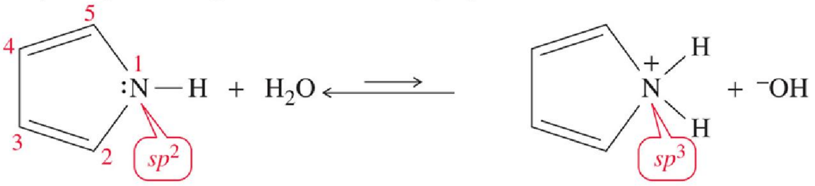
Resonance effect



aniline
stabilized by overlap with the ring

anilinium ion
no overlap is possible

$pK_b = 9.42$



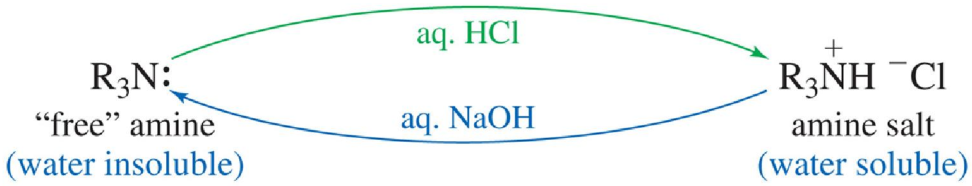
pyrrole, $pK_b = 13.6$
(weak base)

N-protonated pyrrole, $pK_a = 0.4$
(strong acid)

When protonated, stabilization by aromatic stabilization is lost.

Amines

Ammonium salts



$R_3N\!:$ $\xrightarrow{\text{aq. HCl}}$ $R_3\overset{+}{N}H\ {}^{-}Cl$

$R_3\overset{+}{N}H\ {}^{-}Cl$ $\xrightarrow{\text{aq. NaOH}}$ $R_3N\!:$

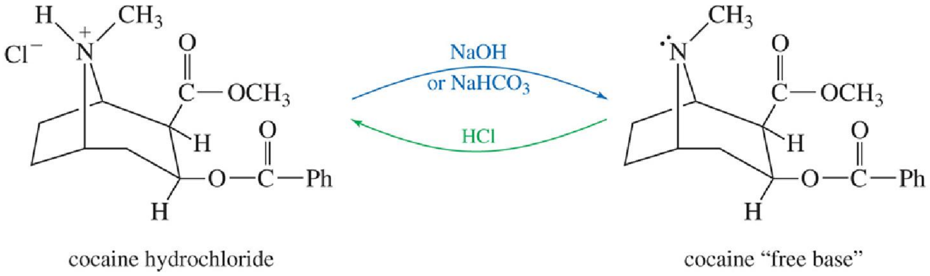
"free" amine (water insoluble)

amine salt (water soluble)

- Ionic solids with high melting points.
- Soluble in water.
- No fishy odor.
- Amines purifications takes advantage of formation of ammonium salts.

Amines

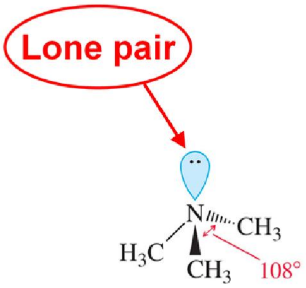
Ammonium salts



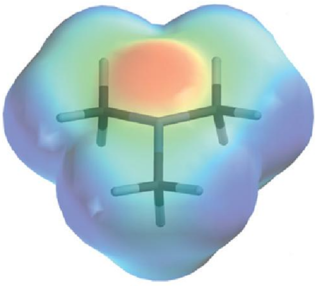
- Cocaine is usually smuggled and "snorted" as the hydrochloride salt.
- Treating cocaine hydrochloride with sodium hydroxide and extracting it into ether converts it back to the volatile "free base" for smoking.

Amines

Reactivity: AMINES AS NUCLEOPHILES



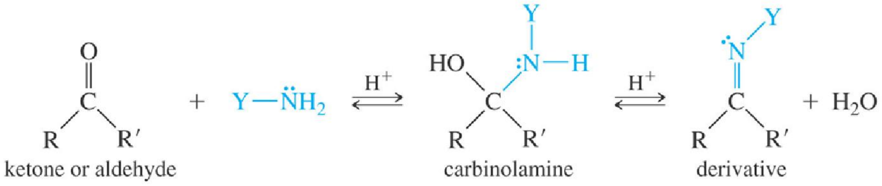
trimethylamine



electrostatic potential
map for trimethylamine

Amines

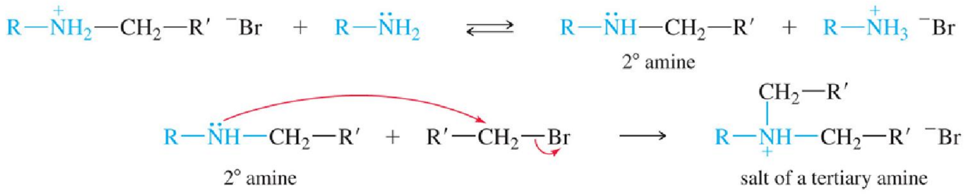
Reactivity: CONSENSATION WITH CARBONYL



Y = H or alkyl	gives an imine (Schiff base)
Y = OH	gives an oxime
Y = NHR	gives a hydrazone

Amines

Reactivity: ALKYLATION



NOT SELECTIVE

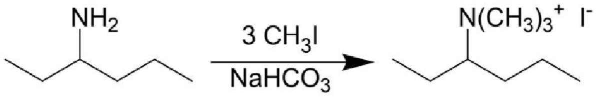
Even if just one equivalent of the halide is added, some amine molecules will react once, some will react twice, and some will react three times (to give the tetraalkylammonium salt).

Amines

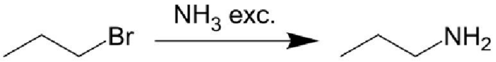
Reactivity: ALKYLATION

Examples of useful alkylation

Exhaustive alkylation to form the tetraalkylammonium salt.

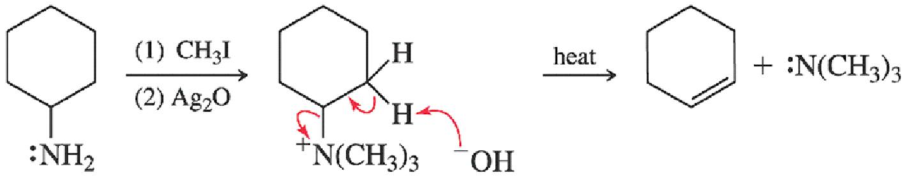


Reaction with large excess of NH_3 to form the primary amine.



Amines

Reactivity: HOFMANN ELIMINATION



- A quaternary ammonium salt has a good leaving group—a neutral amine.
- Heating the hydroxide salt produces the least substituted alkene.

