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 ←

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

↓ Increasing nucleophilicity ↓

General consideration

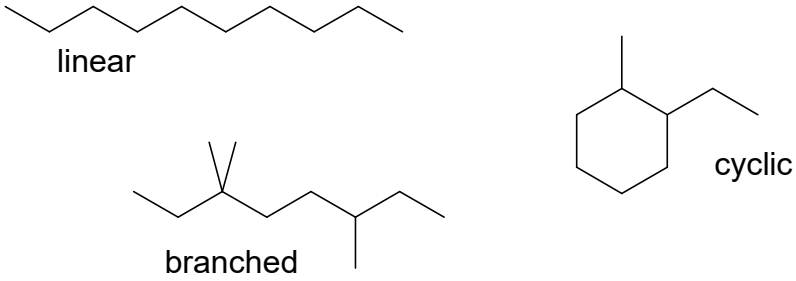
Electrophile

- 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

Alkanes

General formula C_nH_{2n+2}

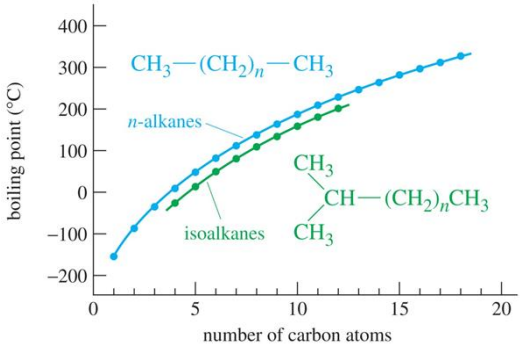
Contains only C – H and C – C σ bonds.



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.



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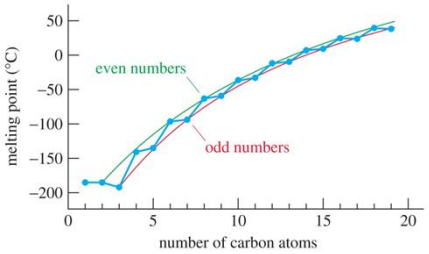
Alkanes

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.



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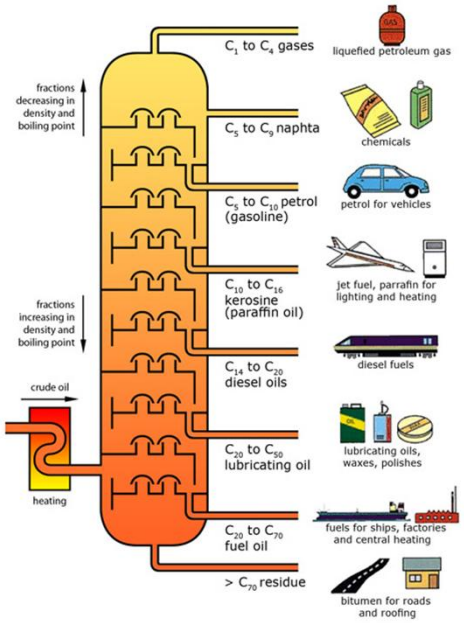
Alkanes

Sources

Alkanes

Oil refining



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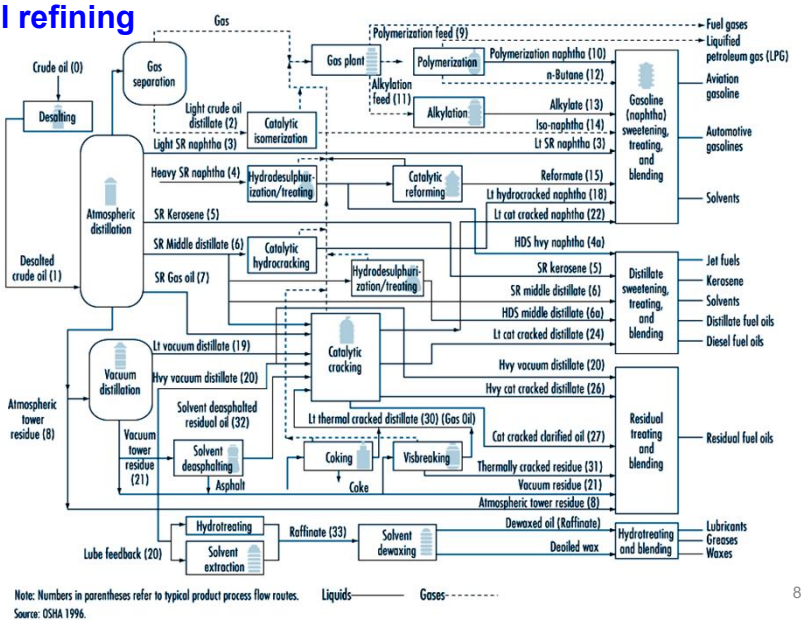
Alkanes

Oil refining

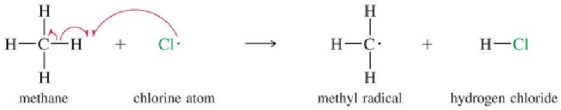


8

Alkanes

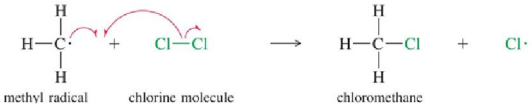
Reactivity

First propagation step

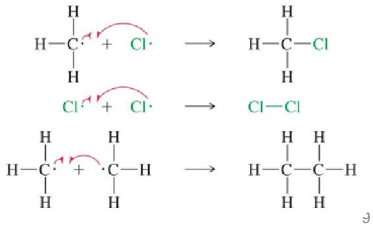


Radical substitution

Second propagation step



Termination steps

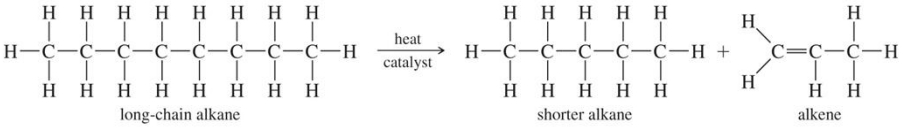


- Not selective process
- A complex mixture of products is obtained

Alkanes

Reactivity

Catalytic cracking



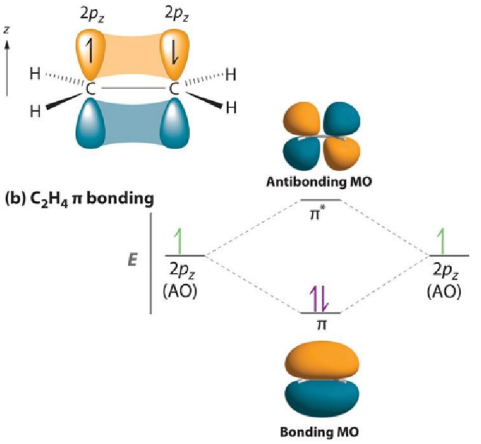
- Long-chain alkane is heated with a catalyst to produce an alkene and shorter alkane.
- Complex mixtures are produced.

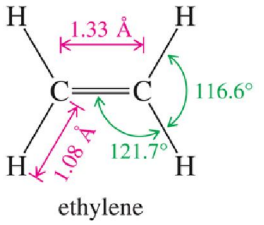
- **Hydrocracking**: with addition of large amounts of H_2, alkenes are converted into alkanes.
- Fundamental for fuel production.

Alkenes

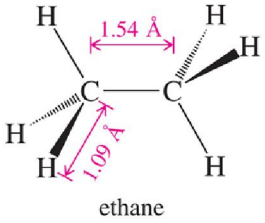
General formula C_nH_{2n}

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





ethylene



ethane

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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.

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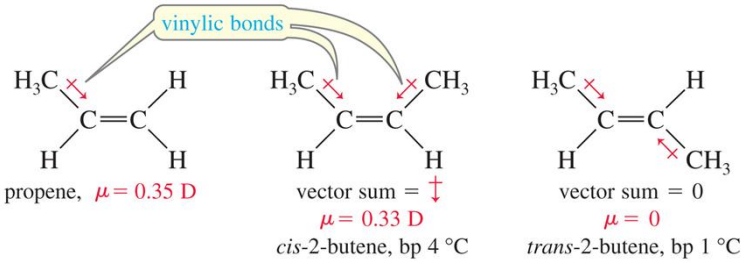
Alkenes

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.



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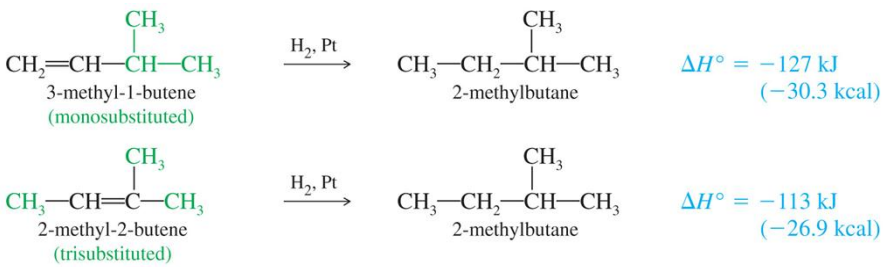
Alkenes

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.



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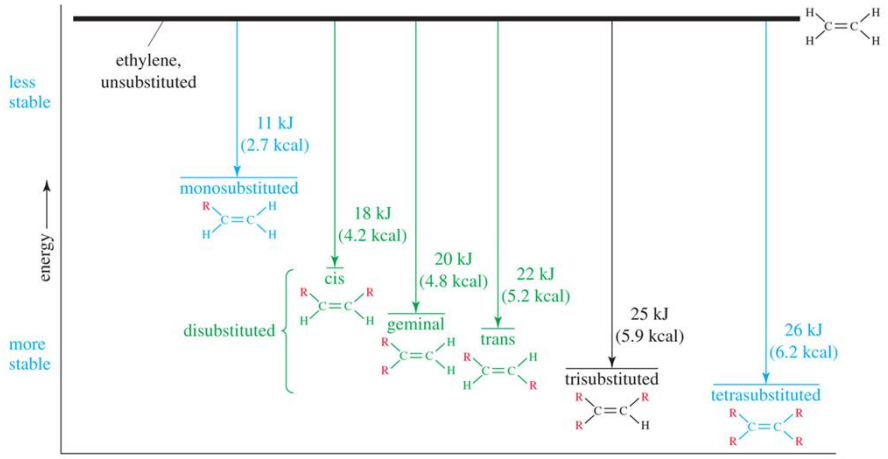
Alkenes

Relative stability



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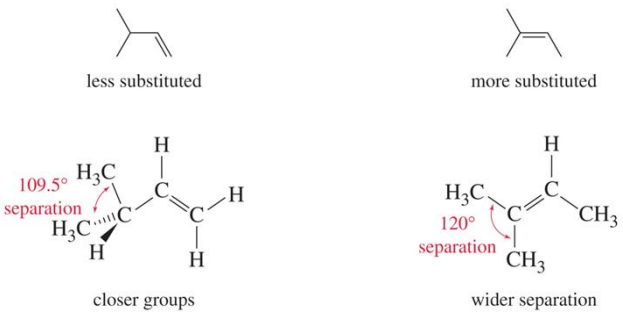
Alkenes

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.



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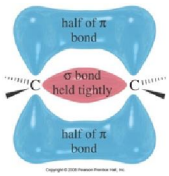
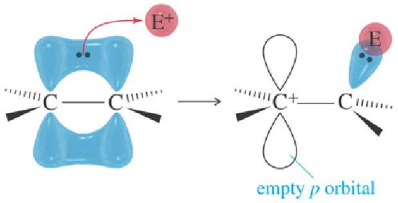
Alkenes

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***.





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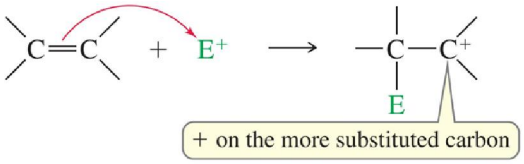
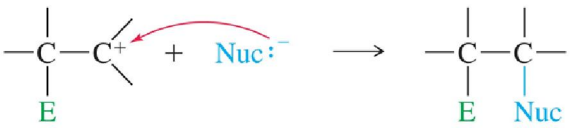
Alkenes

Reactivity: ELECTROPHILIC ADDITION

- Step 1: π electrons attack the electrophile.



- Step 2: Nucleophile attacks the carbocation.



