

Fundamentals of Chemistry, Module III: Organic Chemistry

Semester-1, CCF-2022 (NEP)

Course: CHEM-H-CC-2-2-TH

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata

email: chiralkaushik@gmail.com

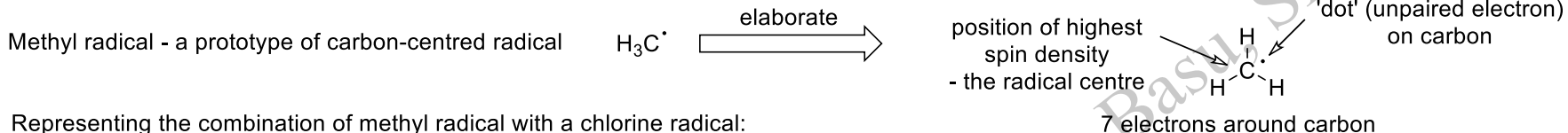
Recommended texts:

1. Study Guide to Organic Chemistry, Volume 1, Second Ed., by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 978-8192669564,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 978-0198728719

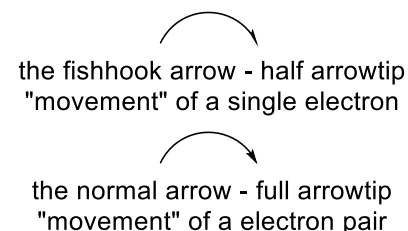
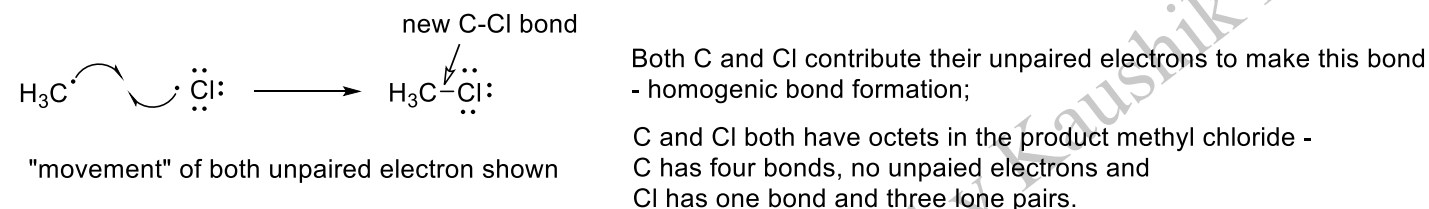
Radicals (free radical) A molecular entity such as $\cdot\text{CH}_3$, $\cdot\text{SnH}_3$, $\text{Cl}\cdot$ possessing an unpaired electron. (In these formulae the dot, symbolizing the unpaired electron, should be placed so as to indicate the atom of *highest spin density*, if this is possible.)

Spin density is defined as the unpaired electron density at a position of interest, usually at carbon, in a radical. It is often measured experimentally by electron paramagnetic resonance [EPR, ESR (electron spin resonance)] spectroscopy.

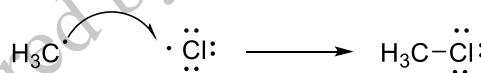
Radical centre: The atom (or group of atoms) in a polyatomic radical on which an unpaired electron is largely localized. Attachment of a monovalent atom to a radical centre gives a molecule for which it is possible to write a Lewis formula (electron dot or Lewis structure) in which the normal stable valencies are assigned to all atoms.



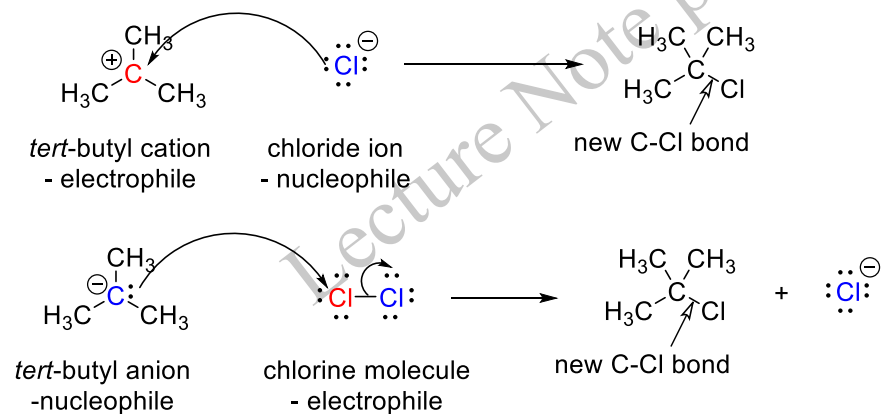
Representing the combination of methyl radical with a chlorine radical:



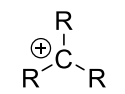
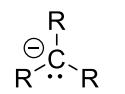
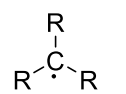
Alternative description: Showing the "movement" of only lone unpaired electron is sufficient, the other unpaired electron's "movement" is implied:



