St Peter’s Institute of Pharmaceutical Sciences

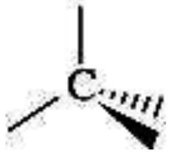
Course : Bachelor of Pharmacy

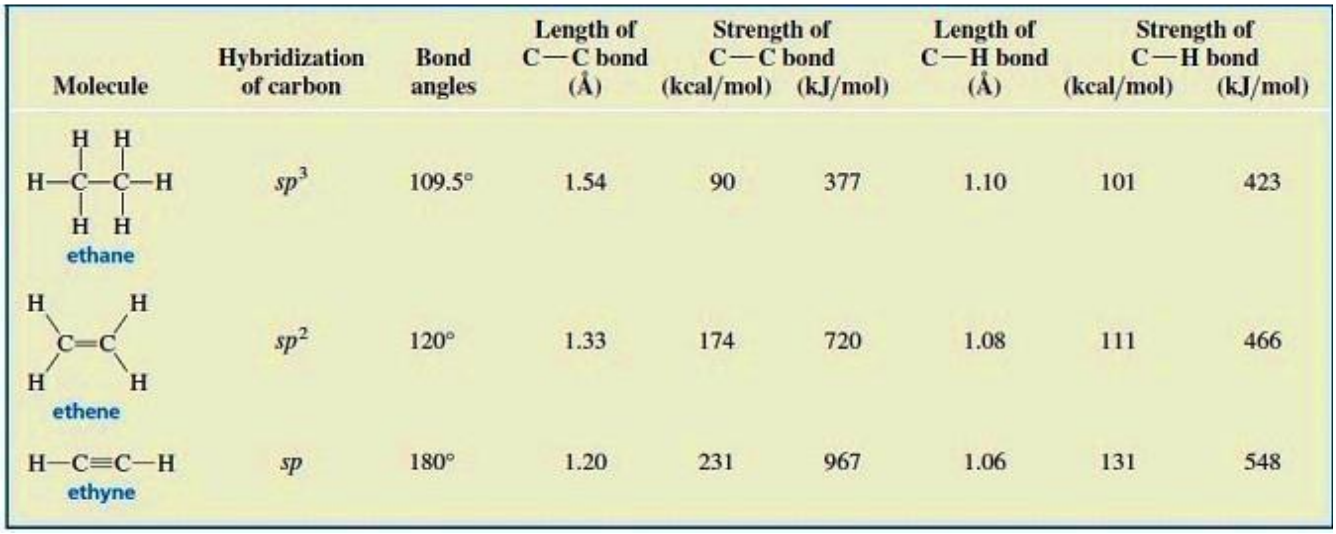
Subject : Pharmaceutical Organic Chemistry I

Subject Code:BP202T

Hybridization:

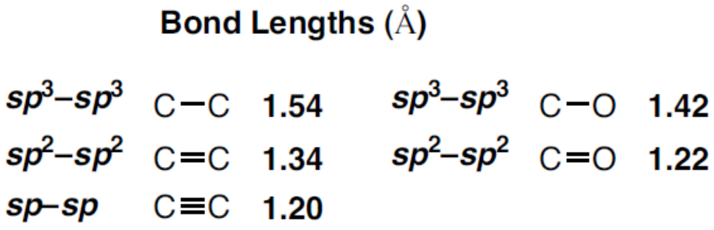
- Hybridization and general principles explain how covalent bonding in organic chemistry is possible.
- Hybridization happens when atomic orbitals mix to form a new atomic orbital. The new orbital can hold the same total number of electrons as the old ones. The properties and energy of the new, hybridized orbital are an 'average' of the original unhybridized orbitals.
- **Types of Hybridization**:

Type of hybrid	***sp3 hybridization***	***sp2 hybridization***	***sp hybridization***
Diagram			
Atomic orbitals used	s, p, p, p	s, p, p	s, p
Orbitals Combined	s-orbital + 3 p-orbitals	s-orbital + 2 p-orbitals	s-orbital + 1 p-orbital
Resulting Orbitals	4 sp^3 orbitals (no p-orbitals)	3 sp^2 orbitals + 1 p-orbital	2 sp orbitals + 2 p-orbitals
Number of hybrid orbitals formed	4	3	2
Number of atoms bonded to the C	4	3	2
Geometry	tetrahedral	flat triangular	Linear
Ideal angle	109.5^0	120^0	180^0
Bonds	single bonds	double bonds	triple bonds



Molecule	Hybridization of carbon	Bond angles	Length of C—C bond (Å)	Strength of C—C bond (kcal/mol)	Strength of C—C bond (kJ/mol)	Length of C—H bond (Å)	Strength of C—H bond (kcal/mol)	Strength of C—H bond (kJ/mol)
ethane	sp^3	109.5°	1.54	90	377	1.10	101	423
ethene	sp^2	120°	1.33	174	720	1.08	111	466
H—C≡C—H ethyne	sp	180°	1.20	231	967	1.06	131	548

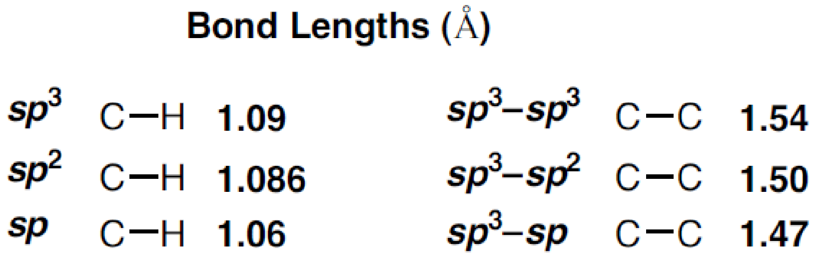
- ***Bond Lengths:*** **mostly dependent on atomic size, bond order, and hybridization**
  - Multiple Bonding: Bond length depends strongly on bond order (length: single > double > triple)