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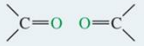
Alkenes

Reactivity: ELECTROPHILIC ADDITION

TABLE 8-1

Types of Additions to Alkenes

Type of Addition [Elements Added][a]	Product
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 [HX] (hydrohalogenation)	
cyclopropanation [CH_2]	

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

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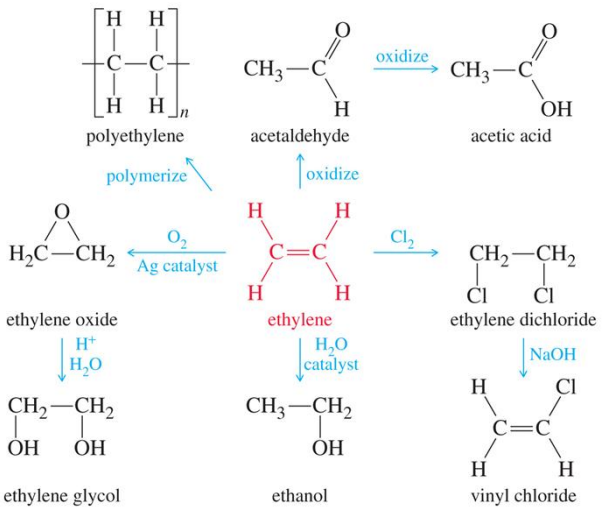
Alkenes

Commercial use of ethylene



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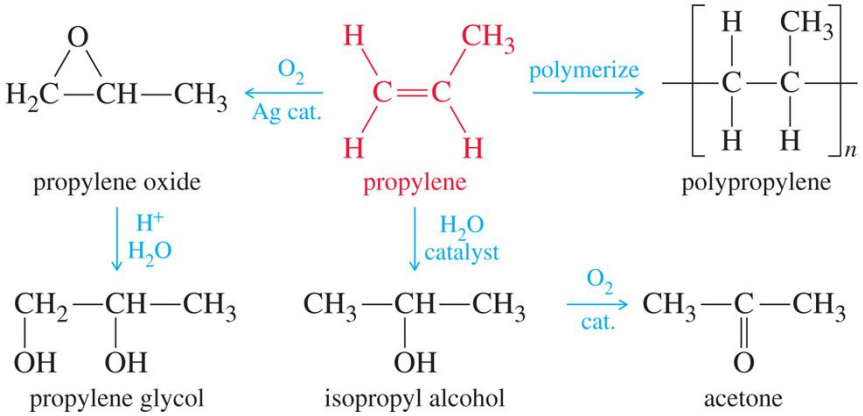
Alkenes

Commercial use of propylene



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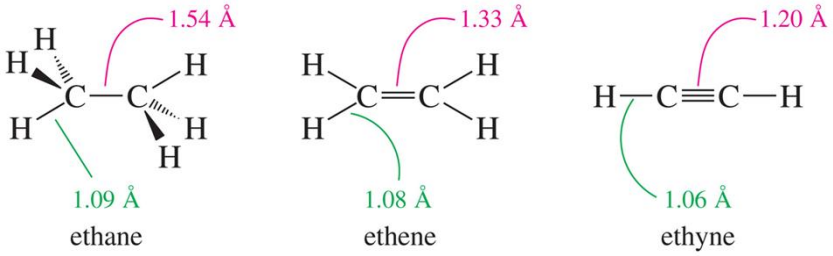
Alkynes

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.

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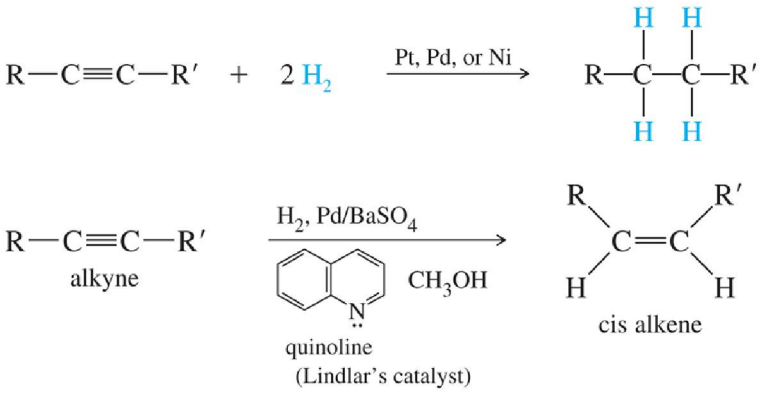
Alkynes

Reactivity: ADDITION

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



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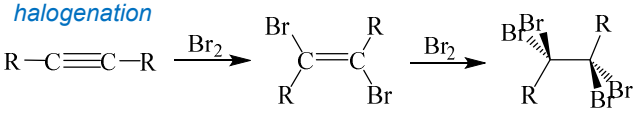
Alkynes

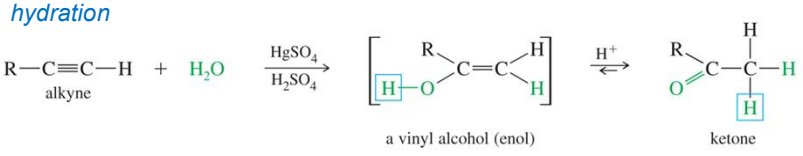
Reactivity: ADDITION

halogenation



HX addition

hydration



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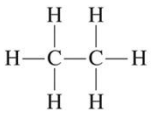
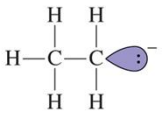
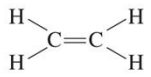
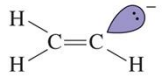
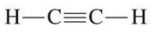
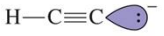
Alkynes

Reactivity: ACIDITY

TABLE 9-2

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

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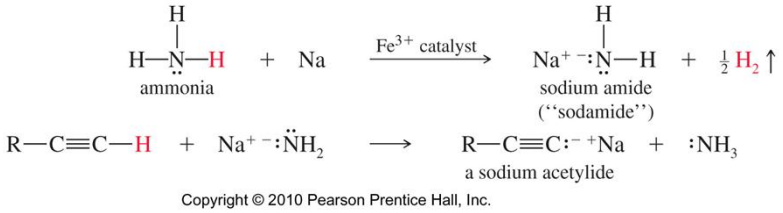
Alkynes

Reactivity: ACIDITY

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



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

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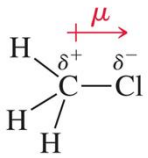
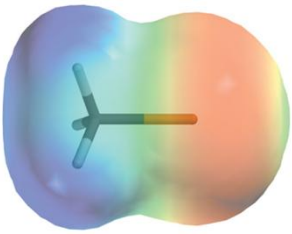
Alkyl halides

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.

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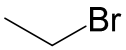
Alkyl halides

Classification

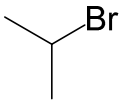
- **Methyl halides**: halide is attached to a methyl group.

CH_3-Br

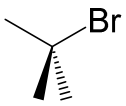
- **Primary alkyl halide**: carbon to which halogen is bonded is attached to only one other carbon.



- **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.



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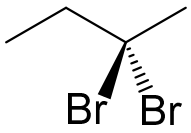
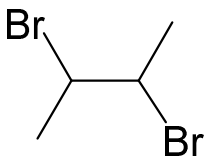
Alkyl halides

Classification

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



- **Vicinal dihalide**: two halogen atoms are bonded to adjacent carbons.



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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

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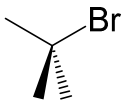
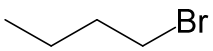
Alkyl halides

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

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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.

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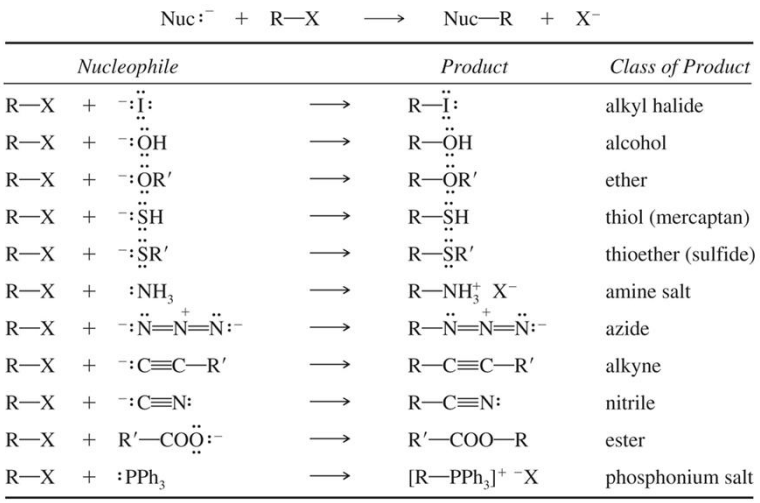
Alkyl halides

Reactivity: NUCLEOPHILIC SUBSTITUTION



Nuc:⁻ + R—X ⟶ Nuc—R + X⁻

Nucleophile		Product	Class of Product
R—X + $^{-}$:Ï:	⟶	R—Ï:	alkyl halide
R—X + $^{-}$:ÖH	⟶	R—ÖH	alcohol
R—X + $^{-}$:ÖR′	⟶	R—ÖR′	ether
R—X + $^{-}$:S̈H	⟶	R—S̈H	thiol (mercaptan)
R—X + $^{-}$:S̈R′	⟶	R—S̈R′	thioether (sulfide)
R—X + :NH_3	⟶	R—NH_3^+ X^-	amine salt
R—X + $^{-}$:N̈=$\overset{+}{N}$=N̈:$^{-}$	⟶	R—N̈=$\overset{+}{N}$=N̈:$^{-}$	azide
R—X + $^{-}$:C≡C—R′	⟶	R—C≡C—R′	alkyne
R—X + $^{-}$:C≡N:	⟶	R—C≡N:	nitrile
R—X + R′—COÖ:$^{-}$	⟶	R′—COO—R	ester
R—X + :PPh_3	⟶	[R—PPh_3]$^{+}$ $^{-}$X	phosphonium salt

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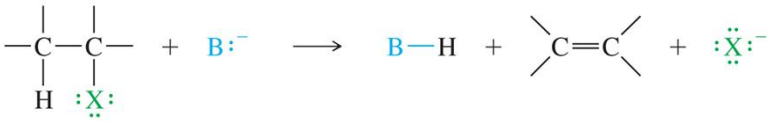
Alkyl halides

Reactivity: ELIMINATION

Elimination



—C—C— + B:$^{-}$ ⟶ B—H + C=C + :Ẍ:$^{-}$

(H and :Ẍ: on the C—C)

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

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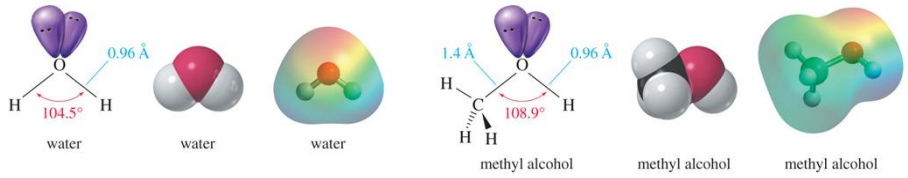
Alcohols and phenols

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°.

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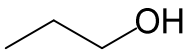
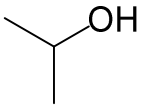
Alcohols and phenols

Classification

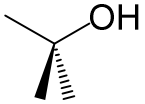
- **Primary alcohol**: carbon to which OH is bonded is attached to only one other carbon.



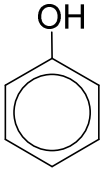
- **Secondary alcohol** : carbon to which OH is bonded is attached to two other carbons.



- **Tertiary alcohol** : carbon to which OH is bonded is attached to three other carbon.



- **Aromatic (phenol)** : OH is bound to a benzene ring



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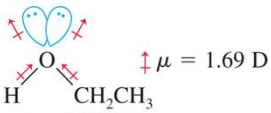
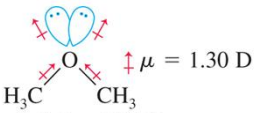
Alcohols and phenols

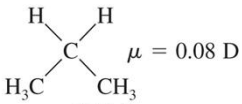
Boiling point



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.

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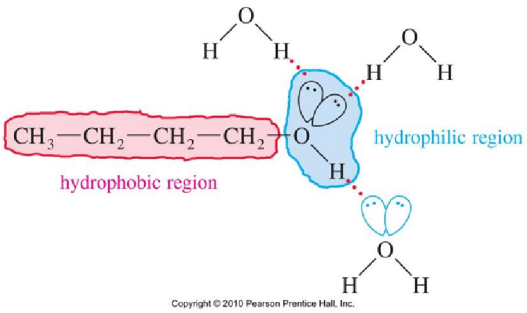
Alcohols and phenols

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.

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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

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Alcohols and phenols

Reactivity: ACIDITY

$$R—O—H + Na \longrightarrow R—O^- {}^+Na + \tfrac{1}{2} H_2 \uparrow$$

Example

$$\underset{\text{ethanol}}{CH_3CH_2OH} + \underset{\text{sodium metal}}{Na} \longrightarrow \underset{\text{sodium ethoxide}}{CH_3CH_2O^- {}^+Na} + \underset{\text{hydrogen gas}}{\tfrac{1}{2} H_2 \uparrow}$$

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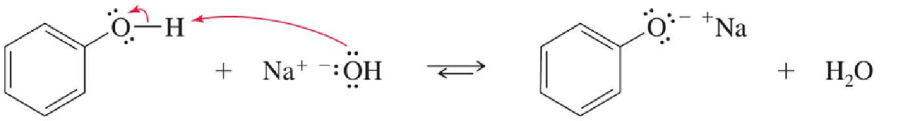
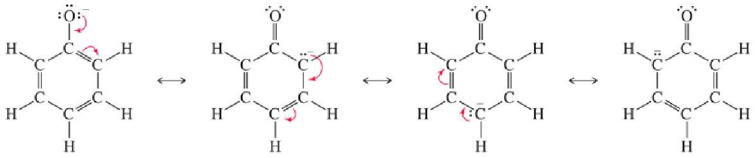
Alcohols and phenols

Reactivity: ACIDITY



phenol, $pK_a = 10.0$ sodium phenoxide $pK_a = 15.7$

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.



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Alcohols

Reactivity: SUBSTITUTION - ELIMINATION

TABLE 11-1

Types of Reactions of Alcohols

R—OH	type of reaction	Product
R—OH	dehydration	alkenes
R—OH	oxidation	ketones, aldehydes, acids
R—OH	substitution	R—X halides
R—OH	reduction	R—H alkanes
R—OH	esterification	R—O—C(=O)—R′ esters
R—OH	tosylation	R—OTs tosylate esters (good leaving group)
R—OH	(1) form alkoxide (2) R′X	R—O—R′ ethers

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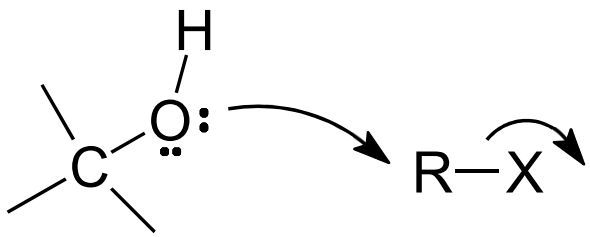
Alcohols

Reactivity: alcohol as a nucleophile



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

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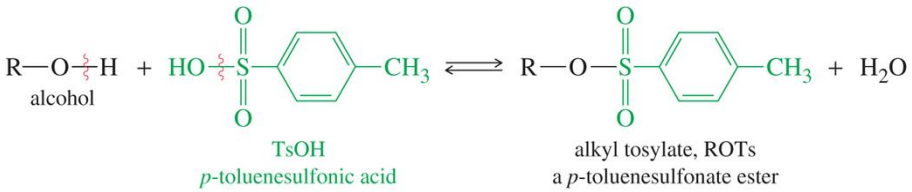
Alcohols

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.