Amines

Reactivity: FORMATION OF DIAZONIUM SALTS

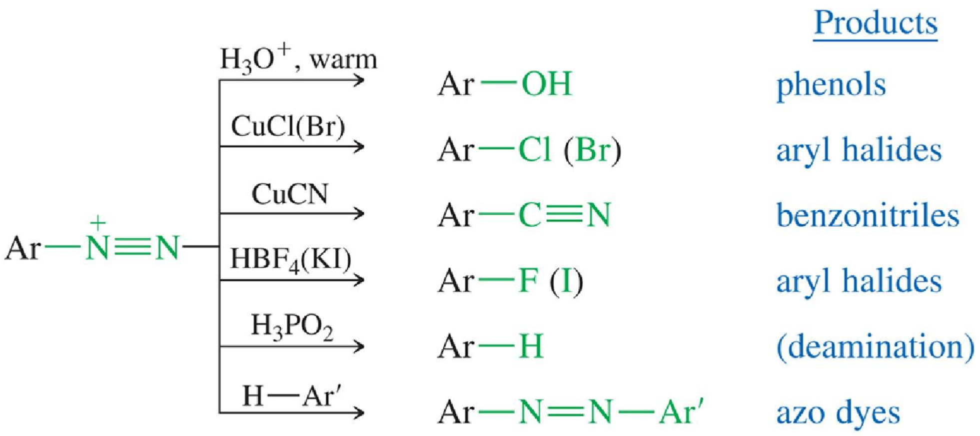
$$R{-}NH_2 + NaNO_2 + 2\,HCl \longrightarrow R{-}\overset{+}{N}{\equiv}N\ Cl^- + 2\,H_2O + NaCl$$

$$R{-}\overset{+}{N}{\equiv}N \longrightarrow R^+ + N{\equiv}N$$

- Primary amines react with nitrous acid (HNO_2) to form dialkyldiazonium salts.
- The diazonium salts are unstable and decompose into carbocations and nitrogen.

Amines

Reactivity: REACTIONS OF ARENEDIAZONIUM SALTS



$Ar-\overset{+}{N}\equiv N$

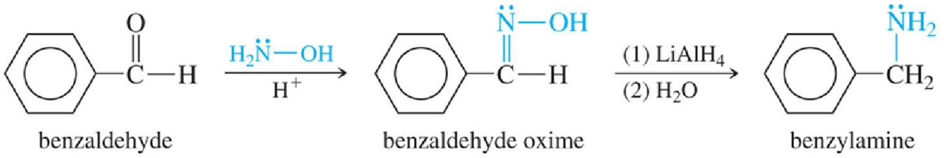
		Products
$\xrightarrow{H_3O^+,\ \text{warm}}$	$Ar-OH$	phenols
$\xrightarrow{CuCl(Br)}$	$Ar-Cl\ (Br)$	aryl halides
$\xrightarrow{CuCN}$	$Ar-C\equiv N$	benzonitriles
$\xrightarrow{HBF_4(KI)}$	$Ar-F\ (I)$	aryl halides
$\xrightarrow{H_3PO_2}$	$Ar-H$	(deamination)
$\xrightarrow{H-Ar'}$	$Ar-N=N-Ar'$	azo dyes

By diazotizing an amine, an aromatic position can be converted into a wide variety of functional groups.

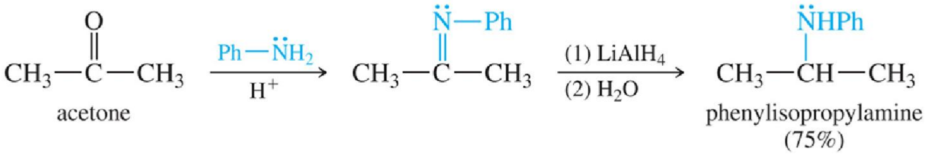
Amines

Synthesis: REDUCTIVE AMINATION

Primary amines



Secondary amines

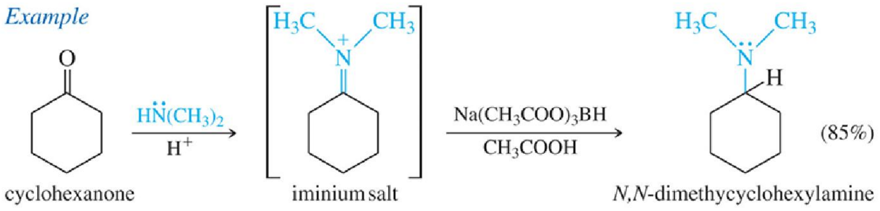


$$CH_3-\overset{\overset{O}{\|}}{C}-CH_3 \xrightarrow[H^+]{Ph-\ddot{N}H_2} CH_3-\overset{\overset{\ddot{N}-Ph}{\|}}{C}-CH_3 \xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4} CH_3-\overset{\overset{\ddot{N}HPh}{|}}{CH}-CH_3$$

Amines

Synthesis: REDUCTIVE AMINATION

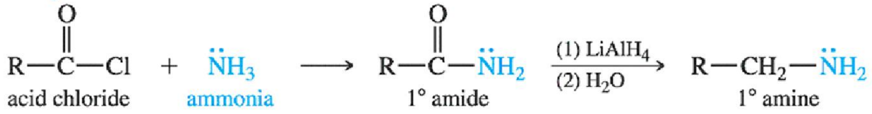
Tertiary amines



Amines

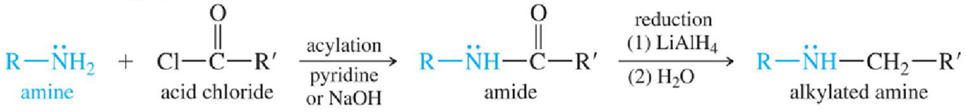
Synthesis: ACYLATION - REDUCTION

Primary amines



$$R-\overset{O}{\overset{\|}{C}}-Cl + \ddot{N}H_3 \longrightarrow R-\overset{O}{\overset{\|}{C}}-\ddot{N}H_2 \xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4} R-CH_2-\ddot{N}H_2$$

Secondary amines



$$R-\ddot{N}H_2 + Cl-\overset{O}{\overset{\|}{C}}-R' \xrightarrow[\text{pyridine or NaOH}]{\text{acylation}} R-\ddot{N}H-\overset{O}{\overset{\|}{C}}-R' \xrightarrow[(2)\ H_2O]{\text{reduction } (1)\ LiAlH_4} R-\ddot{N}H-CH_2-R'$$

Tertiary amines

$$R-\overset{O}{\overset{\|}{C}}-Cl + R'_2\ddot{N}H \longrightarrow R-\overset{O}{\overset{\|}{C}}-\ddot{N}R'_2 \xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4} R-CH_2-\ddot{N}R'_2$$

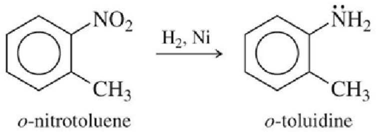
Amines

Synthesis: REDUCTION OF NITRO COMPOUDS

$$R{-}NO_2 \xrightarrow[\text{or active metal and } H^+]{H_2\text{/catalyst}} R{-}NH_2$$

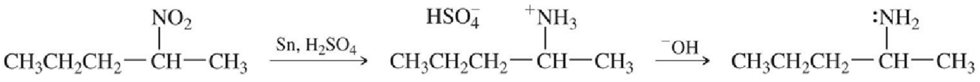
catalyst = Ni, Pd, or Pt
active metal = Fe, Zn, or Sn

Examples



o-nitrotoluene

o-toluidine (90%)



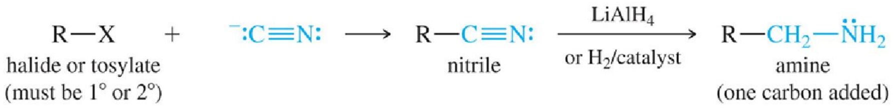
$$CH_3CH_2CH_2{-}\overset{NO_2}{CH}{-}CH_3 \xrightarrow{Sn,\ H_2SO_4} \overset{HSO_4^-}{\ } CH_3CH_2CH_2{-}\overset{^+NH_3}{CH}{-}CH_3 \xrightarrow{^-OH} CH_3CH_2CH_2{-}\overset{:NH_2}{CH}{-}CH_3$$

2-nitropentane

2-aminopentane (85%)