Bond Lengths (Å)

sp^3–sp^3	C–C	1.54	sp^3–sp^3	C–O	1.42
sp^2–sp^2	C=C	1.34	sp^2–sp^2	C=O	1.22
sp–sp	C≡C	1.20			

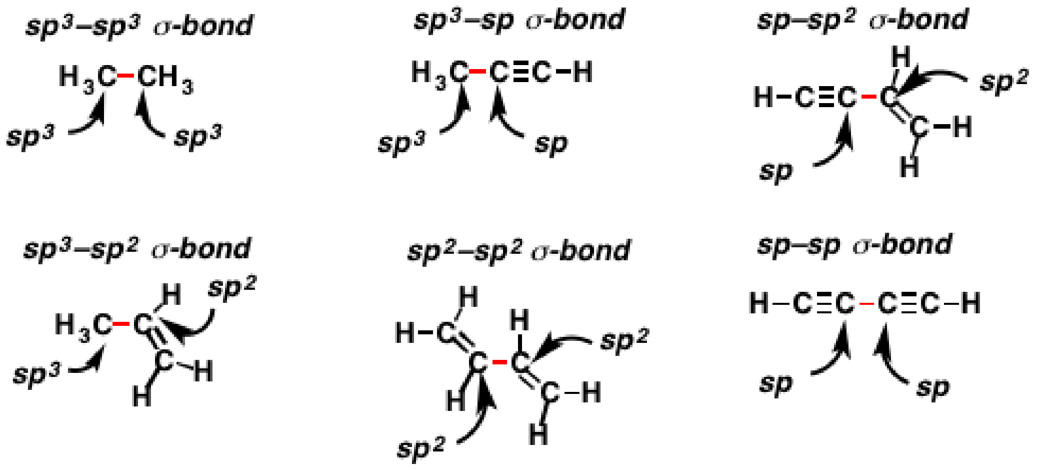
  - Effect of hybridization on length of single bonds: C–H and C–C bonds shorten slightly with increased s character on carbon.



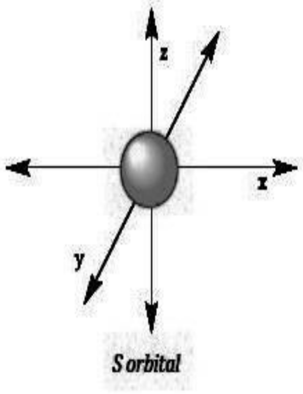
Bond Lengths (Å)

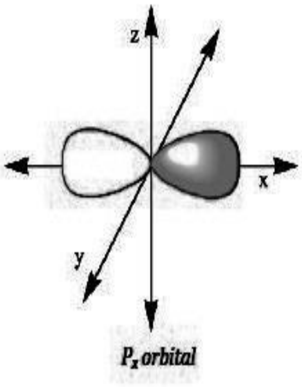
sp^3	C–H	1.09	sp^3–sp^3	C–C	1.54
sp^2	C–H	1.086	sp^3–sp^2	C–C	1.50
sp	C–H	1.06	sp^3–sp	C–C	1.47