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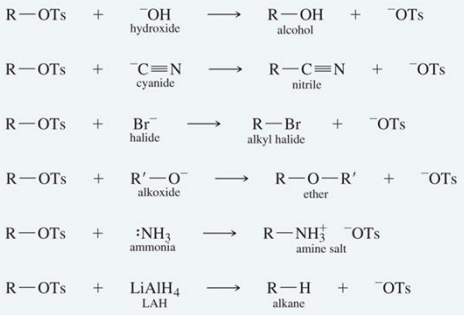
Alcohols

Reactivity: alcohol as an electrophile

SUMMARY S_N2 Reactions of Tosylate Esters



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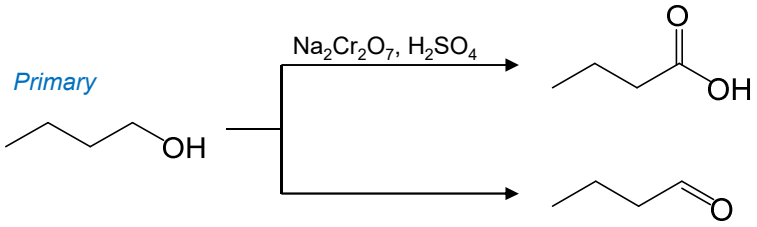
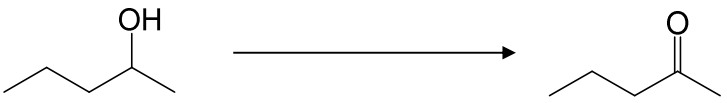
Alcohols

Reactivity: OXIDATION

Primary



Secondary



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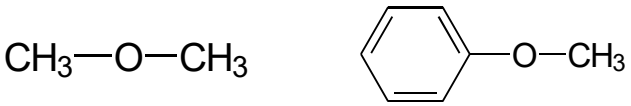
Ethers

General formula

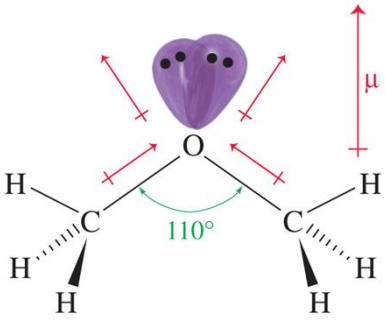
- Formula is R—O—R' where R and R' are alkyl or aryl.
- Symmetrical or unsymmetrical



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

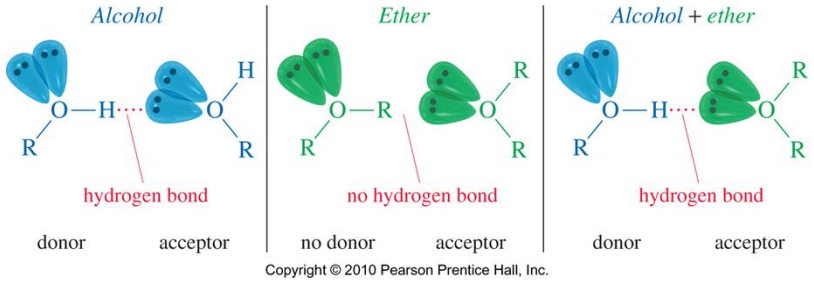
Comparison of the Boiling Points of Ethers, Alkanes, and Alcohols of Similar Molecular Weights

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		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

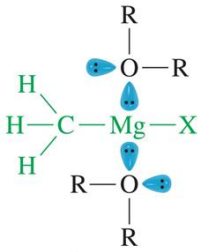


- Ethers cannot hydrogen-bond with other ether molecules.
- Molecules that cannot hydrogen-bond intermolecularly have a lower boiling point.
- Ether molecules can hydrogen-bond with water and alcohol molecules.

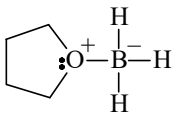
Ethers

Ether complexes

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



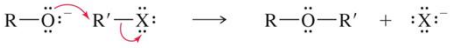
- Electrophiles: The ethers nonbonding electrons stabilize the borane (BH_3).



$BH_3 \circ THF$

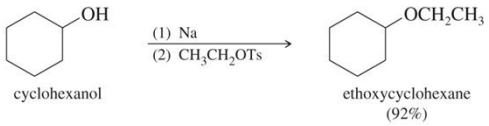
Ethers

Williamson synthesis

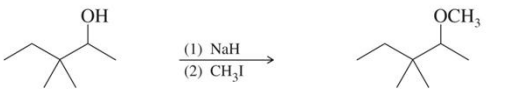


The alkoxide is commonly made by adding Na, K, or NaH to the alcohol (Section 11-14).

Examples



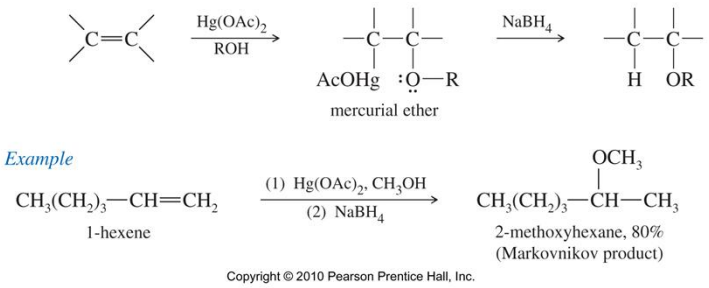
cyclohexanol — ethoxycyclohexane (92%)



3,3-dimethyl-2-pentanol — 2-methoxy-3,3-dimethylpentane (90%)

Ethers

Alkoxymercuration–Demercuration Reaction

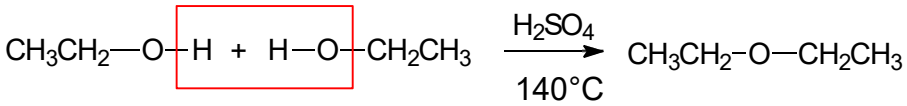


Use mercuric acetate with an alcohol. The alcohol will react with the intermediate mercurinium ion by attacking the more substituted carbon.

Ethers

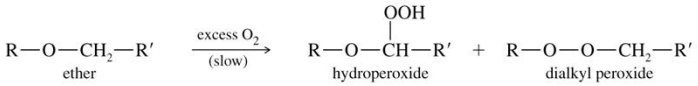
Industrial ether synthesis

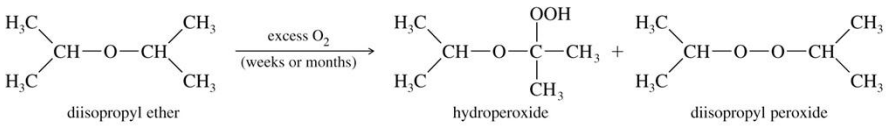
- Industrial method, not good lab synthesis.
- If temperature is too high, alkene forms.



Ethers

Autoxidation of ethers

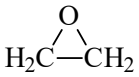
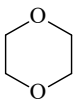




- In the presence of atmospheric oxygen, ethers slowly oxidize to hydroperoxides and dialkyl peroxides. Both are highly explosive.
- Precautions:
  - Do not distill to dryness.
  - Store in full bottles with tight caps.

Epoxides

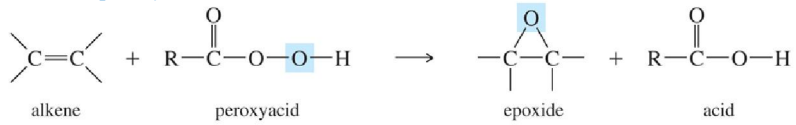
Cyclic ethers

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

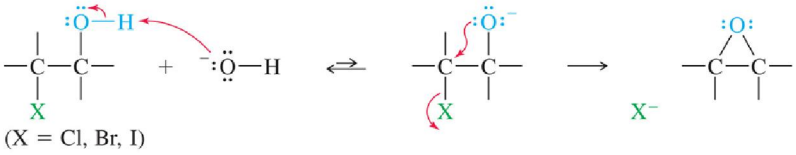
Epoxides

Synthesis

Reaction with peroxyacids

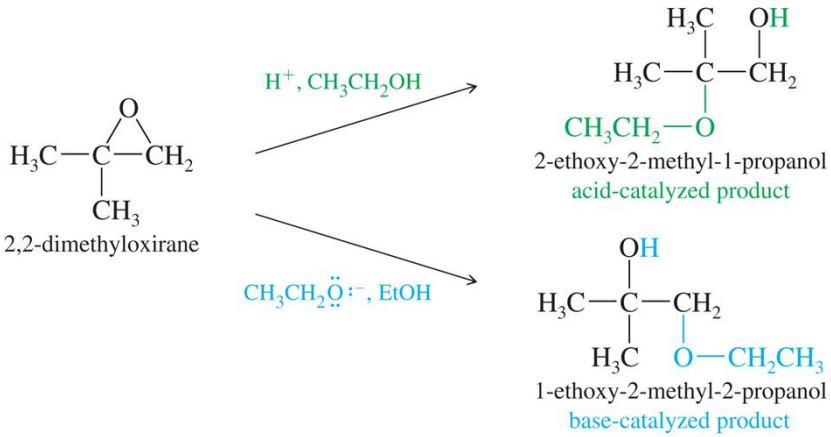


Halohydrin cyclization



Epoxides

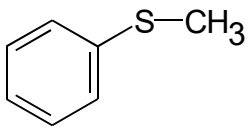
Ring opening



Thioethers (sulphides)

Nomenclature

- R—S—R′, analog of ether.
- Name sulfides like ethers, replacing “sulfide” for “ether” in common name, or “alkylthio” for “alkoxy” in IUPAC system.



methyl phenyl sulfide
or
methylthiobenzene

Thioethers (sulphides)

Williamson synthesis

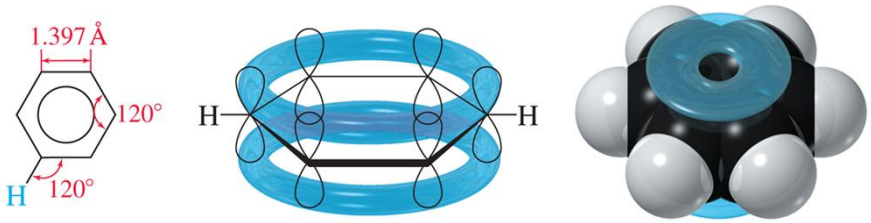
Thiolates are easily synthesized by the Williamson ether synthesis, using dithiolate as the nucleophile.

Aromatic compounds

Hückel's Rule

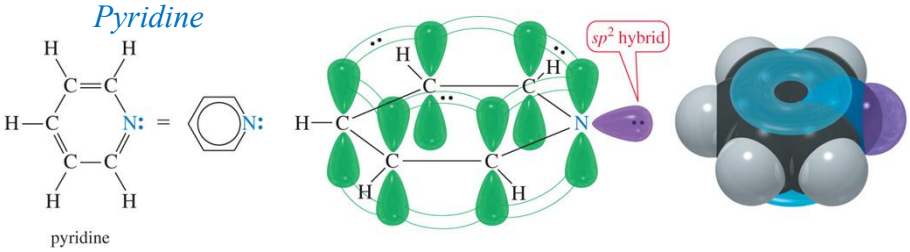
If the number of pi electrons is (4N + 2) the compound is aromatic (where N is an integer)

Benzene

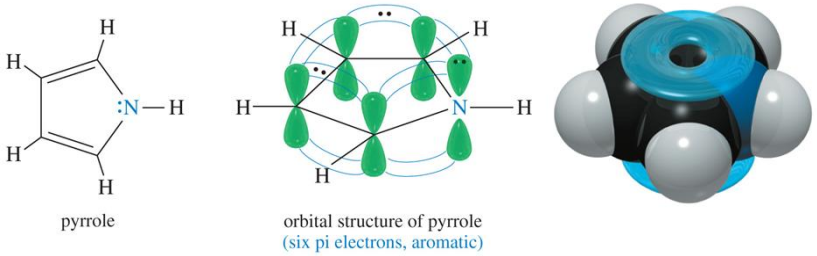


Aromatic compounds

Pyridine

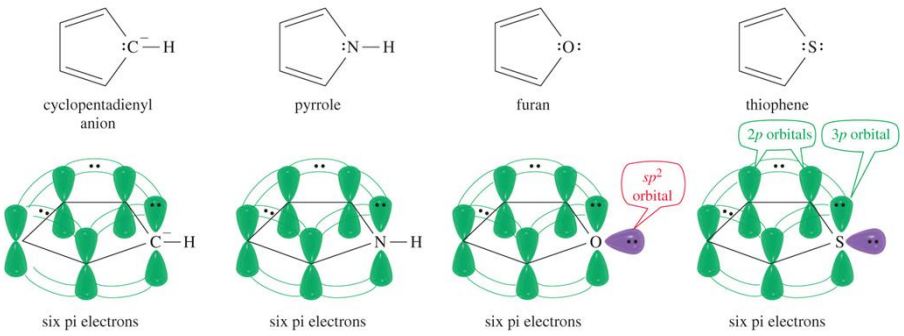


Pyrrole

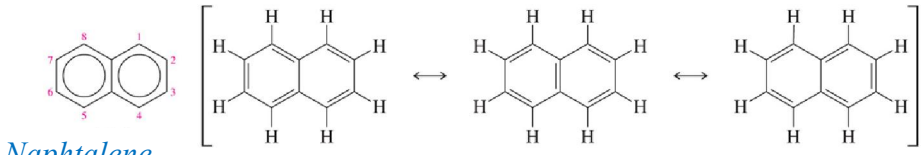


Aromatic compounds

Other heterocyclics

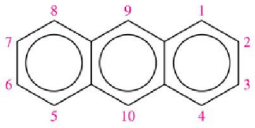


Aromatic compounds

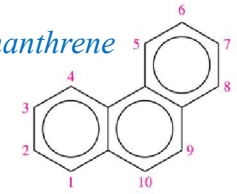


Naphtalene

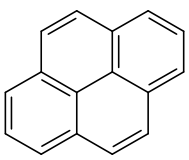
Anthracene



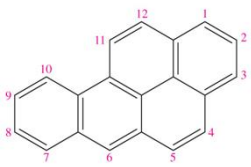
Phenanthrene



Pyrene



Benzo[a]pyrene



Many are carcinogenic

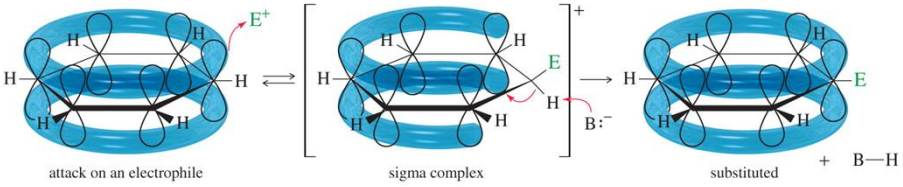
Aromatic compounds

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 nonaromatics, less dense than water.
- Solubility: Generally insoluble in water.