Amines

Synthesis: REDUCTION OF NITRILES



$$R{-}X + {}^{-}{:}C{\equiv}N{:} \longrightarrow R{-}C{\equiv}N{:} \xrightarrow[\text{or } H_2/\text{catalyst}]{LiAlH_4} R{-}CH_2{-}\ddot{N}H_2$$

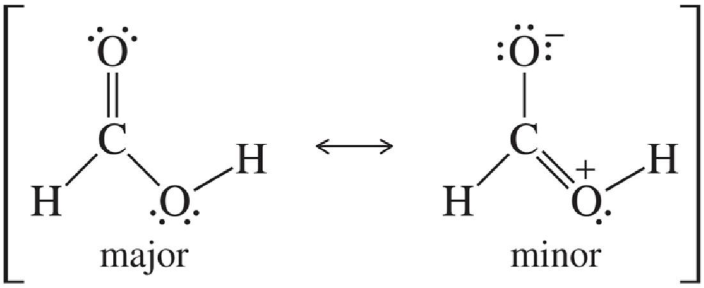
Carboxylic acids

Structure of COOH group

- The sp^2 hybrid carbonyl carbon atom is planar, with nearly trigonal bond angles.
- The O—H bond also lies in this plane, eclipsed with the C=O bond.
- The sp^3 oxygen has a C—O—H angle of 106°.

Carboxylic acids

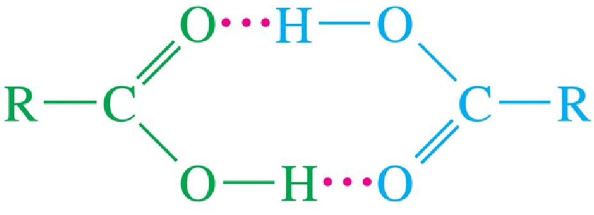
Structure of COOH group



- Carbon is sp^2 hybridized.
- Bond angles are close to 120°.
- O—H eclipsed with C=O, to get overlap of π orbital with orbital of lone pair on oxygen.

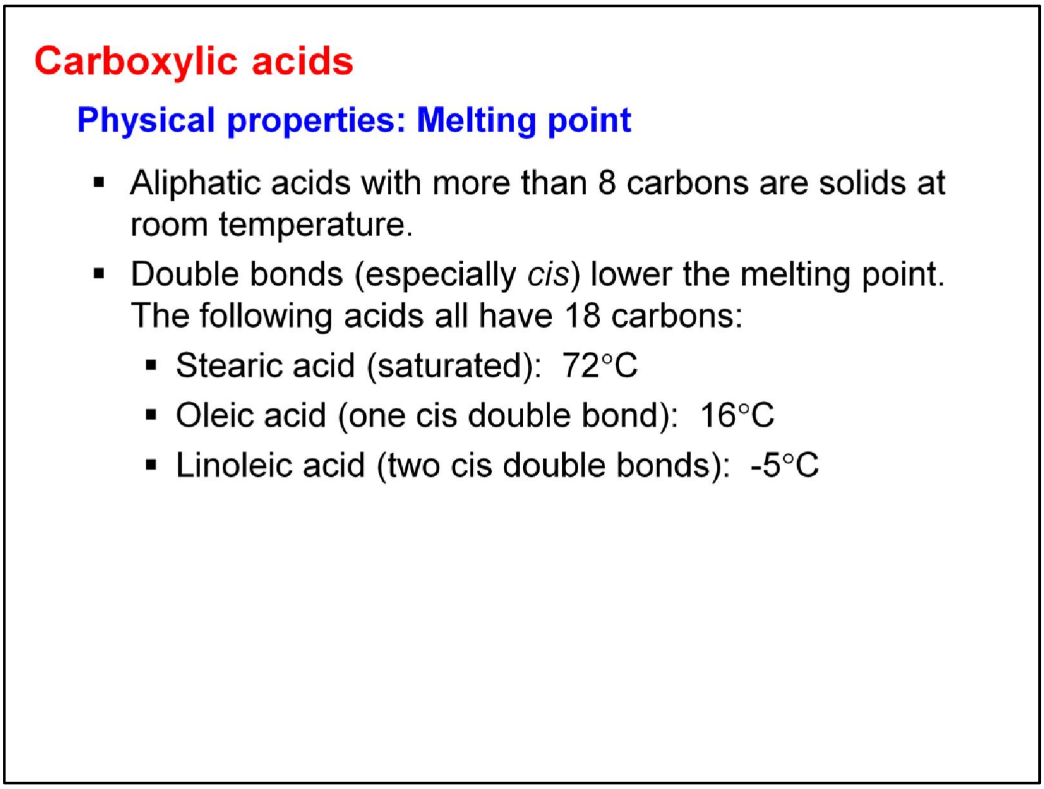
Carboxylic acids

Physical properties: Boiling point



hydrogen-bonded acid dimer

Higher boiling points than similar alcohols, due to the formation of a hydrogen-bonded dimer.



Carboxylic acids

Physical properties: Melting point

- Aliphatic acids with more than 8 carbons are solids at room temperature.
- Double bonds (especially *cis*) lower the melting point. The following acids all have 18 carbons:
    - Stearic acid (saturated): 72°C
    - Oleic acid (one cis double bond): 16°C
    - Linoleic acid (two cis double bonds): -5°C

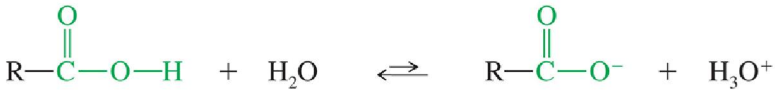
Carboxylic acids

Solubility

- Water solubility decreases with the length of the carbon chain.
- With up to 4 carbons, acid is miscible in water.
- Very soluble in alcohols.
- Also soluble in relatively nonpolar solvents like chloroform because the hydrogen bonds of the dimer are not disrupted by the nonpolar solvent.

Carboxylic acids

Acidity



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-H \;+\; H_2O \;\rightleftharpoons\; R-\overset{\overset{\displaystyle O}{\|}}{C}-O^- \;+\; H_3O^+$$

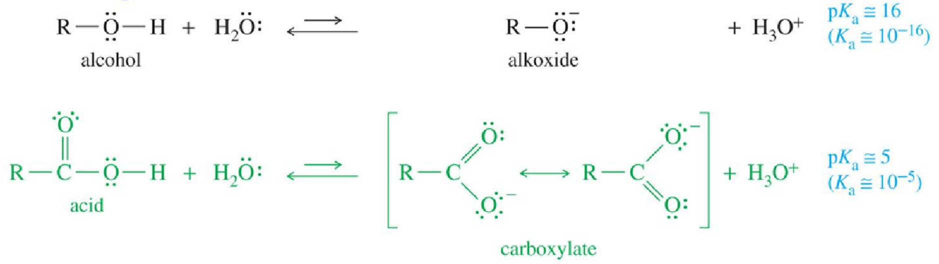
$$K_a = \frac{[R-CO_2^-][H_3O^+]}{[R-CO_2H]}$$

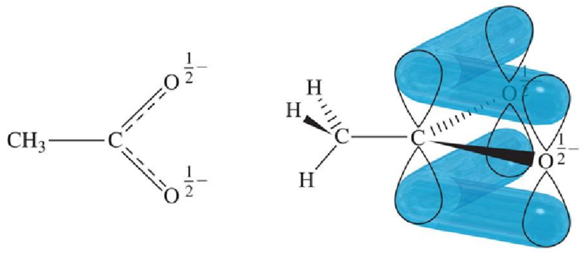
$$pK_a = -\log_{10} K_a$$

- A carboxylic acid may dissociate in water to give a proton and a carboxylate ion.
- The equilibrium constant K_a for this reaction is called the acid-dissociation constant.
- The acid will be mostly dissociated if the pH of the solution is higher than the pK_a of the acid.