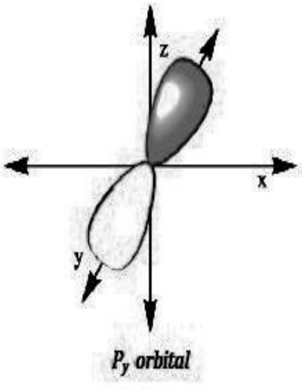
The six types of carbon-carbon σ-bonds

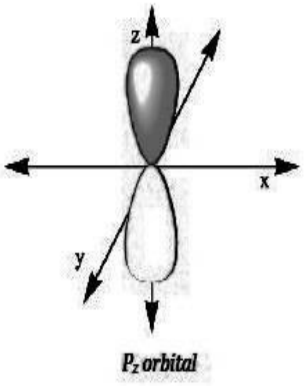


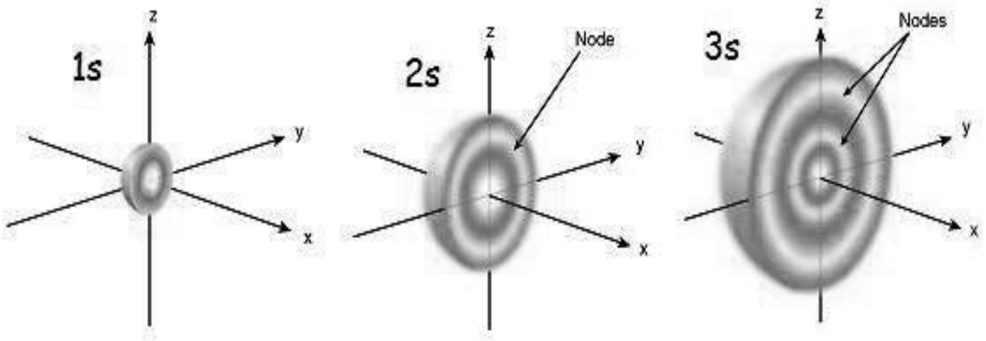
- **Orbital Shapes**



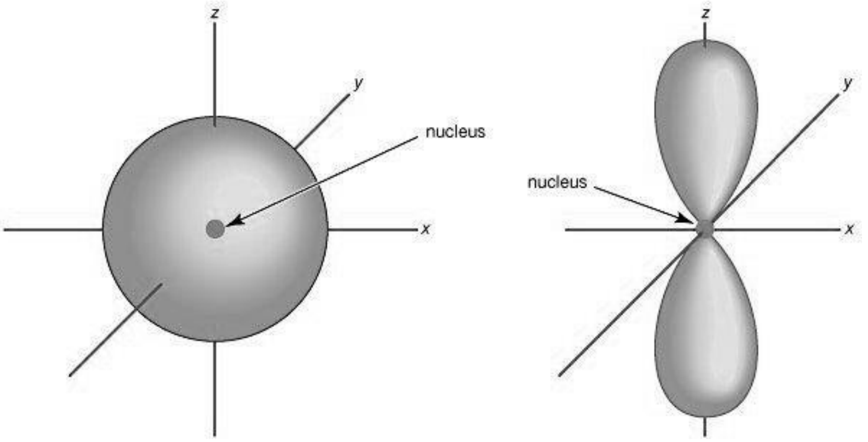








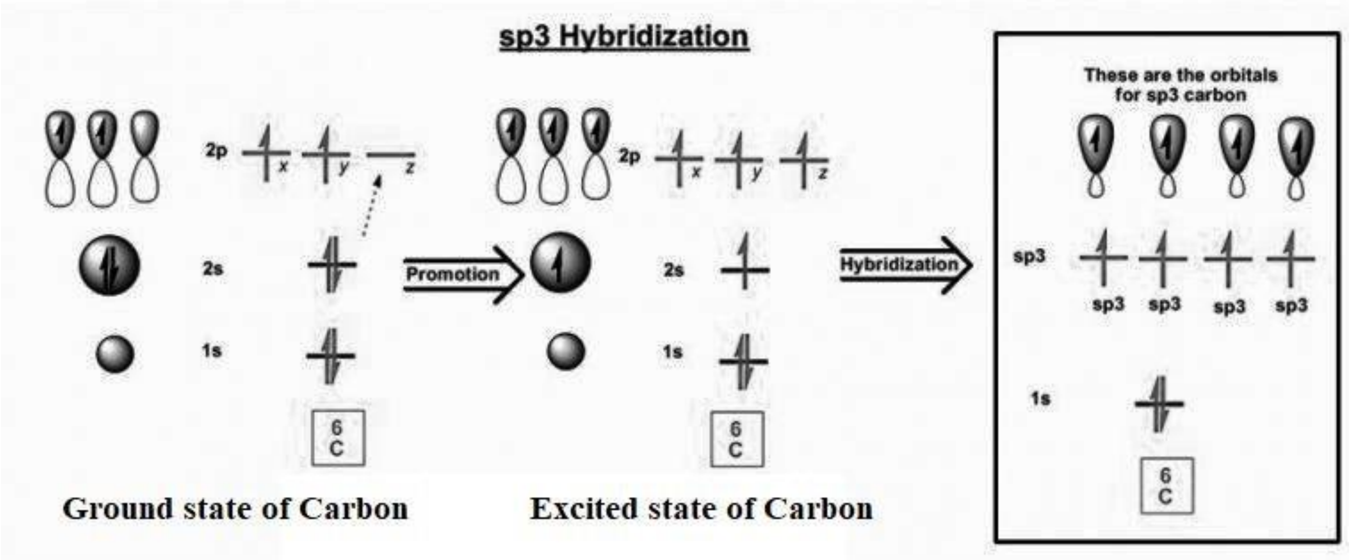
Cross-section of S-orbitals



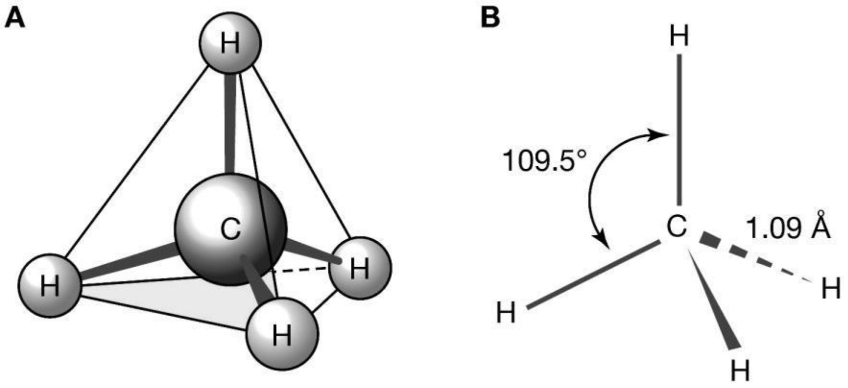
Cross-section of P-orbitals

sp^3 Hybridization

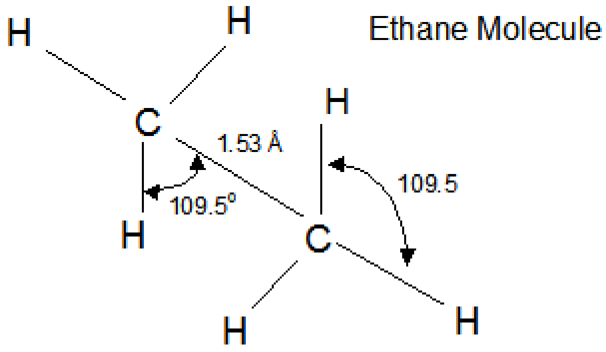
- The process of formation of 4 equivalent orbitals from hybridization or mixing up of one „**S**‟ and three „**P**‟ orbitals is known as sp^3 hybridization. sp³ hybrid orbitals and properties of sigma bonds.
- **Characteristics:**
  - sp^3 has 25% s and 75% p character
  - The 4 sp^3 hybrids point towards the corners of a tetrahedron at 109.5^0 to each other
  - Each sp^3 hybrid is involved in a s bond.