Aromatic compounds

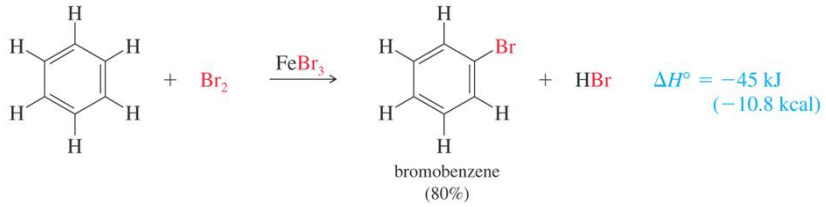
Reactivity: ELECTROPHYLIC SUBSTITUTION



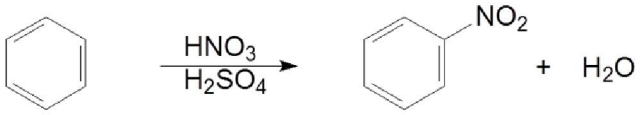
- Although benzene's pi electrons are in a stable aromatic system, they are available to attack a strong electrophile to give a carbocation.
- This resonance-stabilized carbocation is called a ***sigma complex*** because the electrophile is joined to the benzene ring by a new sigma bond.
- Aromaticity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

Aromatic compounds

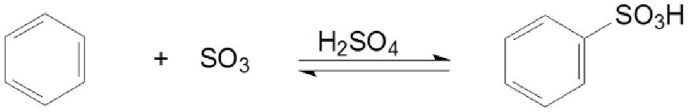
Reactivity: HALOGENATION



NITRATION

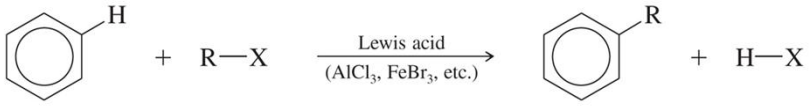


SULFONATION

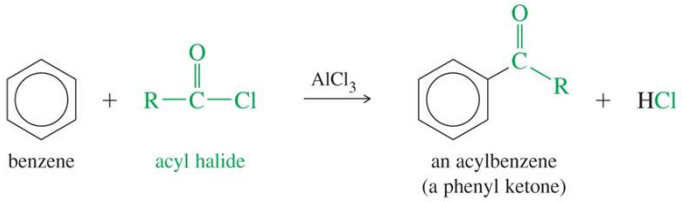


Aromatic compounds

Reactivity: FRIEDEL-CRAFTS ALKYLATION

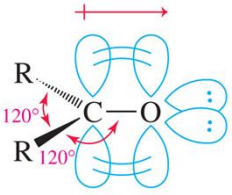


FRIEDEL-CRAFTS ACYLATION



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.

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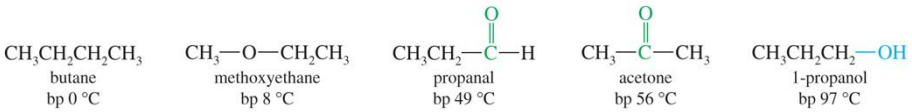
Aldehydes and ketones

Boiling points



- 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.

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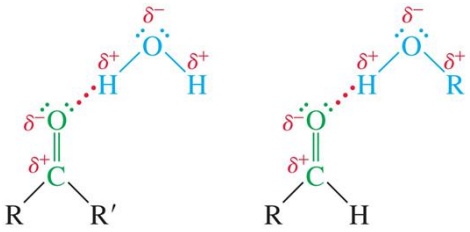
Aldehydes and ketones

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.

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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.

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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

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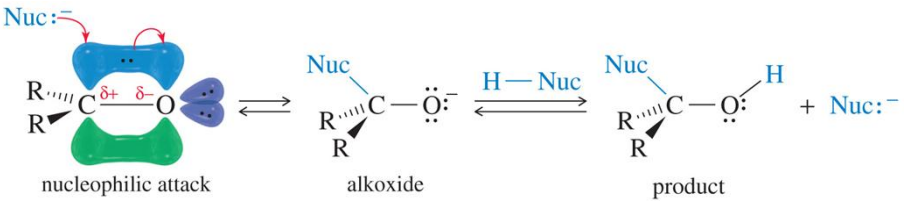
Aldehydes and ketones

Reactivity: NUCLEOPHYLIC ADDITION



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

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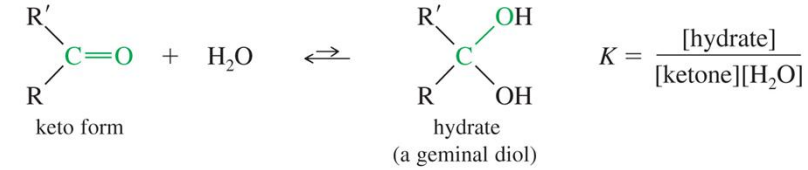
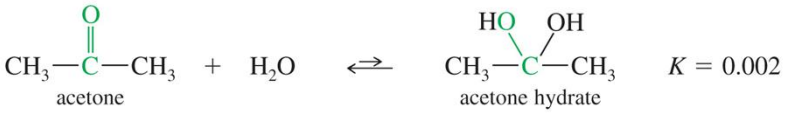
Aldehydes and ketones

Reactivity: HYDRATION



Example



- 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).

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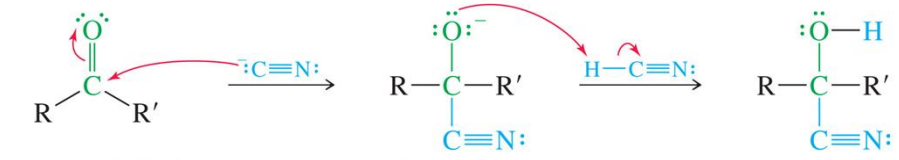
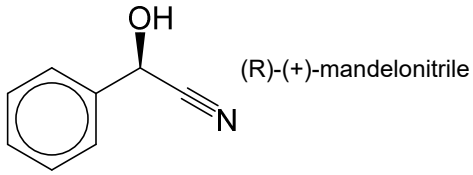
Aldehydes and ketones

Reactivity: CIANOHYDRIN FORMATION



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



(R)-(+)-mandelonitrile

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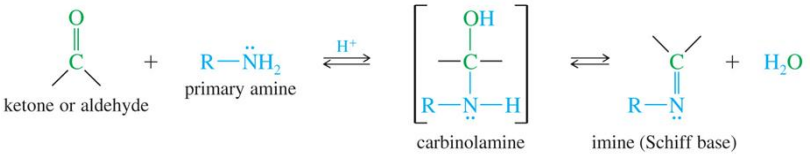
Aldehydes and ketones

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

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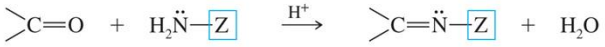
Aldehydes and ketones

Reactivity: CONDENSATION WITH AMINES



Z in Z—NH₂	*Reagent*	*Product*
—H	$H_2\ddot{N}$—H ammonia	>C═N—H an imine
—R	$H_2\ddot{N}$—R primary amine	>C═N—R an imine (Schiff base)
—OH	$H_2\ddot{N}$—OH hydroxylamine	>C═N—OH an oxime
—NH_2	$H_2\ddot{N}$—NH_2 hydrazine	>C═N—NH_2 a hydrazone
—NHPh	$H_2\ddot{N}$—NHPh phenylhydrazine	>C═N—NHPh a phenylhydrazone
—NHCNH₂ (O)	$H_2\ddot{N}$—NH—C(=O)—NH_2 semicarbazide	>C═N—NH—C(=O)—NH_2 a semicarbazone

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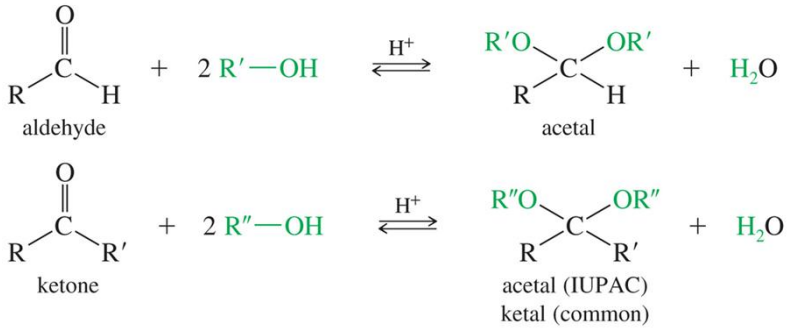
Aldehydes and ketones

Reactivity: FORMATION OF ACETAL



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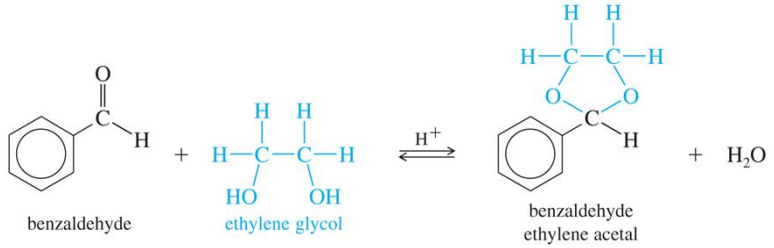
Aldehydes and ketones

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

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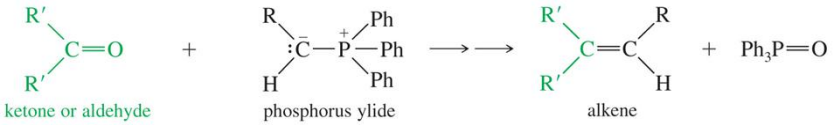
Aldehydes and ketones

Reactivity: WITTIG REACTION

The Wittig reaction



- The Wittig reaction converts the carbonyl group into a new C=C double bond where no bond existed before.
- A phosphorus ylide is used as the nucleophile in the reaction.

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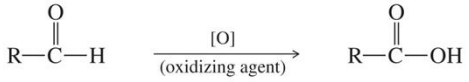
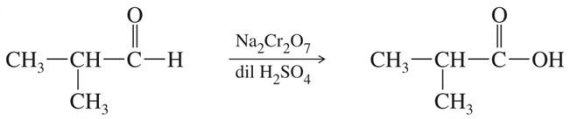
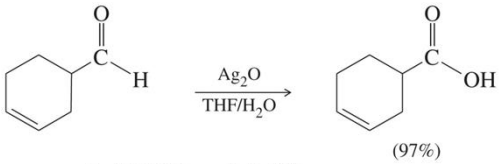
Aldehydes and ketones

Reactivity: OXIDATION



Examples





Aldehydes are easily oxidized to carboxylic acids.

No reaction on ketones.

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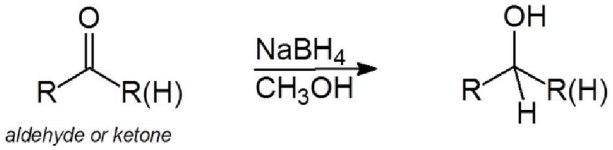
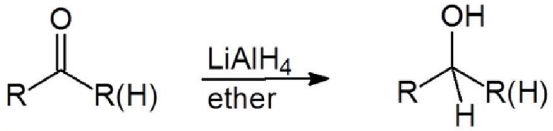
Aldehydes and ketones

Reactivity: REDUCTION



aldehyde or ketone

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



aldehyde or ketone

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

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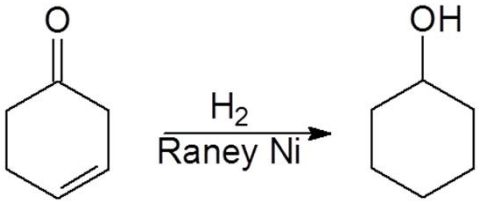
Aldehydes and ketones

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.

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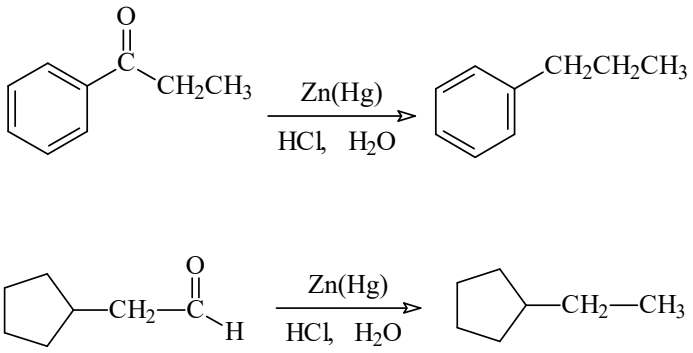
Aldehydes and ketones

Reactivity: CLEMMENSEN REDUCTION



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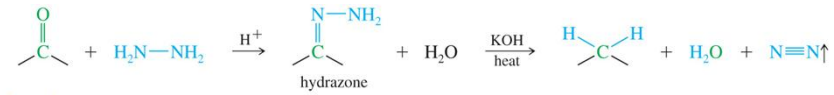
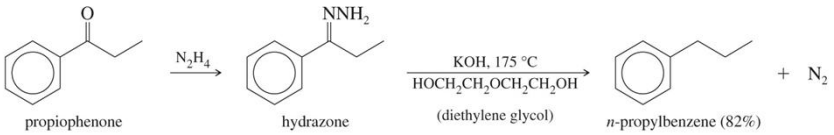
Aldehydes and ketones

Reactivity: WOLFF-KISHNER REDUCTION



Examples



- 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.