Carboxylic acids

Acidity

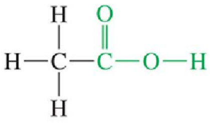




The delocalization of the negative charge over the two oxygens makes the acetate ion more stable than an alkoxide ion.

Carboxylic acids

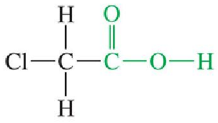
Acidity: effect of substituents



$H-\overset{H}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-O-H$

acetic acid

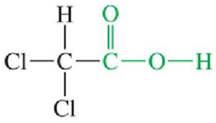
$pK_a = 4.74$



$Cl-\overset{H}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-O-H$

chloroacetic acid

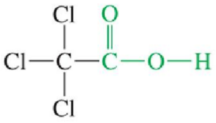
$pK_a = 2.86$



$Cl-\overset{H}{\underset{Cl}{C}}-\overset{O}{\overset{\|}{C}}-O-H$

dichloroacetic acid

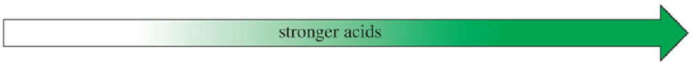
$pK_a = 1.26$

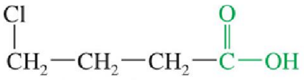


$Cl-\overset{Cl}{\underset{Cl}{C}}-\overset{O}{\overset{\|}{C}}-O-H$

trichloroacetic acid

$pK_a = 0.64$

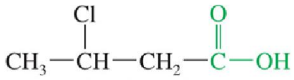




$\overset{Cl}{\overset{|}{CH_2}}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-OH$

4-chlorobutanoic acid

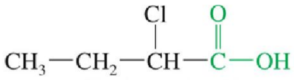
$pK_a = 4.52$



$CH_3-\overset{Cl}{\overset{|}{CH}}-CH_2-\overset{O}{\overset{\|}{C}}-OH$

3-chlorobutanoic acid

$pK_a = 4.05$



$CH_3-CH_2-\overset{Cl}{\overset{|}{CH}}-\overset{O}{\overset{\|}{C}}-OH$

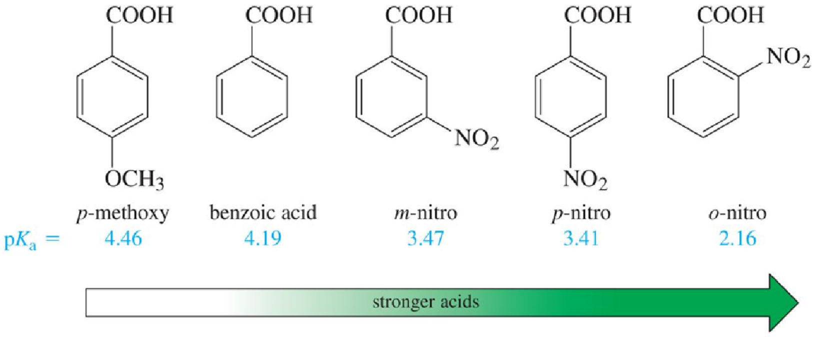
2-chlorobutanoic acid

$pK_a = 2.86$

The magnitude of a substituent effect depends on its distance from the carboxyl group.

Carboxylic acids

Acidity: effect of substituents



- Electron-withdrawing groups enhance the acid strength and electron-donating groups decrease the acid strength.
- Effects are strongest for substituents in the *ortho* and *para* positions.

Carboxylic acids

Acidity: effect of substituents

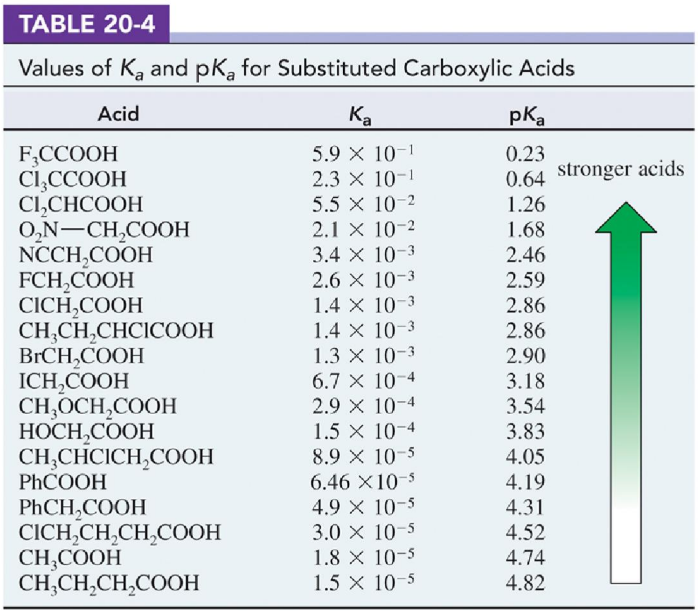


TABLE 20-4

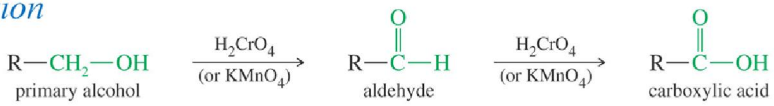
Values of K_a and pK_a for Substituted Carboxylic Acids

Acid	K_a	pK_a
F_3CCOOH	5.9×10^{-1}	0.23
Cl_3CCOOH	2.3×10^{-1}	0.64
$Cl_2CHCOOH$	5.5×10^{-2}	1.26
$O_2N{-}CH_2COOH$	2.1×10^{-2}	1.68
$NCCH_2COOH$	3.4×10^{-3}	2.46
FCH_2COOH	2.6×10^{-3}	2.59
$ClCH_2COOH$	1.4×10^{-3}	2.86
$CH_3CH_2CHClCOOH$	1.4×10^{-3}	2.86
$BrCH_2COOH$	1.3×10^{-3}	2.90
ICH_2COOH	6.7×10^{-4}	3.18
CH_3OCH_2COOH	2.9×10^{-4}	3.54
$HOCH_2COOH$	1.5×10^{-4}	3.83
$CH_3CHClCH_2COOH$	8.9×10^{-5}	4.05
PhCOOH	6.46×10^{-5}	4.19
$PhCH_2COOH$	4.9×10^{-5}	4.31
$ClCH_2CH_2CH_2COOH$	3.0×10^{-5}	4.52
CH_3COOH	1.8×10^{-5}	4.74
$CH_3CH_2CH_2COOH$	1.5×10^{-5}	4.82

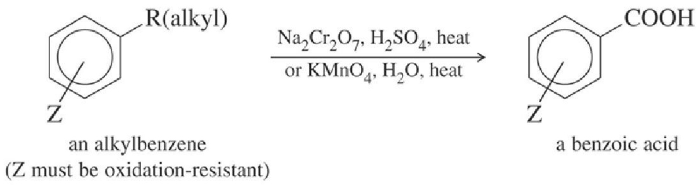
Carboxylic acids

Synthesis

Oxidation



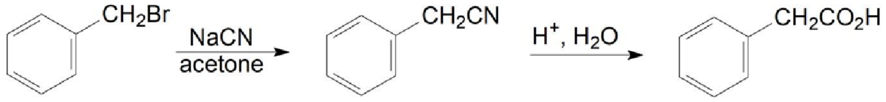
$$\underset{\text{primary alcohol}}{R-CH_2-OH} \xrightarrow[\text{(or }KMnO_4)]{H_2CrO_4} \underset{\text{aldehyde}}{R-\overset{\overset{\displaystyle O}{\|}}{C}-H} \xrightarrow[\text{(or }KMnO_4)]{H_2CrO_4} \underset{\text{carboxylic acid}}{R-\overset{\overset{\displaystyle O}{\|}}{C}-OH}$$