- **Bond Angle and Bond Length of Methane**

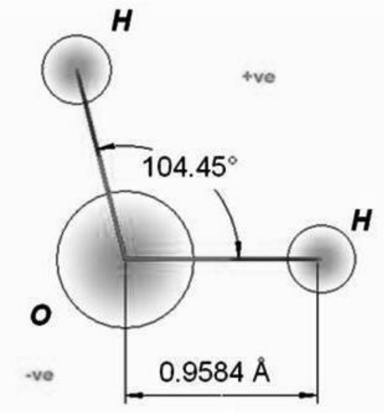


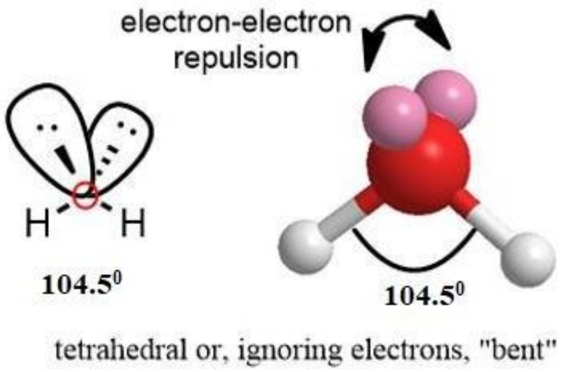
- ***Bond Angle and Bond Length of Ethane***



Why does the bond angle go from 104.5^0 to 109.5^0 when water freezes to form ice?

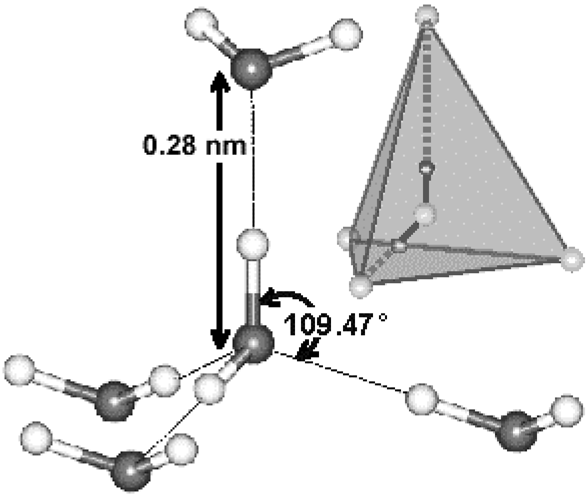
- The reason water has an angle of 104.5^0 is because its two lone pairs are closer to the oxygen than the two bonding pairs. The electron pairs repel each other, which pushes the two bonding pairs closer together. This is what compresses the H-O-H bond angle in water.
- In ice the molecules line up to form a network of hydrogen bonds. This means every lone pair has a hydrogen from a neighbouring molecule very close to it. This pulls the lone pairs away from the oxygen atom which increases the H-O-H bond angle back to 109.5^0





tetrahedral or, ignoring electrons, "bent"

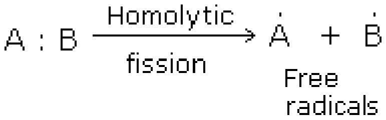
- The oxygen in water is essentially tetrahedral. Since it is only singly-bonded, it must be sp^3 and have angles that approximate 109.5^0. It does but since oxygen has two lone pairs of electrons that are diffuse (larger). These larger orbitals occupy greater volumes than covalent bonds to hydrogen, when only the geometry of bonds is considered, it is called bent. Organic chemists care about all attachments, particularly lone pairs of electrons.



Bond Angle of Ice

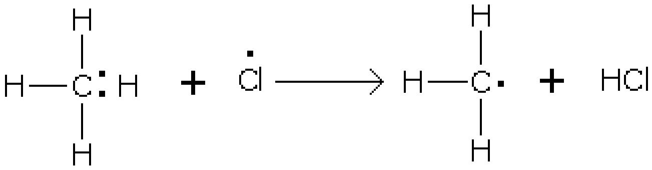
❖ Free Radical

- A free radical may be defined as an atom or group of atoms having an unpaired electron. Free radicals are produced during the homolytic fission of a covalent bond.



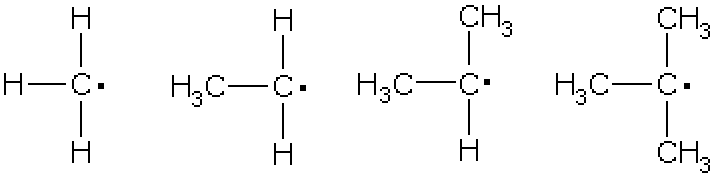
- Free radicals are very reactive as they have strong tendency to pair up their unpaired electron with another electron from wherever available. These pairs are very short lived and occur only as reaction intermediates during reactions.
- For example, dissociation of chlorine gas in the presence of ultra-violet light produces chlorine free radicals:

- The alkyl free radical may be obtained when free radical chlorine attacks methane.



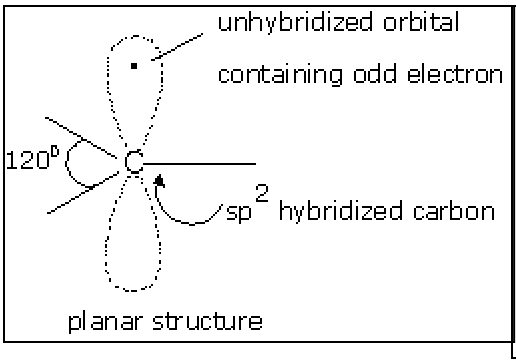
Methyl free radical

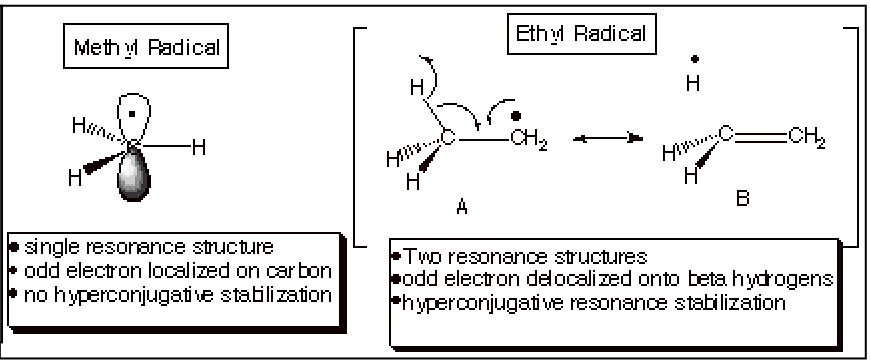
- Free radicals may be classified as primary, secondary or tertiary depending upon whether one, two or three carbon atoms are attached to the carbon atom carrying the odd electron:



Methyl Primary (1°) Secondary (2°) Tertiary (3°)

- ***Structure of alkyl free radical:*** The carbon atom in alkyl free radicals involves **sp^2 hybridization**. Therefore, it has a **planar structure**. Three hybrid orbitals are used in the formation of three **s-bonds** with three **H atoms** or **alkyl group**. The unpaired electron is present in unhybridized **p orbital**.



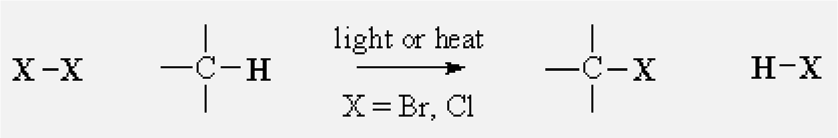


- single resonance structure
- odd electron localized on carbon
- no hyperconjugative stabilization

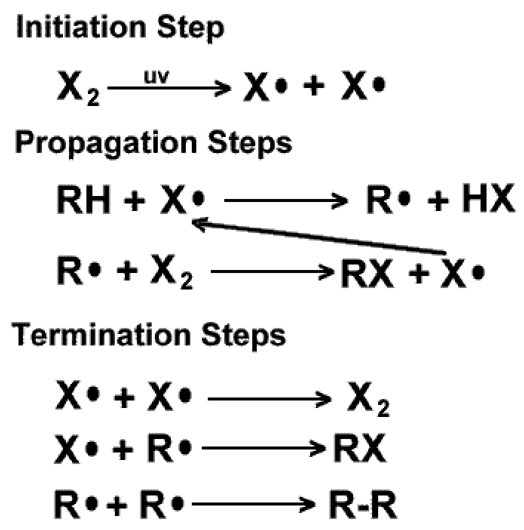
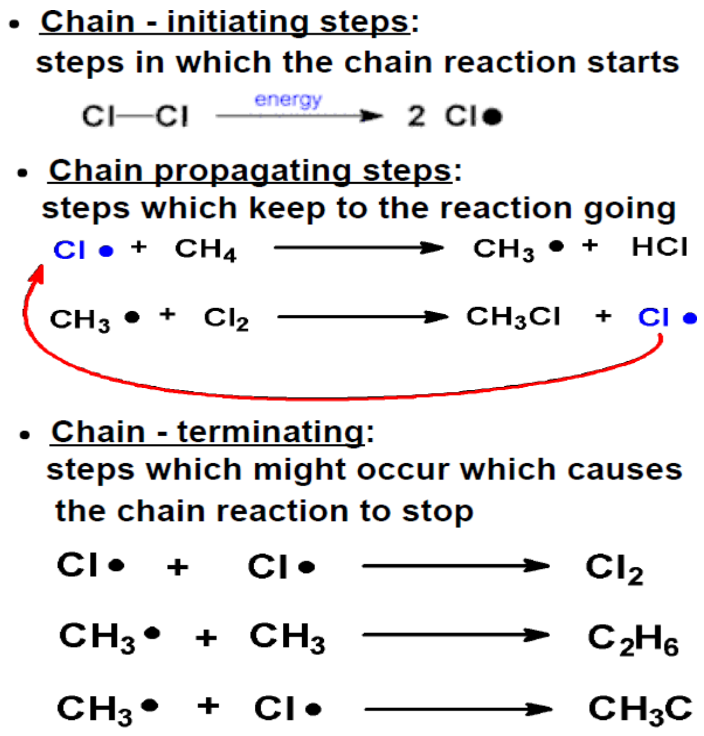
- Two resonance structures
- odd electron delocalized onto beta hydrogens
- hyperconjugative resonance stabilization

❖ Halogenation of Alkanes (Free Radical Substitution Reaction)

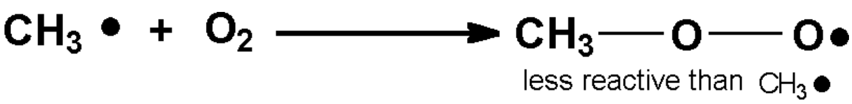
- The reaction of a halogen with an alkane in the presence of ultraviolet (UV) light or heat leads to the formation of a haloalkane (alkyl halide). An example is the chlorination of methane.
- Radical Halogenation of Alkanes (Reaction type: Free Radical Substitution)



- Summary:
    - When treated with Br_2 or Cl_2, radical substitution of R-H generates the alkyl halide and HX.
    - Alkane R-H relative reactivity order: tertiary > secondary > primary > methyl.
    - Halogen reactivity $F_2 > Cl_2 > Br_2 > I_2$
    - Only chlorination and bromination are useful in the laboratory.
    - Bromination is selective for the R-H that gives the most stable radical.
    - Chlorination is less selective