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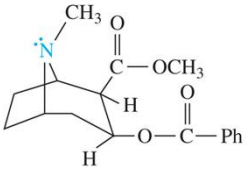
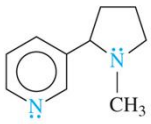
Amines

Biological activity of amines

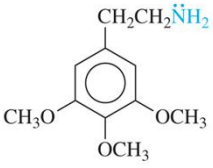
- Dopamine is a neurotransmitter.
- Epinephrine is a bioregulator.
- Niacin, Vitamin B_6, is an amine.
- Alkaloids: nicotine, morphine, cocaine
- Amino acids



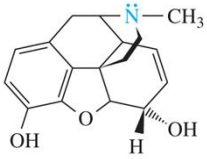
cocaine
in coca leaves



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.

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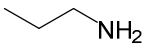
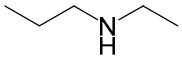
Amines

Classification

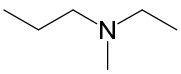
- ***Primary (1°)***: Has one alkyl group bonded to the nitrogen (RNH_2).



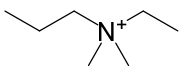
- ***Secondary (2°)***: Has two alkyl groups bonded to the nitrogen (R_2NH).



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

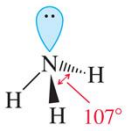


- ***Quaternary (4°)***: Has four alkyl groups bonded to the nitrogen and the nitrogen bears a positive charge (R_4N^+).

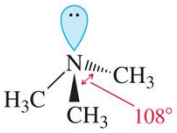


Amines

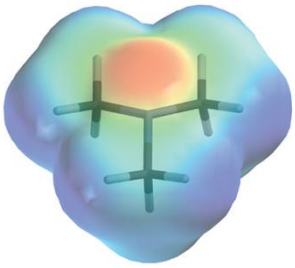
Structure of amines



ammonia



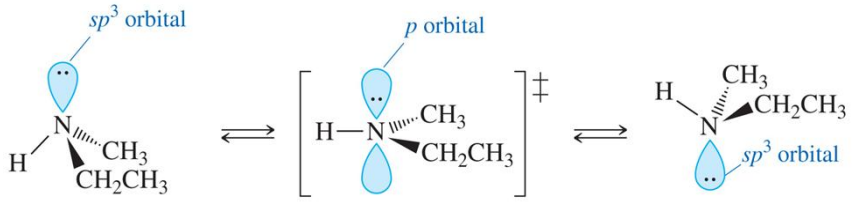
trimethylamine


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

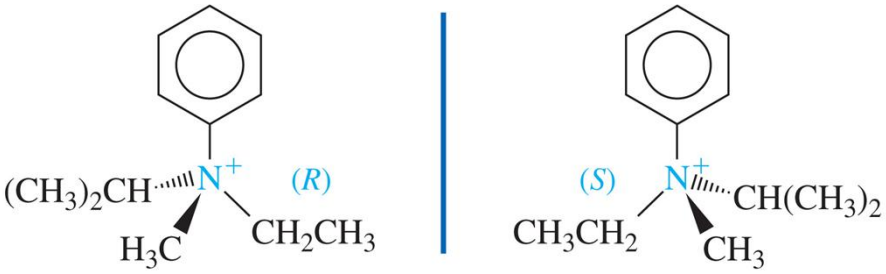


(*R*)-ethylmethylamine [transition state] (*S*)-ethylmethylamine

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

Amines

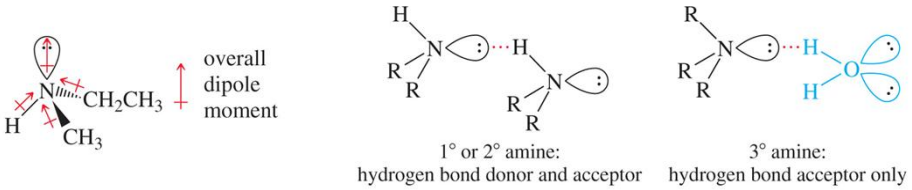
Chiral quaternary ammonium salts



- 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



- 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.

$NH_2CH_2CH_2CH_2CH_2CH_2NH_2$

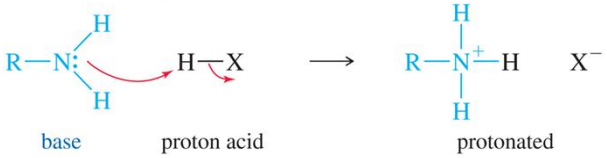
1,5-pentanediamine or cadaverine

Amines

Basicity of amines

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

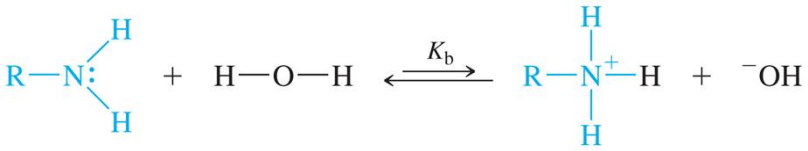
Reaction of an amine as a proton base



- 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

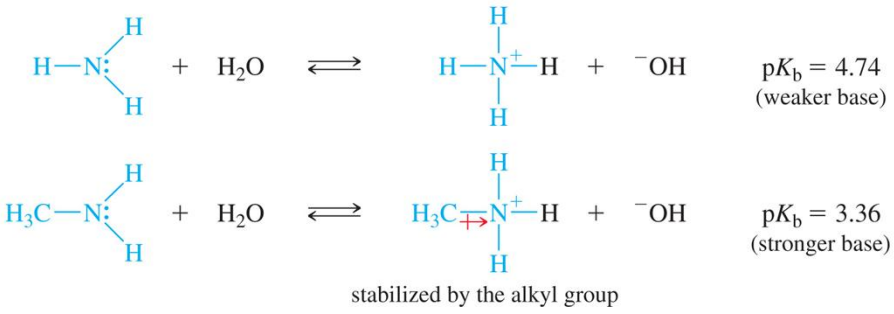


$$K_b = \frac{[RNH_3^+][^-OH]}{[RNH_2]} \qquad pK_b = -\log_{10} K_b$$

- 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

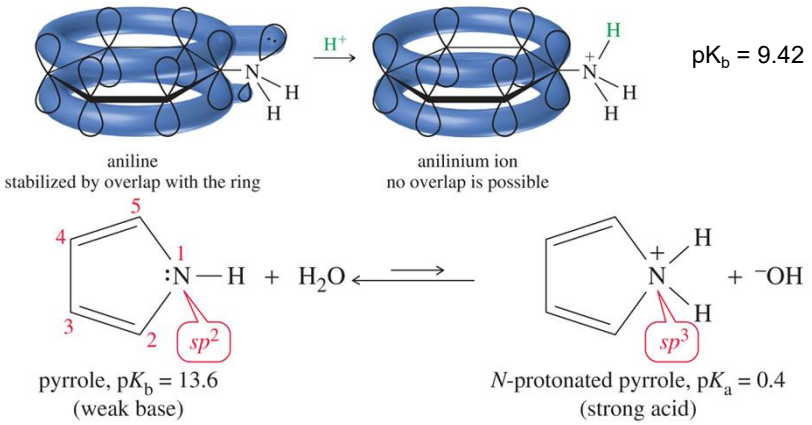
Alkyl groups stabilization of amines



Alkyl groups make the nitrogen a stronger base than ammonia.

Amines

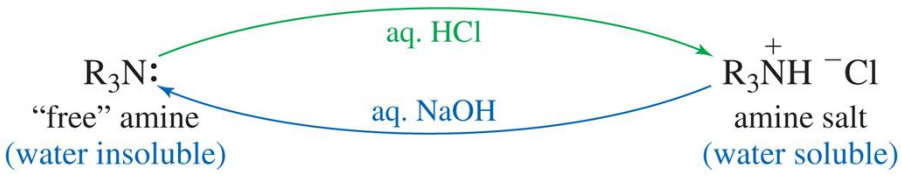
Resonance effect



When protonated, stabilization by aromatic stabilization is lost.

Amines

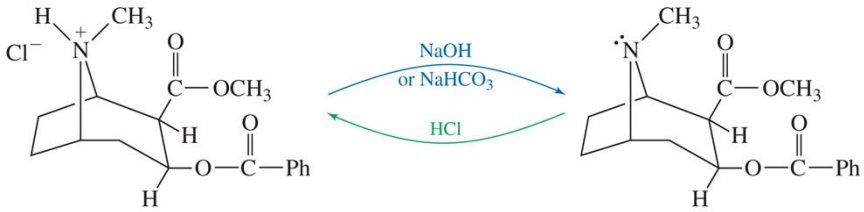
Ammonium salts



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

Amines

Ammonium salts



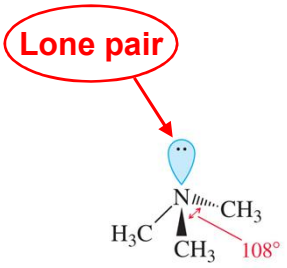
cocaine hydrochloride

cocaine "free base"

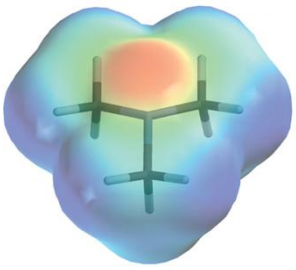
- Cocaine is usually smuggled and "snorted" as the hydrochloride salt.
- Treating cocaine hydrochloride with sodium hydroxide and extracting it into ether converts it back to the volatile "free base" for smoking.

Amines

Reactivity: AMINES AS NUCLEOPHILES



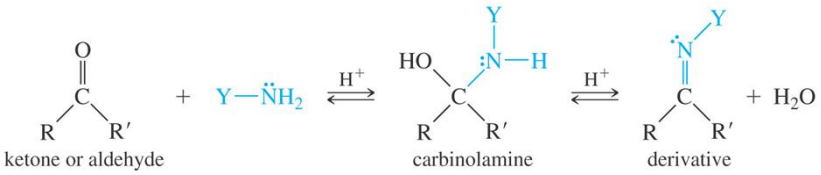
trimethylamine



electrostatic potential map for trimethylamine

Amines

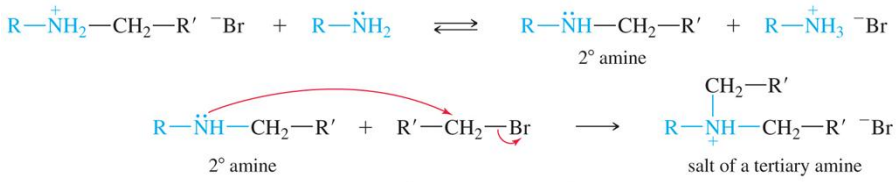
Reactivity: CONSENSATION WITH CARBONYL



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

Amines

Reactivity: ALKYLATION



NOT SELECTIVE

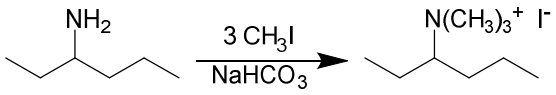
Even if just one equivalent of the halide is added, some amine molecules will react once, some will react twice, and some will react three times (to give the tetraalkylammonium salt).

Amines

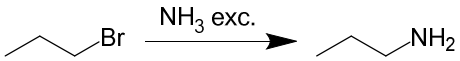
Reactivity: ALKYLATION

Examples of useful alkylation

Exhaustive alkylation to form the tetraalkylammonium salt.



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



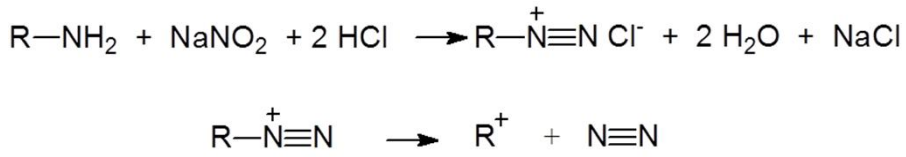
Amines

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

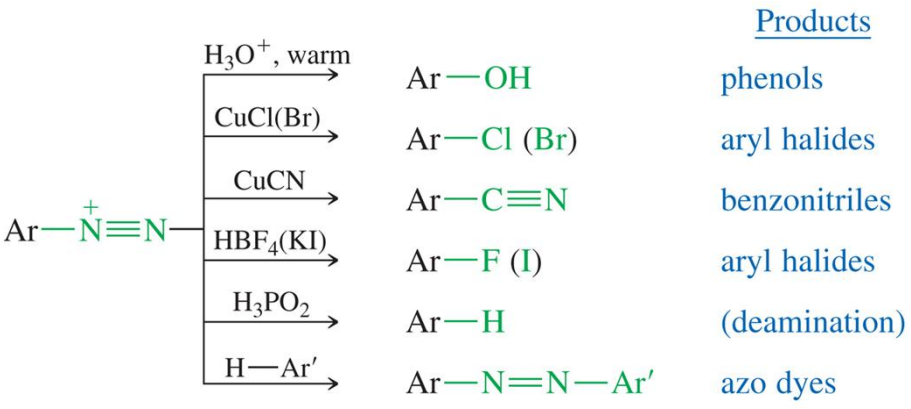
Reactivity: FORMATION OF DIAZONIUM SALTS



- 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

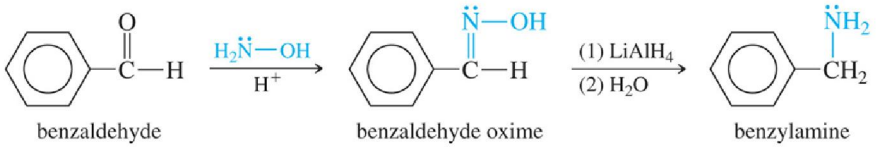


By diazotizing an amine, an aromatic position can be converted into a wide variety of functional groups.