Carboxylic acids

Synthesis

Hydrolysis of nitriles

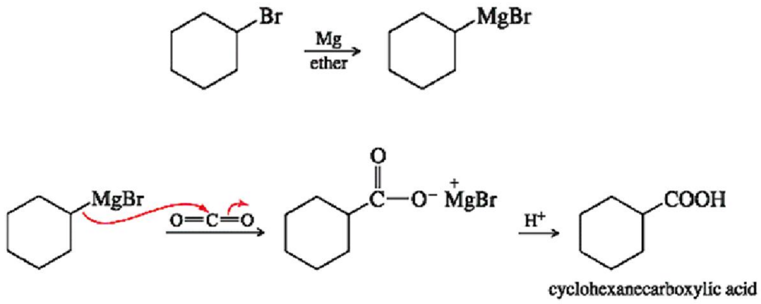


- Basic or acidic hydrolysis of a nitrile (—CN) produces a carboxylic acid.
- The overall reaction, starting from the alkyl halide, adds an extra carbon to the molecule.

Carboxylic acids

Synthesis

Grignard + CO_2

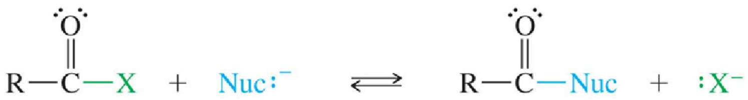


- Grignard reagent react with CO_2 to produce, after protonation, a carboxylic acid.
- This reaction is sometimes called "CO_2 insertion" and it increases the number of carbons in the molecule by one.

Carboxylic acids

Reactivity: NUCLEOPHILIC ACYL SUBSTITUTION

Nucleophilic acyl substitution

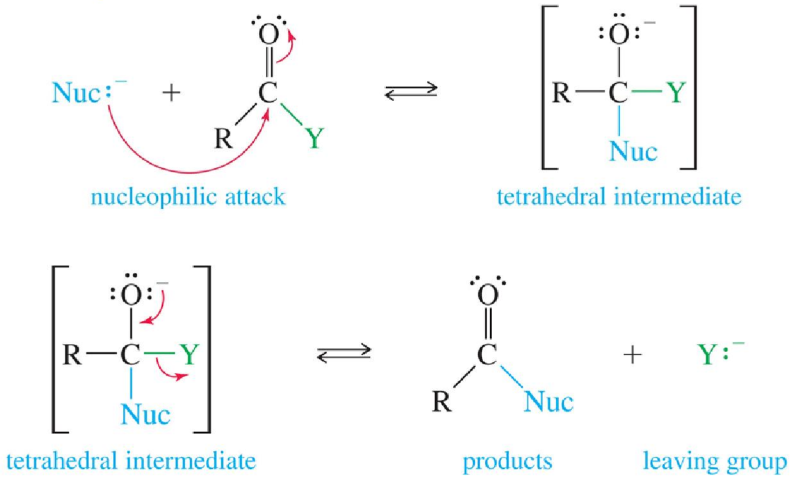


$$R-\overset{\overset{\ddot{O}}{\|}}{C}-X + Nuc:^- \rightleftarrows R-\overset{\overset{\ddot{O}}{\|}}{C}-Nuc + :X^-$$

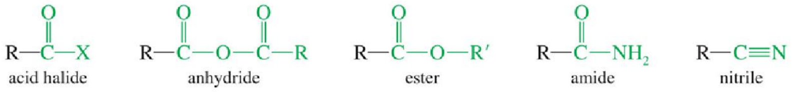
- Carboxylic acids react by nucleophilic acyl substitution, where one nucleophile replaces another on the acyl (C═O) carbon atom.

Carboxylic acids

Reactivity: NUCLEOPHILIC ACYL SUBSTITUTION



Derivatives of carboxylic acids



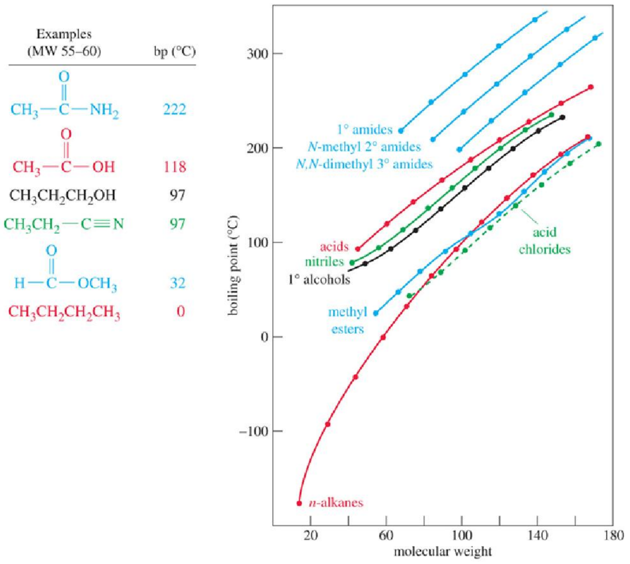
$$R-\overset{O}{\overset{\|}{C}}-X \quad R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R \quad R-\overset{O}{\overset{\|}{C}}-O-R' \quad R-\overset{O}{\overset{\|}{C}}-NH_2 \quad R-C\equiv N$$

Condensed structure: $RCOX$ $(RCO)_2O$ RCO_2R' $RCONH_2$ RCN

- All the derivatives can be converted to the carboxylic acid by acidic or basic hydrolysis.
- Esters and amides are commonly found in nature.

Derivatives of carboxylic acids

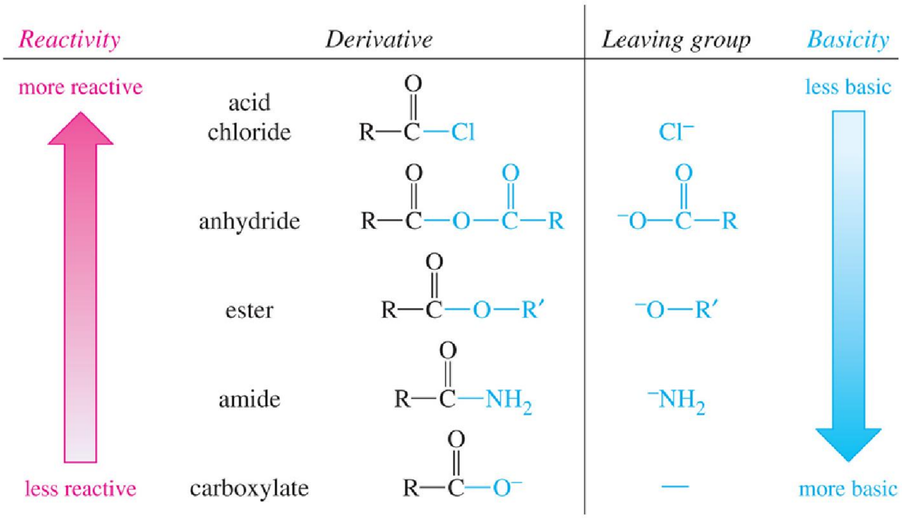
Physical properties



Examples (MW 55–60)	bp (°C)
$CH_3-\overset{\overset{O}{\|}}{C}-NH_2$	222
$CH_3-\overset{\overset{O}{\|}}{C}-OH$	118
$CH_3CH_2CH_2OH$	97
$CH_3CH_2-C\equiv N$	97
$H-\overset{\overset{O}{\|}}{C}-OCH_3$	32
$CH_3CH_2CH_2CH_3$	0