- ***Mechanism Of Halogenation***	*Radical chain mechanism for reaction of methane with Cl_2*
 **Initiation Step** $X_2 \xrightarrow{uv} X\bullet + X\bullet$ **Propagation Steps** $RH + X\bullet \longrightarrow R\bullet + HX$ $R\bullet + X_2 \longrightarrow RX + X\bullet$ **Termination Steps** $X\bullet + X\bullet \longrightarrow X_2$ $X\bullet + R\bullet \longrightarrow RX$ $R\bullet + R\bullet \longrightarrow R\text{-}R$	 • **Chain - initiating steps**: steps in which the chain reaction starts $Cl{-}Cl \xrightarrow{energy} 2\ Cl\bullet$ • **Chain propagating steps**: steps which keep to the reaction going $Cl\bullet + CH_4 \longrightarrow CH_3\bullet + HCl$ $CH_3\bullet + Cl_2 \longrightarrow CH_3Cl + Cl\bullet$ • **Chain - terminating**: steps which might occur which causes the chain reaction to stop $Cl\bullet + Cl\bullet \longrightarrow Cl_2$ $CH_3\bullet + CH_3 \longrightarrow C_2H_6$ $CH_3\bullet + Cl\bullet \longrightarrow CH_3C$

- **INHIBITORS**
    - Inhibitor - a substance which slows down or stops a reaction even though the inhibitor is present in small amounts.
    - Inhibition period - time during which the inhibitor lasts.
    - Example: If oxygen is present during halogenation, the oxygen slows down the reaction.



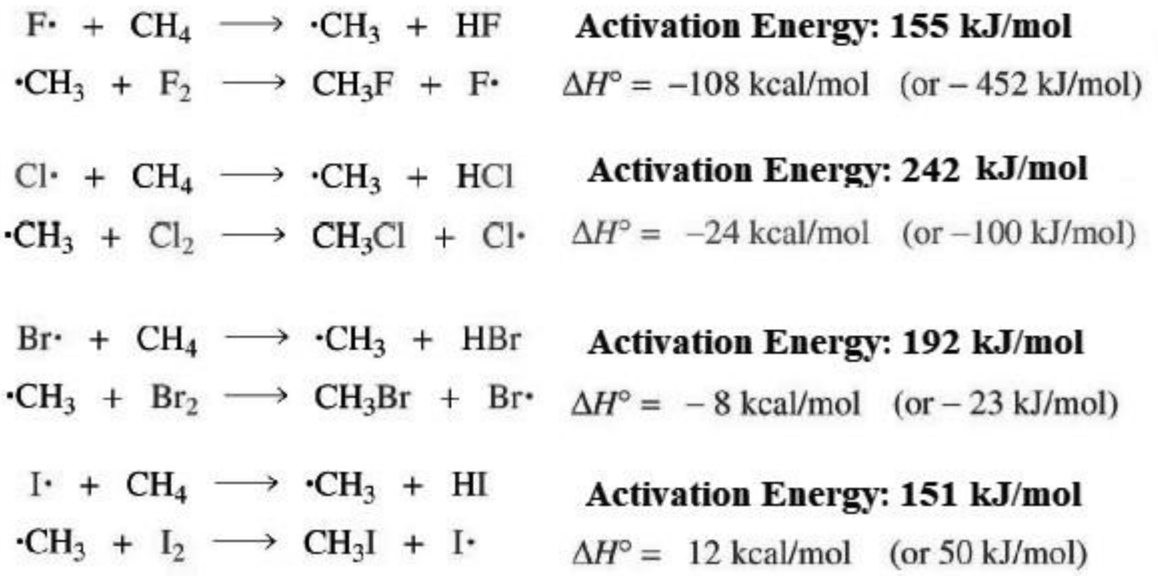
$$CH_3\bullet + O_2 \longrightarrow CH_3{-}O{-}O\bullet$$

less reactive than $CH_3\bullet$

- This breaks the cycle (propagating steps) and slows down the reaction.
- When the oxygen molecules are all reacted (inhibition period), the reaction then speeds up.

- ***Why is the direct fluorination and iodination of alkanes via a free radical mechanism not possible?***

- **Fluorination**
  - Fluorination (155 kJ/mol) seems to have relatively high activation energy. The initial reaction (chain initiation) - that is, the homolytic cleavage of a halogen molecule - must, however, occur only a few times. The subsequent reactions (chain propagation) between a halogen radical and methane, and then between a methyl radical and a halogen molecule, yield another halogen radical. Therefore, one start reaction may initiate thousands of fluorination reactions. In addition, fluorination is very exothermic; the reaction enthalpy is -431 kJ/mol. As a result, the reaction itself provides enough energy for additional initiation reactions.
  - As a result, an explosion occurs.
  - Nevertheless, methane fluorination may be carried out in a controlled reaction, so as to prohibit an explosion. Diluting the starting products with an inert gas or absorbing the reaction heat with copper granulate can help in this case.
- **Chlorination**
  - As a result of higher activation energy in chain initiation as well as a less exothermic character (ΔH° = -115 kJ/mol) of the chain propagation, the reaction rate of methane chlorination is comparatively lower than that of the fluorination. Therefore, the reaction of methane chlorination is easier to control.
- **Bromination**
  - In the chain initiation of methane bromination, the activation energy is lower than that in chlorination. However, the chain propagation is far less exothermic, and the first reaction of the chain propagation is even much more endothermic (+75 kJ/mol) than in the case of chlorination (+8 kJ/mol). Therefore, the chain propagation proceeds extremely slowly, even at 300 °C, and bromine is by far less reactive than chlorine against methane.
- **Iodination**
  - In the chain initiation of methane iodination, the activation energy is even lower than it is in fluorination. Therefore, one could assume that methane iodination runs more rapidly than fluorination. However, this is not the case! The complete chain propagation (+54 kJ/mol), and, in particular, the first reaction (+142 kJ/mol), is very endothermic. As a result, the radical iodination of methane does not take place.