Amines

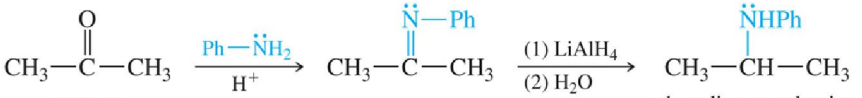
Synthesis: REDUCTIVE AMINATION

Primary amines



benzaldehyde — benzaldehyde oxime — benzylamine

Secondary amines

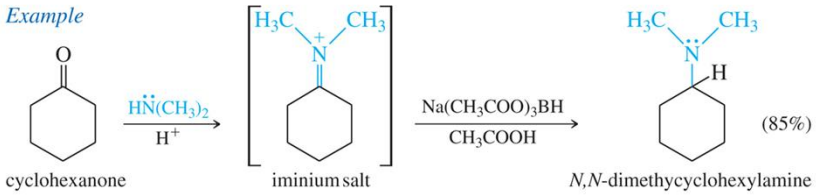


acetone — phenylisopropylamine (75%)

Amines

Synthesis: REDUCTIVE AMINATION

Tertiary amines

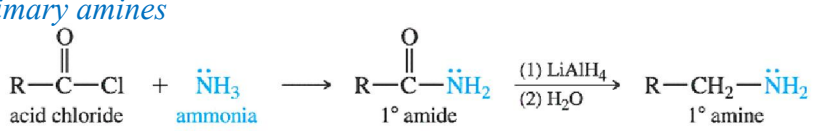


cyclohexanone — iminium salt — *N,N*-dimethycyclohexylamine

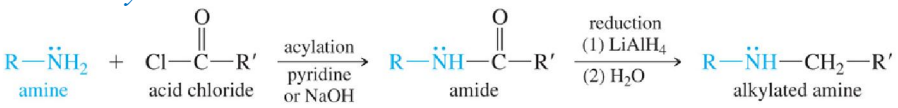
Amines

Synthesis: ACYLATION - REDUCTION

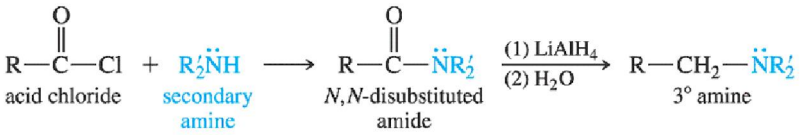
Primary amines



Secondary amines

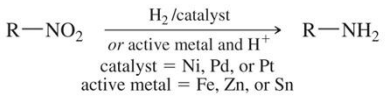


Tertiary amines

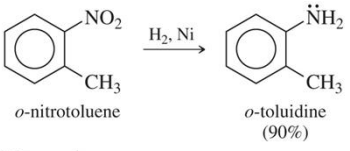


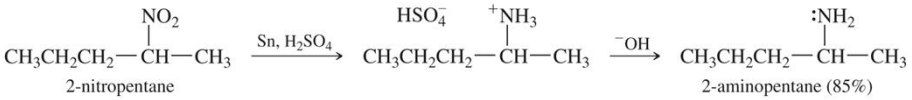
Amines

Synthesis: REDUCTION OF NITRO COMPOUDS



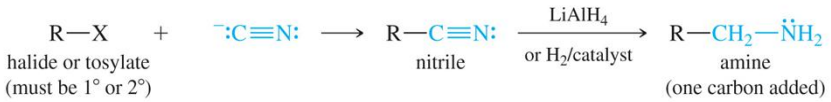
Examples





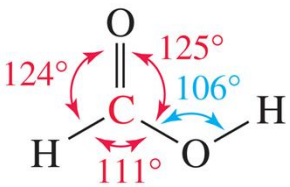
Amines

Synthesis: REDUCTION OF NITRILES

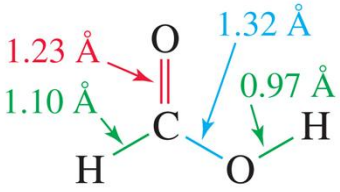


Carboxylic acids

Structure of COOH group



bond angles

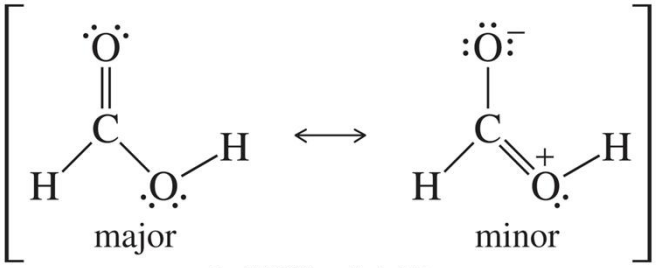


bond lengths

- 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

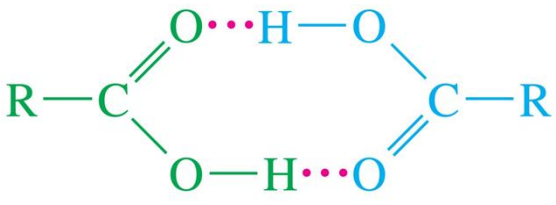
Structure of COOH group



- 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

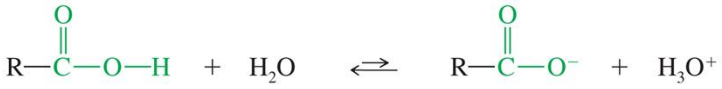
Carboxylic acids

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



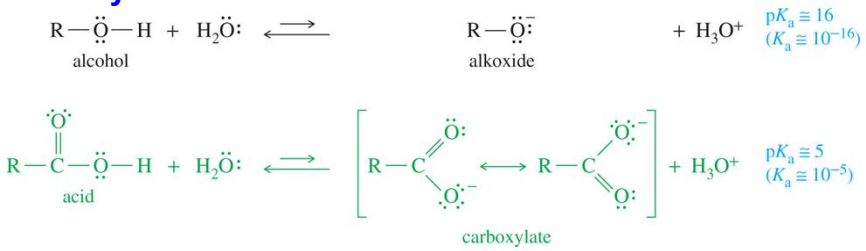
$$K_a = \frac{[R{-}CO_2^-][H_3O^+]}{[R{-}CO_2H]}$$

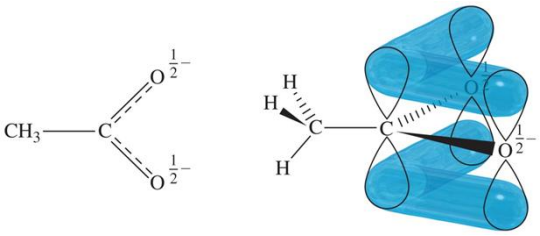
$$pK_a = -\log_{10} K_a$$

- 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

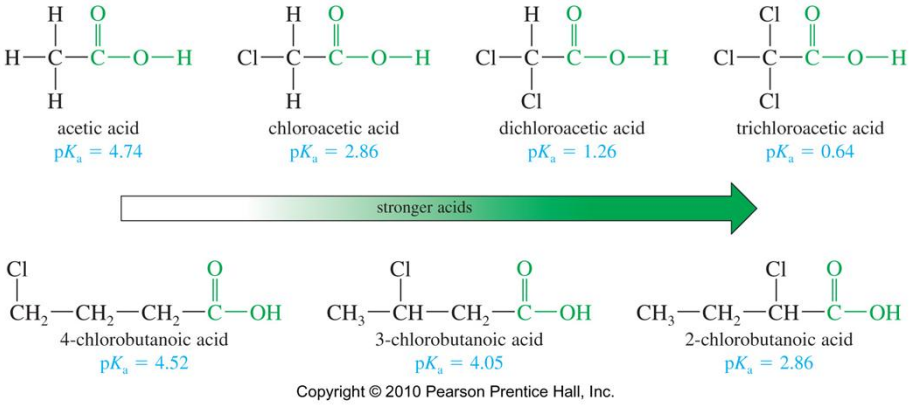




The delocalization of the negative charge over the two oxygens makes the acetate ion more stable than an alkoxide ion.

Carboxylic acids

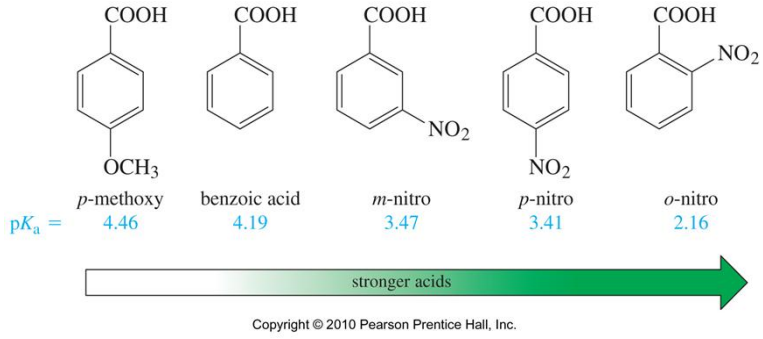
Acidity: effect of substituents



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

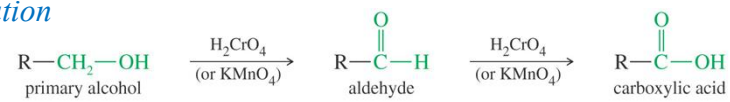
Values of K_a and pK_a for Substituted Carboxylic Acids

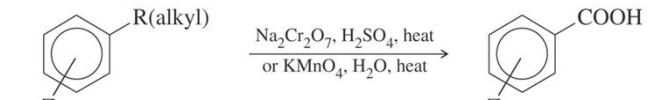
Acid	K_a	pK_a	
F_3CCOOH	5.9×10^{-1}	0.23	stronger acids
Cl_3CCOOH	2.3×10^{-1}	0.64	
$Cl_2CHCOOH$	5.5×10^{-2}	1.26	
$O_2N—CH_2COOH$	2.1×10^{-2}	1.68	
$NCCH_2COOH$	3.4×10^{-3}	2.46	
FCH_2COOH	2.6×10^{-3}	2.59	
$ClCH_2COOH$	1.4×10^{-3}	2.86	
$CH_3CH_2CHClCOOH$	1.4×10^{-3}	2.86	
$BrCH_2COOH$	1.3×10^{-3}	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

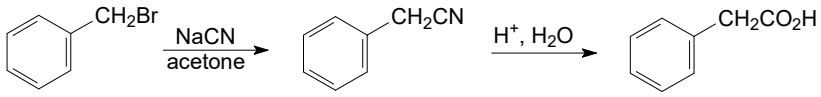




Carboxylic acids

Synthesis

Hydrolysis of nitriles

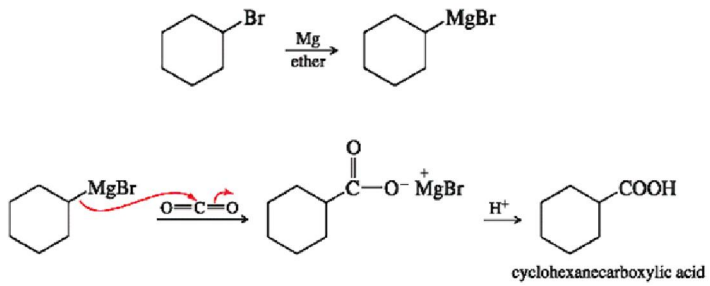


- Basic or acidic hydrolysis of a nitrile (—CN) produces a carboxylic acid.
- The overall reaction, starting from the alkyl halide, adds an extra carbon to the molecule.

Carboxylic acids

Synthesis

Grignard + CO_2

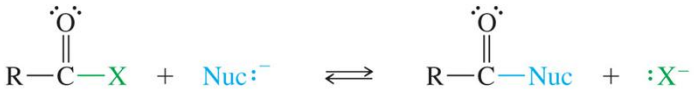


- Grignard reagent react with CO_2 to produce, after protonation, a carboxylic acid.
- This reaction is sometimes called "CO_2 insertion" and it increases the number of carbons in the molecule by one.

Carboxylic acids

Reactivity: NUCLEOPHILIC ACYL SUBSTITUTION

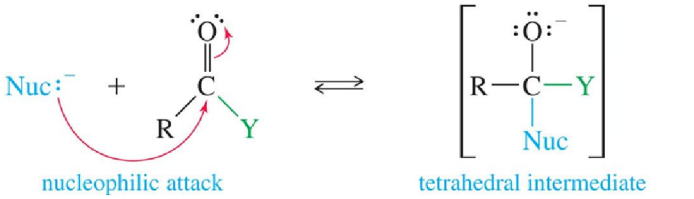
Nucleophilic acyl substitution

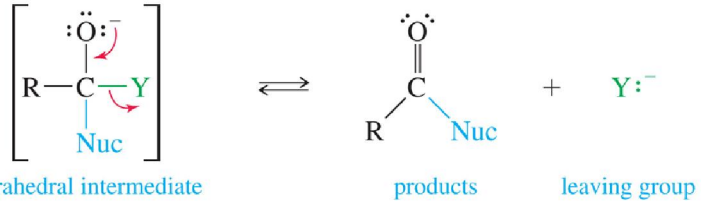


- Carboxylic acids react by nucleophilic acyl substitution, where one nucleophile replaces another on the acyl (C═O) carbon atom.