Derivatives of carboxylic acids

Reactivity

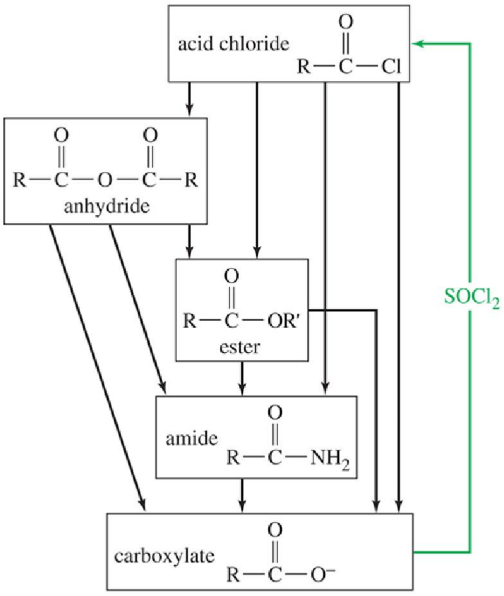


Reactivity	*Derivative*		*Leaving group*	*Basicity*
more reactive	acid chloride	$R-\overset{O}{\overset{\|}{C}}-Cl$	Cl^-	less basic
	anhydride	$R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R$	$^-O-\overset{O}{\overset{\|}{C}}-R$	
	ester	$R-\overset{O}{\overset{\|}{C}}-O-R'$	$^-O-R'$	
	amide	$R-\overset{O}{\overset{\|}{C}}-NH_2$	$^-NH_2$	
less reactive	carboxylate	$R-\overset{O}{\overset{\|}{C}}-O^-$	—	more basic

Derivatives of carboxylic acids

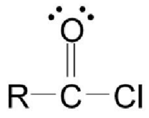
Reactivity

Interconversions of acid derivatives



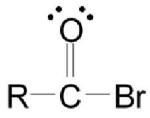
More reactive derivatives can be converted to less reactive derivatives.

Acyl halides



$\mathrm{R-\overset{\overset{\displaystyle O}{\|}}{C}-Cl}$

acyl chloride



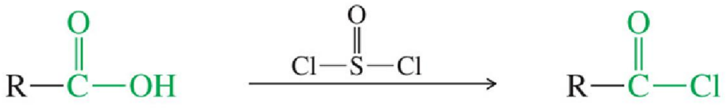
$\mathrm{R-\overset{\overset{\displaystyle O}{\|}}{C}-Br}$

acyl bromide

- Also called ***acyl halides***.
- These are more reactive than carboxylic acids, so they are used to synthesize other acid derivatives such as esters and amides.
- Used in the Friedel–Crafts acylation to make acylbenzenes.

Acyl halides

Synthesis



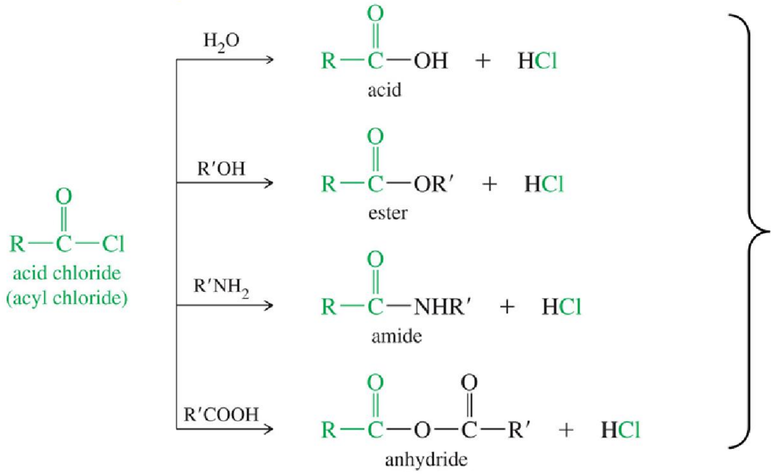
$$R-\overset{\overset{\displaystyle O}{\|}}{C}-OH \xrightarrow{Cl-\overset{\overset{\displaystyle O}{\|}}{S}-Cl} R-\overset{\overset{\displaystyle O}{\|}}{C}-Cl$$

+ SO_2 + HCl
(gaseous products)

- The best reagent for converting carboxylic acids to acid chlorides is thionyl chloride ($SOCl_2$) because it forms gaseous by-products that do not contaminate the product.
- Thionyl chloride reaction produces SO_2.

Acyl halides

Reactivity



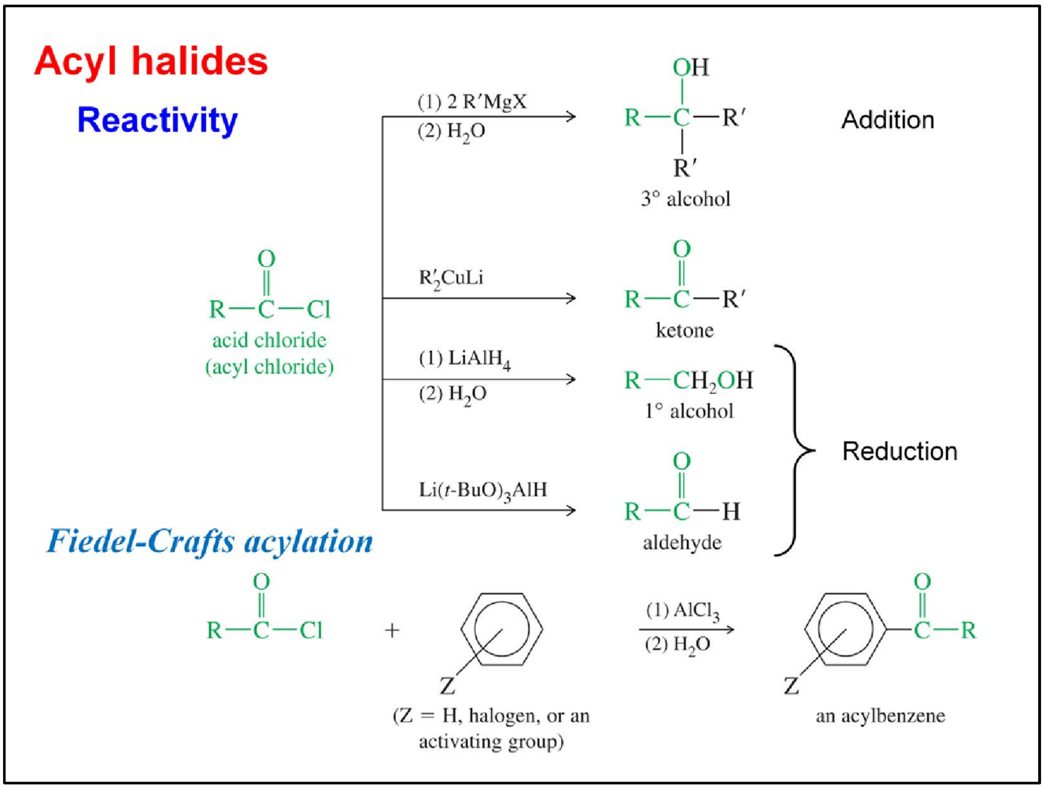
$$\mathrm{R{-}\overset{\overset{\Large O}{\|}}{C}{-}Cl} \xrightarrow{H_2O} \mathrm{R{-}\overset{\overset{\Large O}{\|}}{C}{-}OH} + \mathrm{HCl}$$

$$\mathrm{R{-}\overset{\overset{\Large O}{\|}}{C}{-}Cl} \xrightarrow{R'OH} \mathrm{R{-}\overset{\overset{\Large O}{\|}}{C}{-}OR'} + \mathrm{HCl}$$

$$\mathrm{R{-}\overset{\overset{\Large O}{\|}}{C}{-}Cl} \xrightarrow{R'NH_2} \mathrm{R{-}\overset{\overset{\Large O}{\|}}{C}{-}NHR'} + \mathrm{HCl}$$

$$\mathrm{R{-}\overset{\overset{\Large O}{\|}}{C}{-}Cl} \xrightarrow{R'COOH} \mathrm{R{-}\overset{\overset{\Large O}{\|}}{C}{-}O{-}\overset{\overset{\Large O}{\|}}{C}{-}R'} + \mathrm{HCl}$$