$F\cdot + CH_4 \longrightarrow \cdot CH_3 + HF$ **Activation Energy: 155 kJ/mol**

$\cdot CH_3 + F_2 \longrightarrow CH_3F + F\cdot$ $\Delta H^\circ = -108$ kcal/mol (or – 452 kJ/mol)

$Cl\cdot + CH_4 \longrightarrow \cdot CH_3 + HCl$ **Activation Energy: 242 kJ/mol**

$\cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$ $\Delta H^\circ = -24$ kcal/mol (or –100 kJ/mol)

$Br\cdot + CH_4 \longrightarrow \cdot CH_3 + HBr$ **Activation Energy: 192 kJ/mol**

$\cdot CH_3 + Br_2 \longrightarrow CH_3Br + Br\cdot$ $\Delta H^\circ = -8$ kcal/mol (or – 23 kJ/mol)

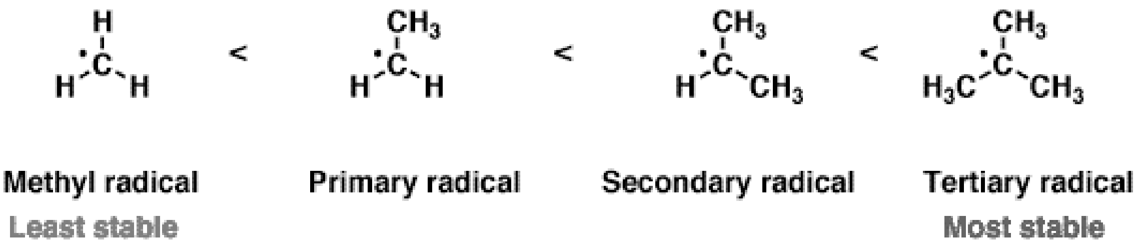
$I\cdot + CH_4 \longrightarrow \cdot CH_3 + HI$ **Activation Energy: 151 kJ/mol**

$\cdot CH_3 + I_2 \longrightarrow CH_3I + I\cdot$ $\Delta H^\circ = 12$ kcal/mol (or 50 kJ/mol)

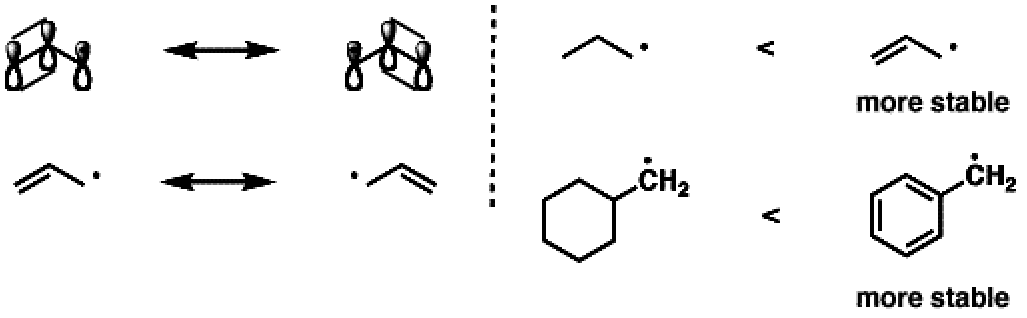
Factors That Affect Free Radical Stability

1. Free radicals are electron-deficient species. [Helpful to know: the factors which affect the stability of free radicals are the same which influence the stability of carbocations.] They can be stabilized through donation of electron density by neighbours; for this reason, radical stability increases in the order methyl < primary < secondary < tertiary. [Radicals are also stabilized by adjacent atoms with lone pairs, such as oxygen and nitrogen].

Radical stability increases in the order methyl < primary < secondary < tertiary

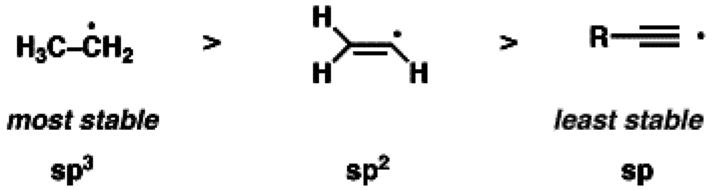


2. A second important factor which stabilizes free radicals is "delocalization" – that is, if the radical can be spread out over two or more carbons. A more familiar way of saying this is that free radicals are stabilized by resonance.



3. Free radicals decrease in stability as the **%** of ***s-character*** in the orbital increases [i.e. as the half-empty orbital becomes closer to the nucleus].

   For that reason, free radical stability decreases as the atom goes from **$sp^3 > sp^2 > sp$**.

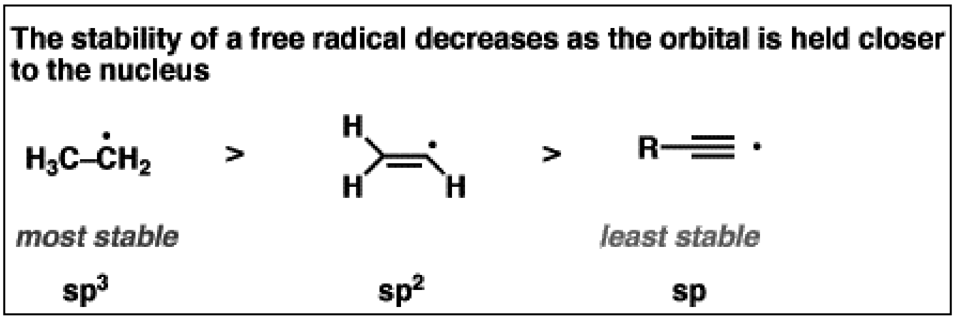


Across a row of the periodic table, free radicals decrease in stability as the electronegativity increases

Free radicals increase in stability going down a column of the periodic table, **F• < Cl• < Br• < I•** since the electron-deficient orbital is spread out over a greater volume.