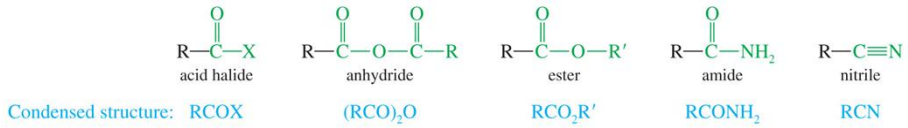
Carboxylic acids

Reactivity: NUCLEOPHILIC ACYL SUBSTITUTION





Derivatives of carboxylic acids

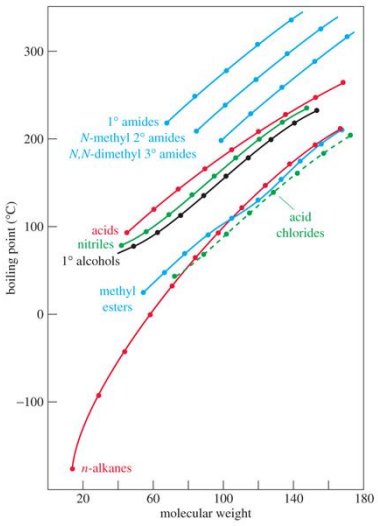


- All the derivatives can be converted to the carboxylic acid by acidic or basic hydrolysis.
- Esters and amides are commonly found in nature.

Derivatives of carboxylic acids

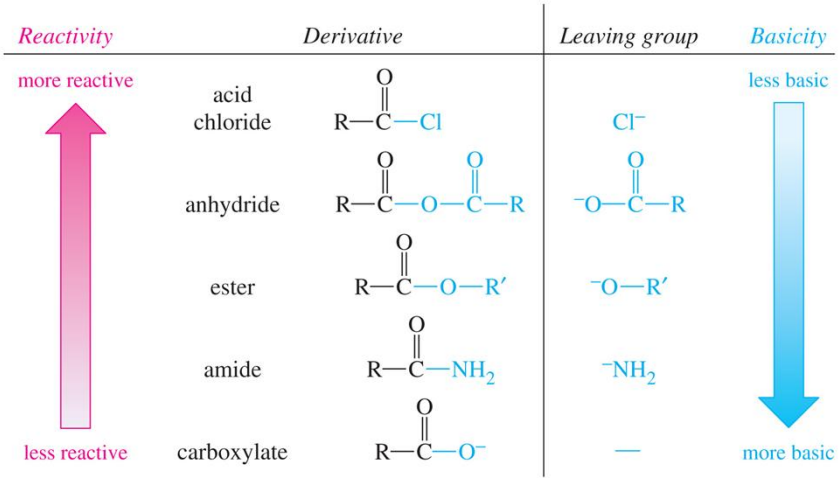
Physical properties

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



Derivatives of carboxylic acids

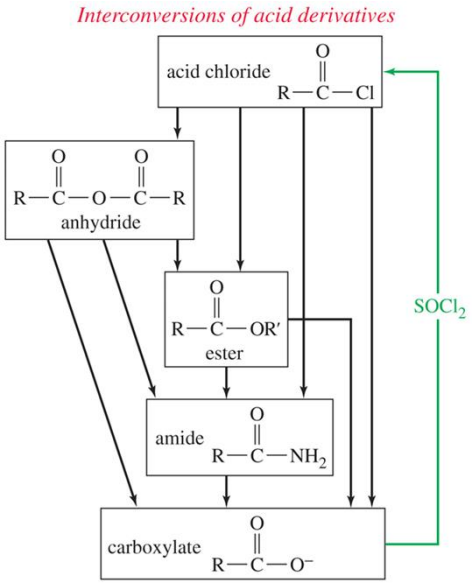
Reactivity



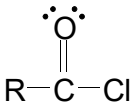
Derivatives of carboxylic acids

Reactivity

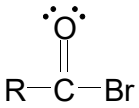
More reactive derivatives can be converted to less reactive derivatives.



Acyl halides



acyl chloride

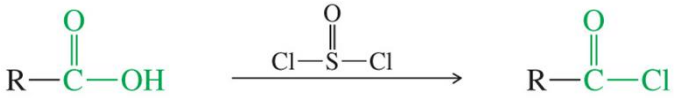


acyl bromide

- 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

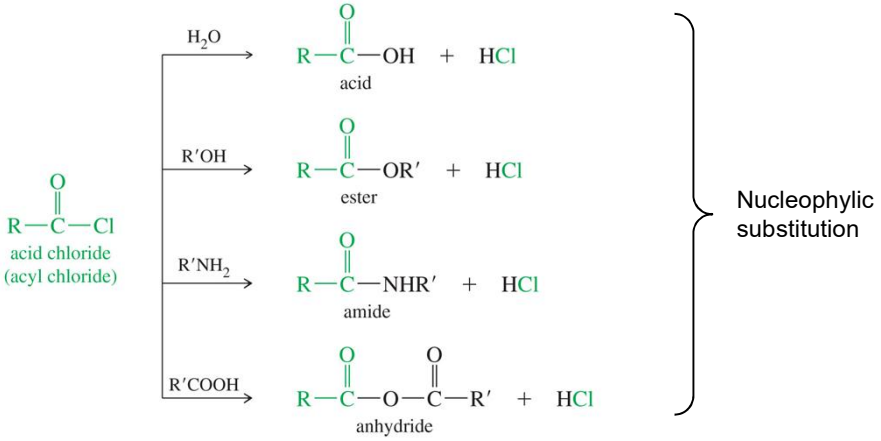
Synthesis



- 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.

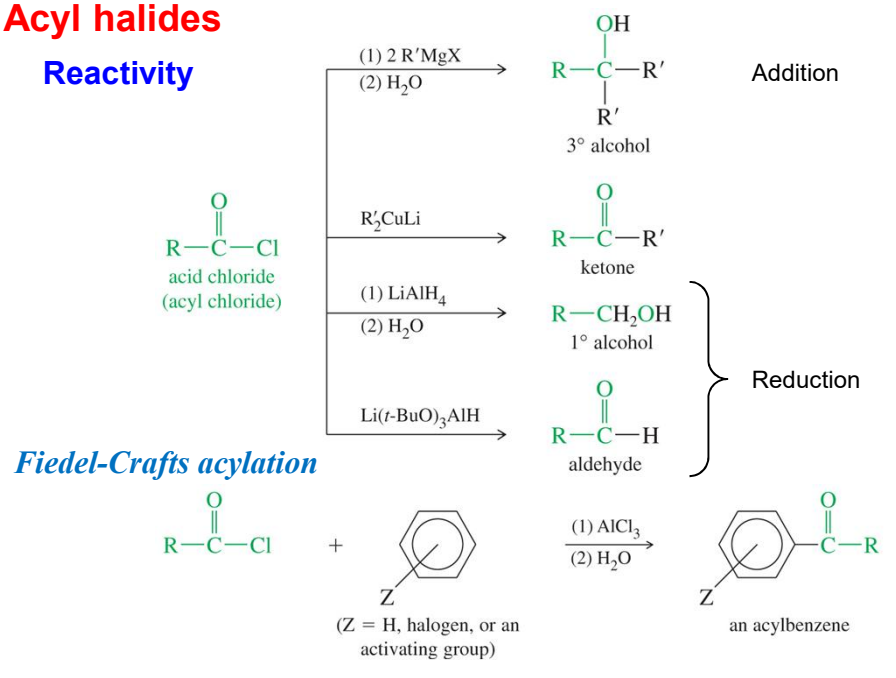
Acyl halides

Reactivity



Acyl halides

Reactivity



Anhydrides

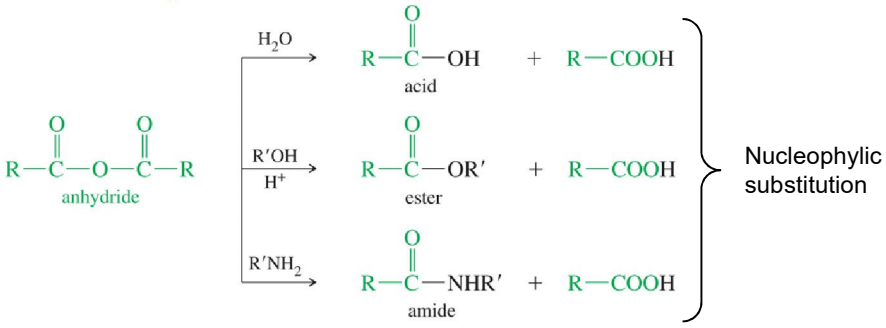
Synthesis

Examples

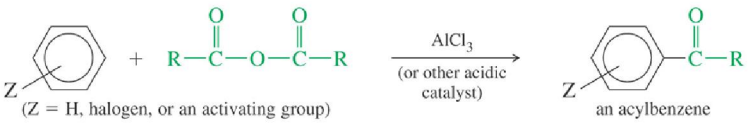
- The most generalized method for making anhydrides is the reaction of an acid chloride with a carboxylic acid or a carboxylate salt.
- Pyridine is sometimes used to deprotonate the acid and form the carboxylate.

Anhydrides

Reactivity

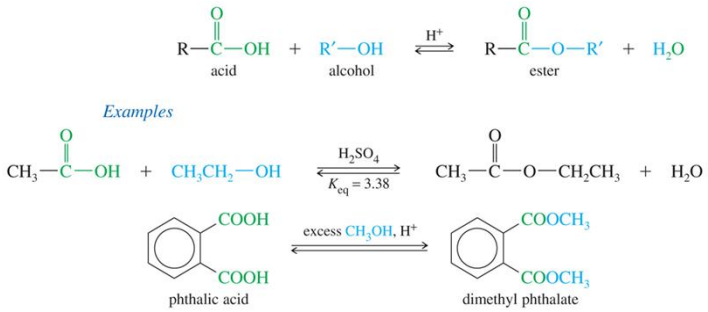


Fiedel-Crafts acylation



Esters

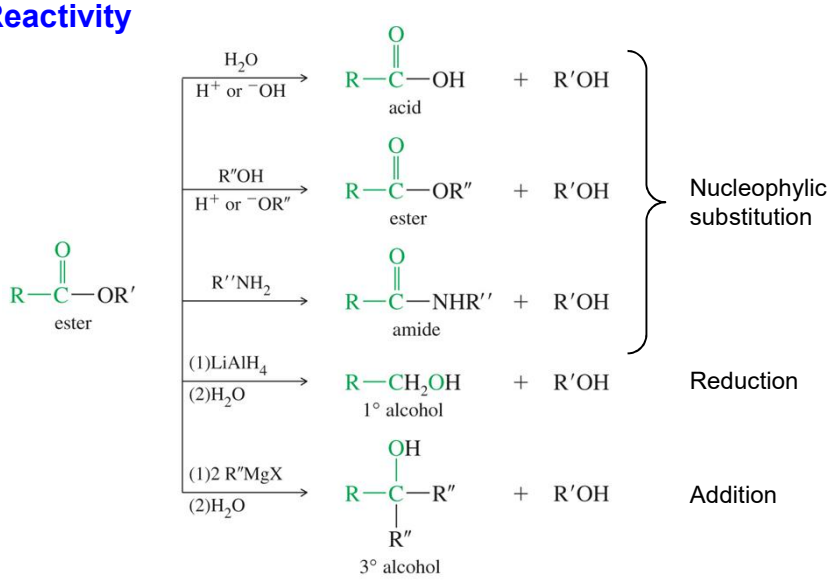
Fisher esterification



- 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.