Nucleophylic substitution



Acyl halides

Reactivity

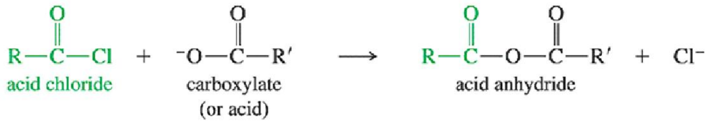
Addition

Reduction

Fiedel-Crafts acylation

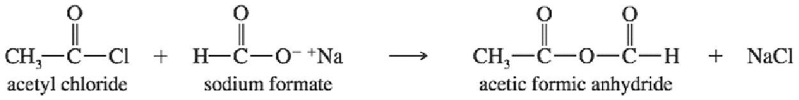
Anhydrides

Synthesis



$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}Cl} + \mathrm{{}^{-}O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R'} \longrightarrow \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R'} + \mathrm{Cl^{-}}$$

Examples

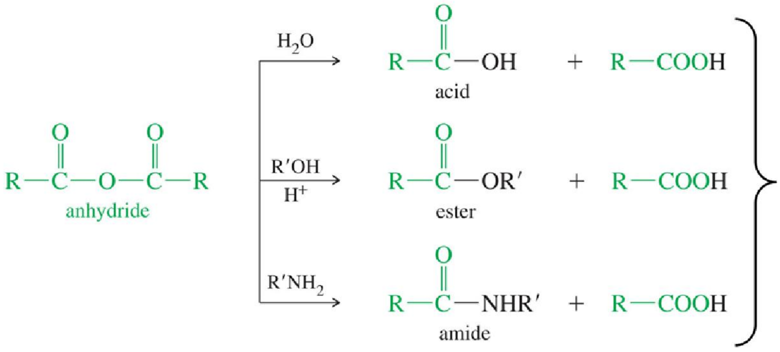


$$\mathrm{CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}Cl} + \mathrm{H{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^{-}\ {}^{+}Na} \longrightarrow \mathrm{CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}H} + \mathrm{NaCl}$$

- The most generalized method for making anhydrides is the reaction of an acid chloride with a carboxylic acid or a carboxylate salt.
- Pyridine is sometimes used to deprotonate the acid and form the carboxylate.

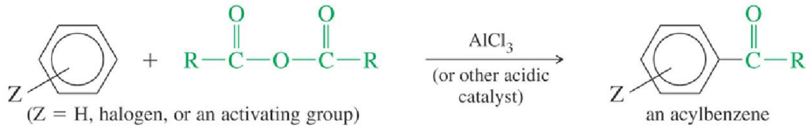
Anhydrides

Reactivity



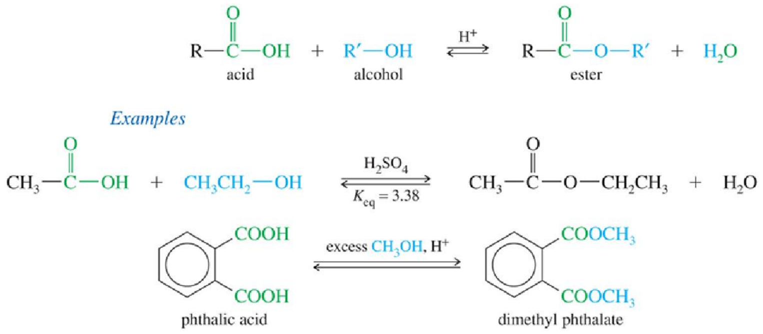
Nucleophylic substitution

Fiedel-Crafts acylation



Esters

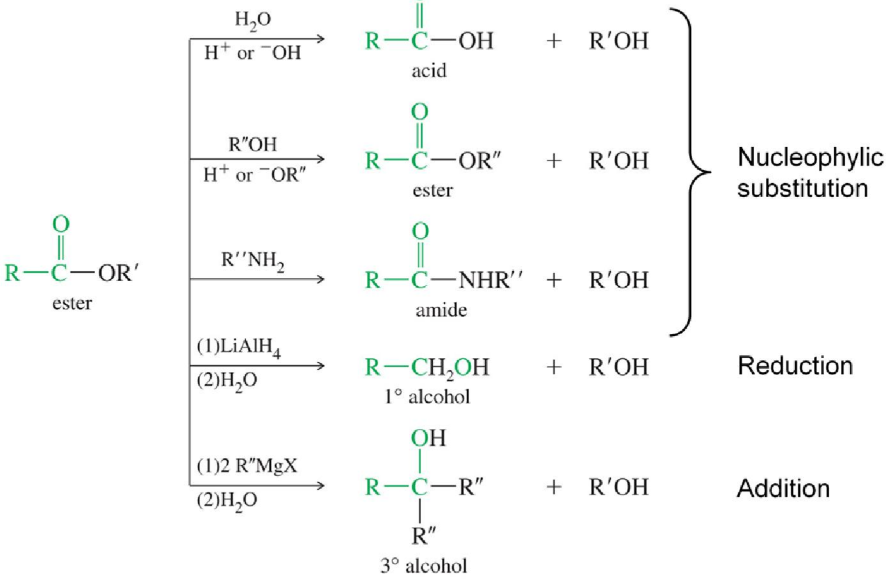
Fisher esterification



- Reaction of a carboxylic acid with an alcohol under acidic conditions produces an ester.
- Reaction is an equilibrium, the yield of ester is not high.
- To drive the equilibrium to the formations of products, use a large excess of alcohol or remove H_2O from the reaction.

Esters

Reactivity



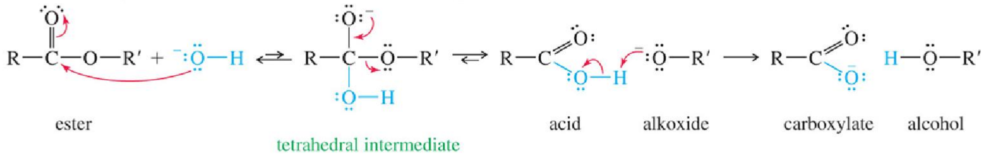
Esters

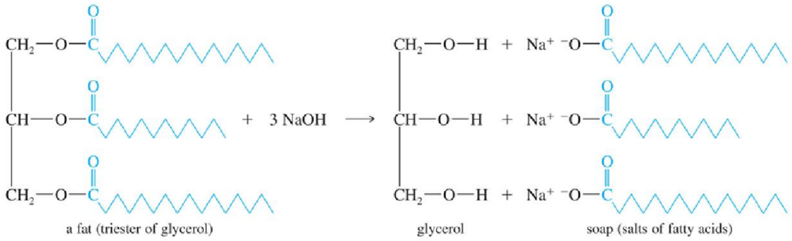
Reactivity: saponification

Step 1: Addition of the nucleophile.