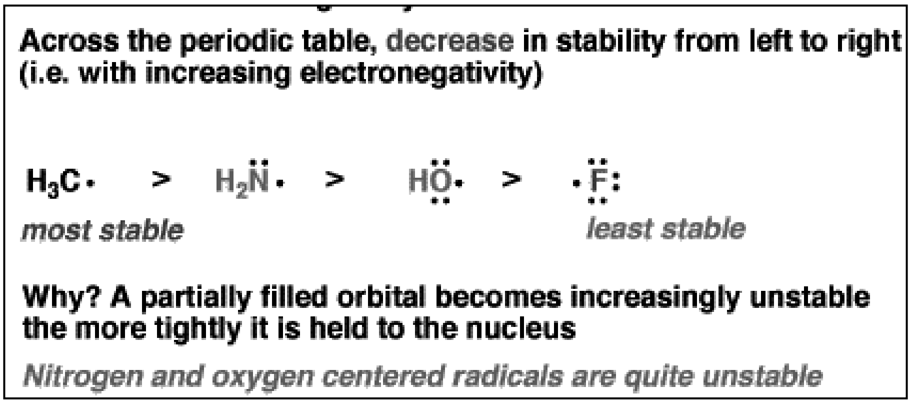
• Factors Destabilize Free Radicals:

- **Factor 1: Hybridization**



The stability of a free radical decreases as the orbital is held closer to the nucleus

- **Factor 2: Electronegativity**

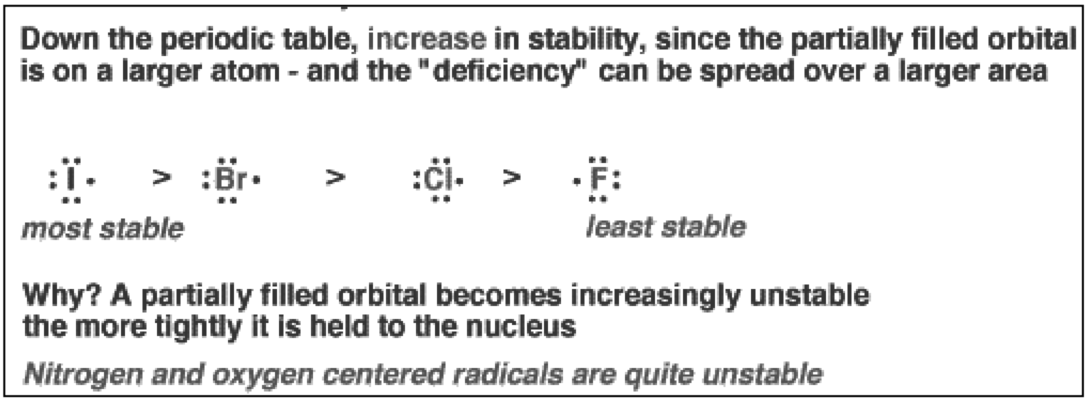


Across the periodic table, decrease in stability from left to right (i.e. with increasing electronegativity)

Why? A partially filled orbital becomes increasingly unstable the more tightly it is held to the nucleus

Nitrogen and oxygen centered radicals are quite unstable

- **Factor 3: Polarizability**

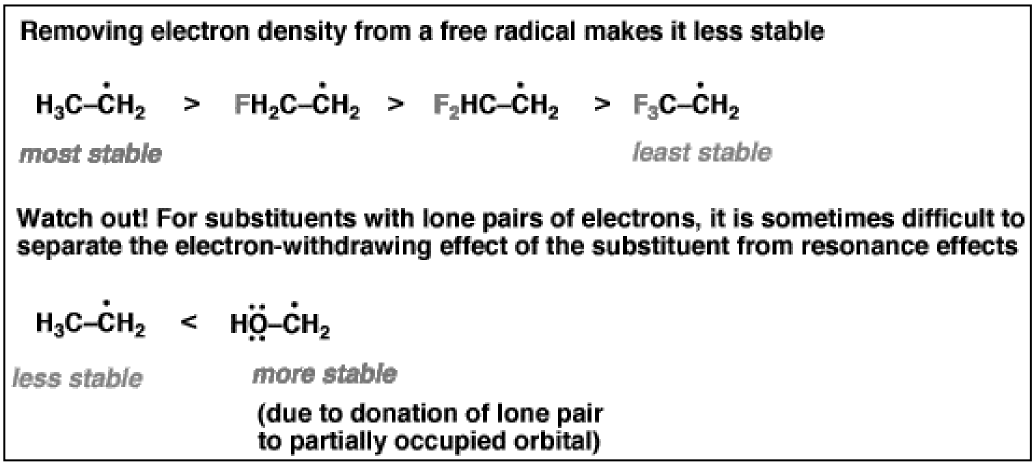


Down the periodic table, increase in stability, since the partially filled orbital is on a larger atom - and the "deficiency" can be spread over a larger area

Why? A partially filled orbital becomes increasingly unstable the more tightly it is held to the nucleus

Nitrogen and oxygen centered radicals are quite unstable

- **Factor 4: Electron withdrawing groups**



Removing electron density from a free radical makes it less stable

$$H_3C{-}\dot{C}H_2 > FH_2C{-}\dot{C}H_2 > F_2HC{-}\dot{C}H_2 > F_3C{-}\dot{C}H_2$$

Watch out! For substituents with lone pairs of electrons, it is sometimes difficult to separate the electron-withdrawing effect of the substituent from resonance effects

$$H_3C{-}\dot{C}H_2 < H\ddot{\underset{\cdot\cdot}{O}}{-}\dot{C}H_2$$

(due to donation of lone pair to partially occupied orbital)

References:

- Organic Chemistry by Morrison and Boyd
- Organic Chemistry by I.L. Finar , Volume-I
- Textbook of Organic Chemistry by B.S. Bahl & Arun Bahl.
- Organic Chemistry by P.L.Soni
- Practical Organic Chemistry by Mann and Saunders.
- Vogel’s text book of Practical Organic Chemistry
- Advanced Practical organic chemistry by N.K.Vishnoi.
- Introduction to Organic Laboratory techniques by Pavia, Lampman and Kriz.
- Reaction and reaction mechanism by Ahluwaliah/Chatwal.