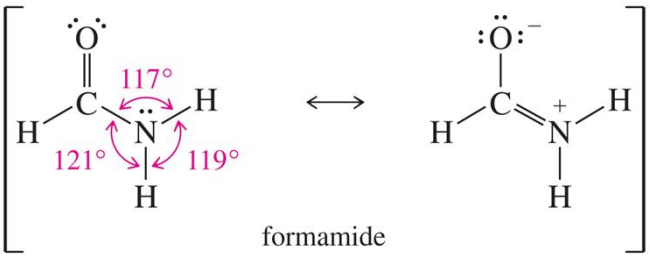
Esters

Reactivity



Amides

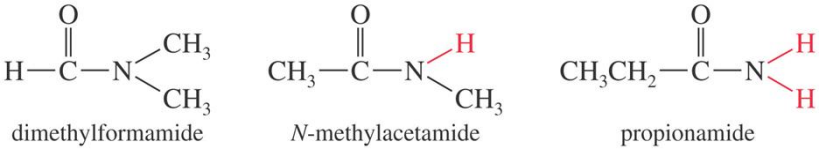
Structure



- 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

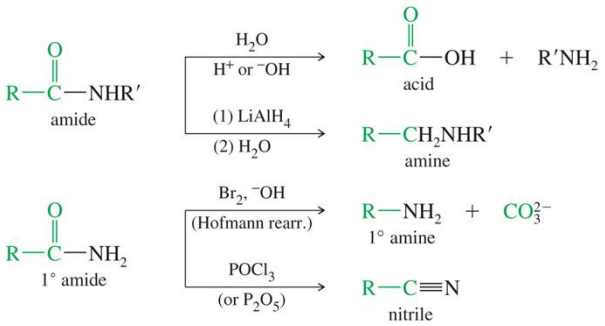


3º amide 2º amide 1º amide

- 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

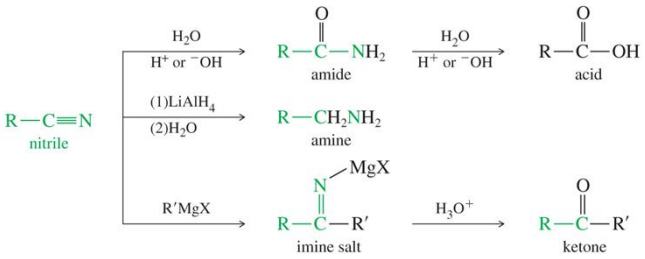
Reduction

Elimination

Dehydration

Nitriles

Reactivity

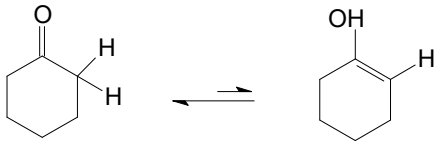


Hydrolysis

Reduction

Addition

Keto-enol tautomerism

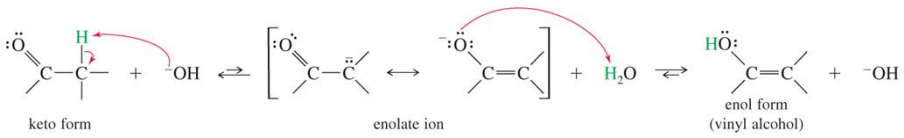


keto form (99.99%) *enol form (0.01%)*

- 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

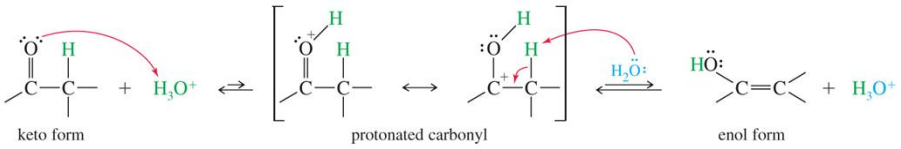
Base-catalyzed tautomerism



- 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

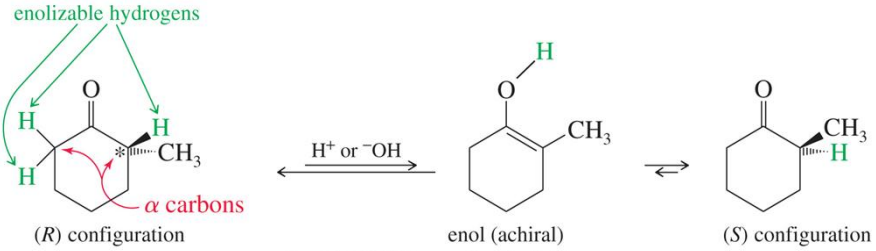
Base-catalyzed tautomerism



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

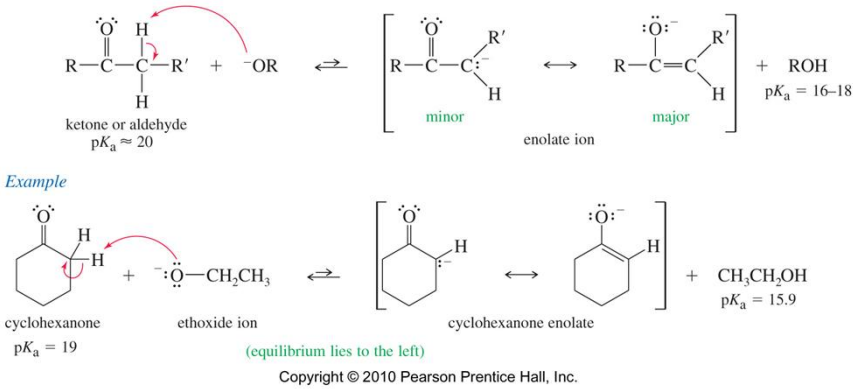
Keto-enol tautomerism

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***.

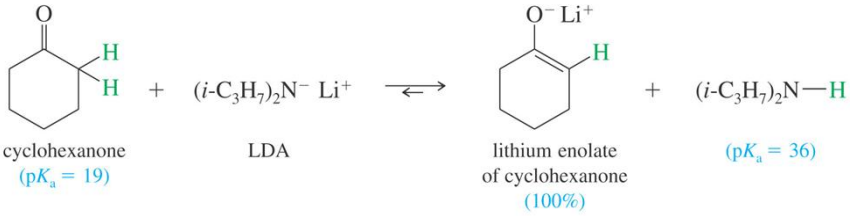
Acidity of α Hydrogen



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.

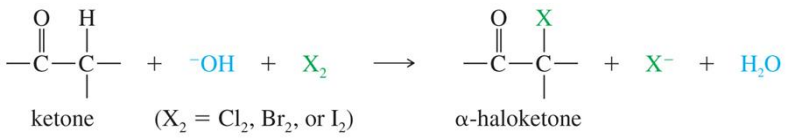
Acidity of α Hydrogen

TABLE 22-1

Typical Acidities of Carbonyl Compounds

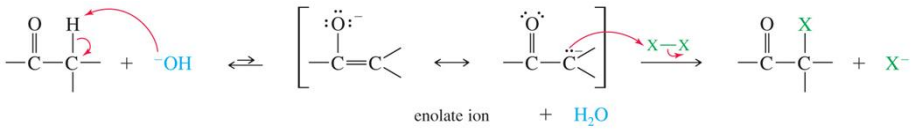
Conjugate Acid	Conjugate Base	pK_a
Simple ketones and esters		
$CH_3-\overset{O}{\overset{\|}{C}}-CH_3$ (acetone)	$^-:CH_2-\overset{O}{\overset{\|}{C}}-CH_3$	20
$CH_3-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$ (ethyl acetate)	$^-:CH_2-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$	24
β-dicarbonyl compounds		
$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$ (2,4-pentanedione (acetylacetone))	$CH_3-\overset{O}{\overset{\|}{C}}-\ddot{C}H-\overset{O}{\overset{\|}{C}}-CH_3$	9
$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$ (ethyl acetoacetate (acetoacetic ester))	$CH_3-\overset{O}{\overset{\|}{C}}-\ddot{C}H-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$	11
$CH_3CH_2O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$ (diethyl malonate (malonic ester))	$CH_3CH_2O-\overset{O}{\overset{\|}{C}}-\ddot{C}H-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$	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.

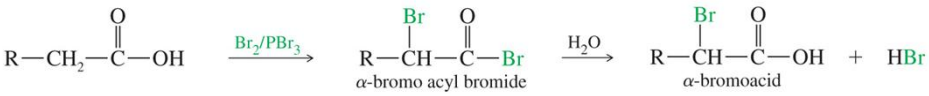
α Halogenation of ketones



- 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 Halogenation of esters

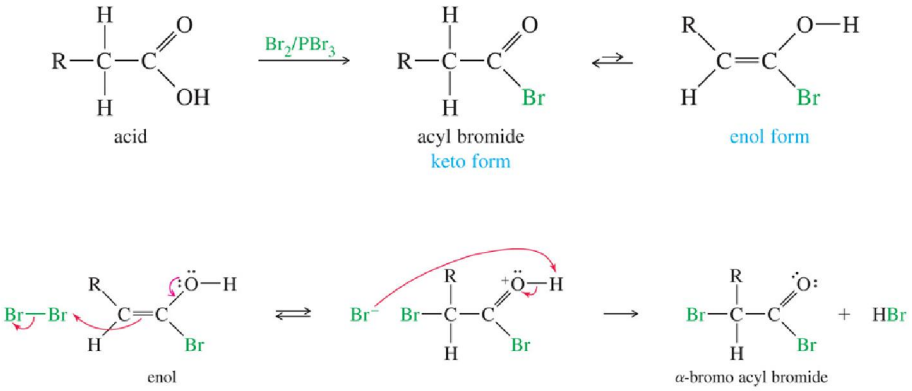
Hell-Volard-Zelinsky (HVZ) Reaction



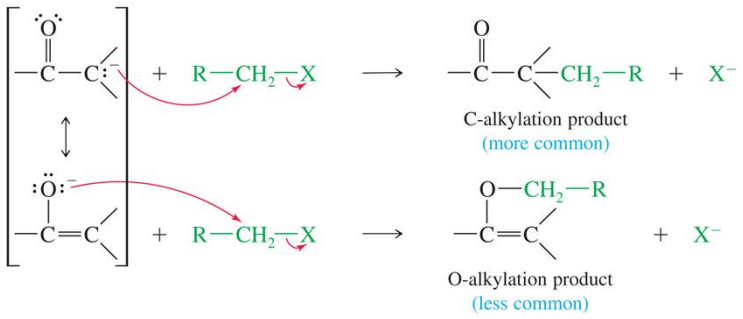
- The HVZ reaction replaces a hydrogen atom with a bromine atom on the alpha-carbon of a carboxylic acid (α-bromoacid).
- The acid is treated with bromine and phosphorus tribromide, followed by hydrolysis.

α Halogenation of esters

Hell-Volard-Zelinsky (HVZ) Reaction



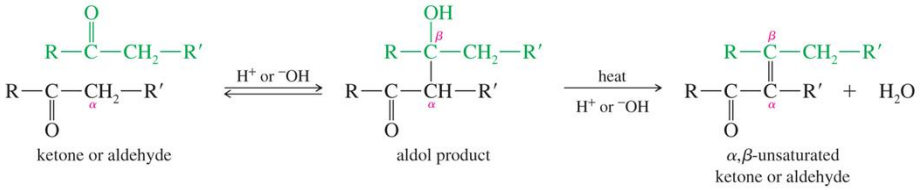
α Alkylation



- 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

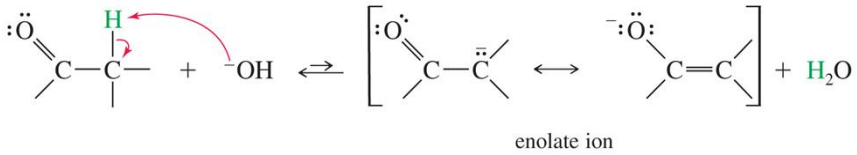
The aldol condensation



- 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.

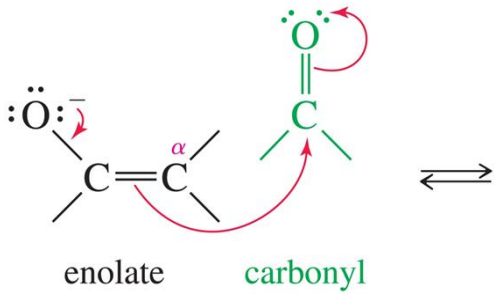
Aldol condensation

Step 1



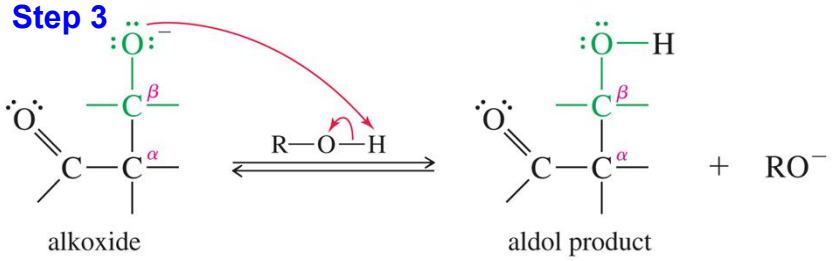
enolate ion

Step 2

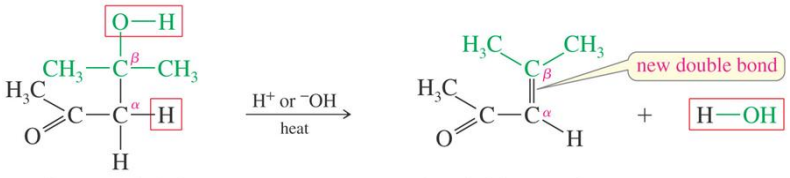


Aldol condensation

Step 3



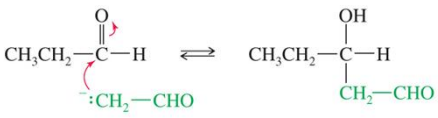
Step 4



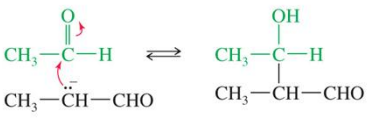
Aldol condensation

Crossed aldol condensation

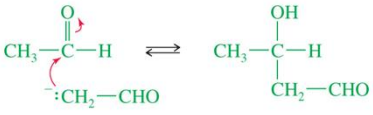
Enolate of ethanal adds to propanal



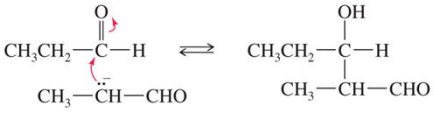
Enolate of propanal adds to ethanal



Self-condensation of ethanal

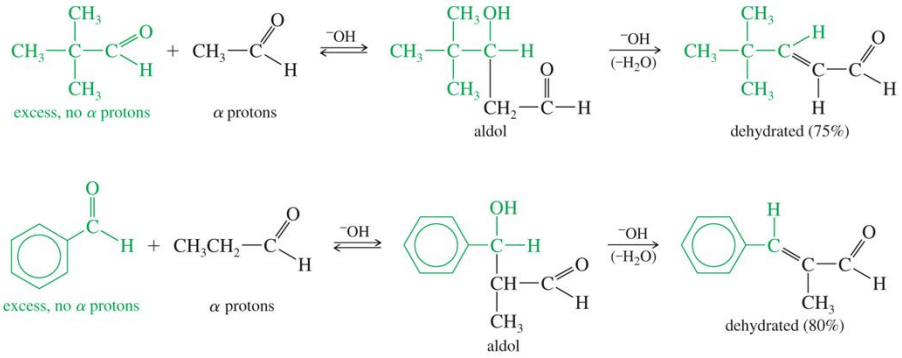


Self-condensation of propanal



Aldol condensation

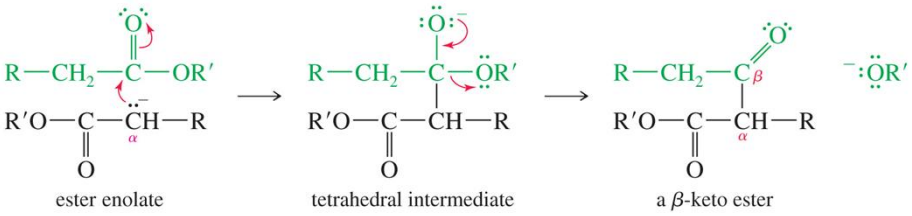
Successful aldol condensation



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

Aldol condensation

Claisen condensation



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