Step 2: Elimination of the leaving group.

Step 3: Proton transfer.

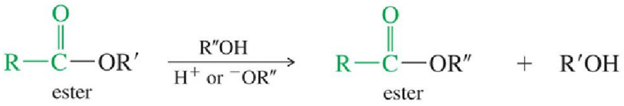




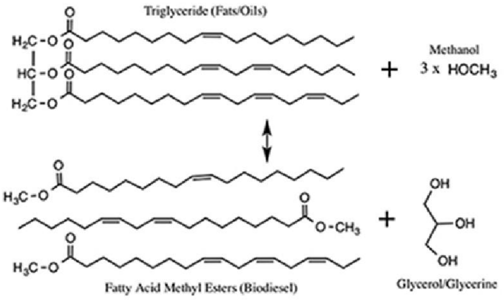
Marseille soap

Esters

Reactivity: Transesterifaction

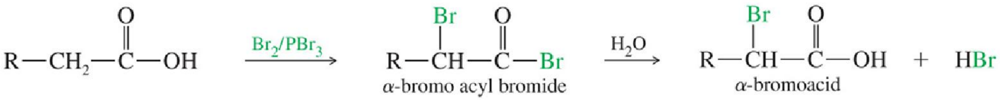


$$\underset{\text{ester}}{R-\overset{O}{\overset{\|}{C}}-OR'} \xrightarrow[H^+ \text{ or } {}^-OR'']{R''OH} \underset{\text{ester}}{R-\overset{O}{\overset{\|}{C}}-OR''} + R'OH$$



α Halogenation of esters

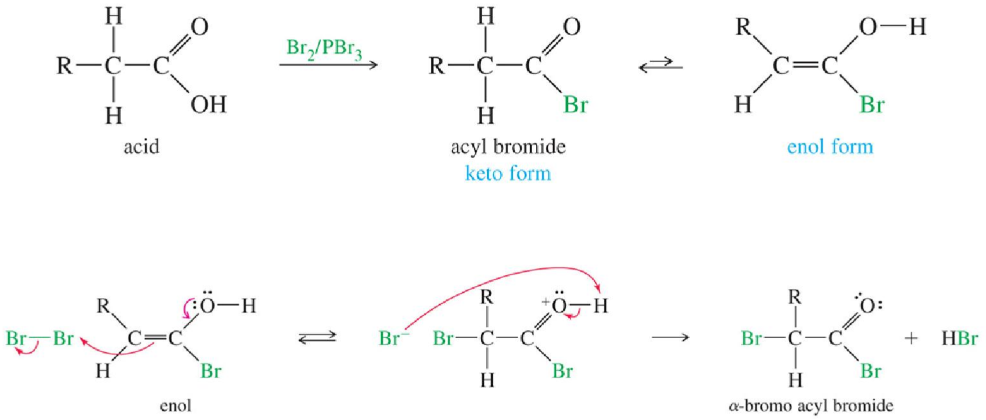
Hell-Volard-Zelinsky (HVZ) Reaction



- The HVZ reaction replaces a hydrogen atom with a bromine atom on the alpha-carbon of a carboxylic acid (α-bromoacid).
- The acid is treated with bromine and phosphorus tribromide, followed by hydrolysis.

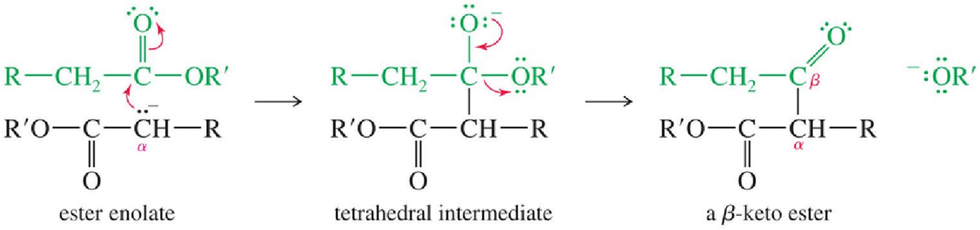
α Halogenation of esters

Hell-Volard-Zelinsky (HVZ) Reaction



Aldol condensation

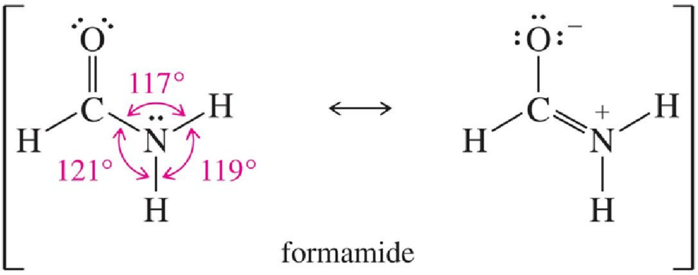
Claisen condensation



- The ***Claisen condensation*** results when an ester molecule undergoes nucleophilic acyl substitution by an enolate.

Amides

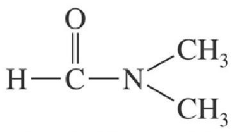
Structure



- Amides are the product of the reaction of a carboxylic acid with ammonia or an amine.
- Not basic because the lone pair on nitrogen is delocalized by resonance.
- The C—N bond has double-bond character: rotation is not allowed. The 6 atoms lie on the same plane.

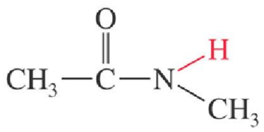
Amides

Classification



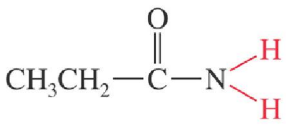
dimethylformamide

3º amide



N-methylacetamide

2º amide



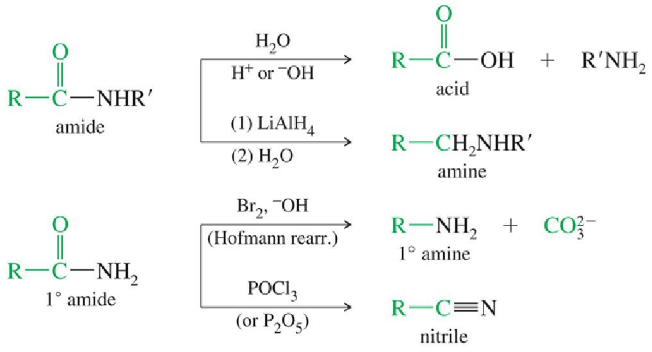
propionamide

1º amide

- 1° amide has one C—N bond (two N—H).
- 2° amide or *N*-substituted amide has two C—N bonds (one N—H).
- 3° amide or *N,N*-disubstituted amide has three C—N bonds (no N—H).

Amides

Reactivity



Hydrolysis

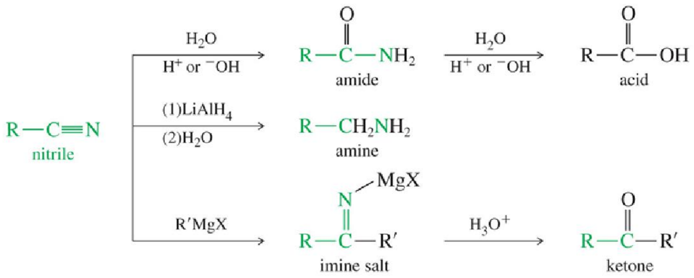
Reduction

Elimination

Dehydration

Nitriles

Reactivity



Hydrolysis

Reduction

Addition