Contrast the homogenic bond formation between radicals with the heterogenic bond formation between electrophiles and nucleophiles:

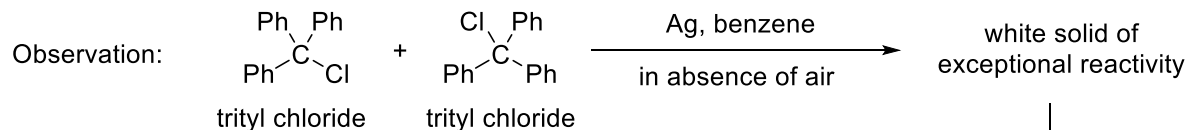
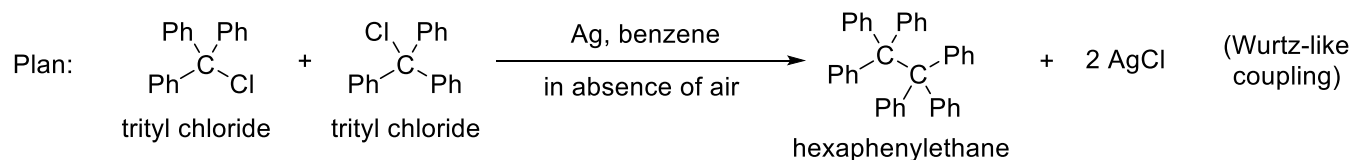


As we can see, carbon-centred radicals are halfway between carbocations and carbanions:

			
No. of electrons around carbon:	6	8	7
Nature:	electrophilic	nucleophilic	nucleophilic / electrophilic (depends on R)

Reactive Intermediates in Organic Chemistry:

History of free radicals in organic chemistry: Moses Gomberg's attempt (1900) to prepare hexaphenylethane -

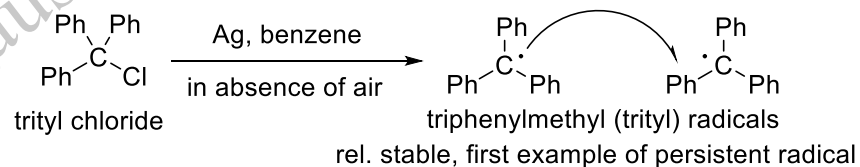


Oxidized rapidly in the air and reacted readily with halogens, including iodine.



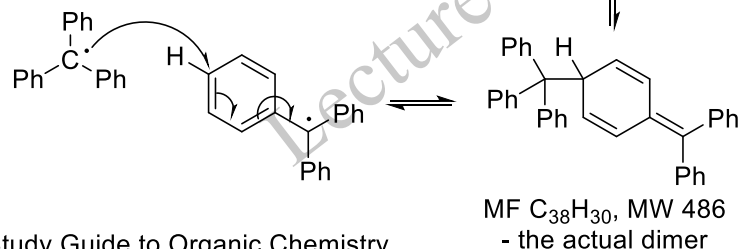
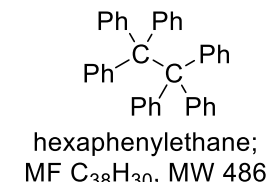
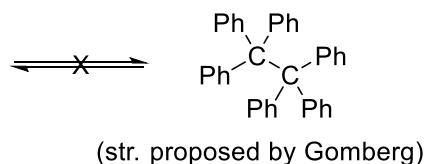
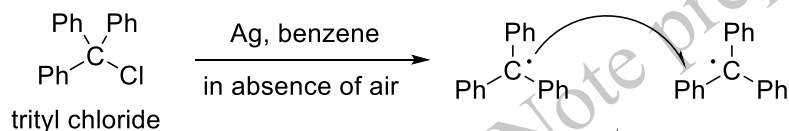
Moses Gomberg (1866-1947)

The high reactivity was unexpected of hexaphenylethane, Gomberg concluded that "The experimental evidence...forces me to the conclusion that we have to deal here with a free radical, triphenylmethyl.". Gomberg also postulated that the trityl radicals exist in equilibrium with the dimer hexaphenylethane.

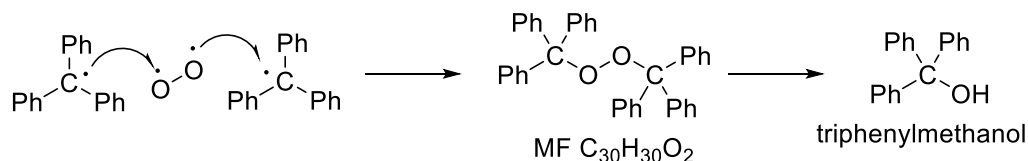


Gomberg's proposal of *trivalent carbon* was greeted with skepticism from the contemporary chemists.

Reality (not discovered until many years later): revised structure of the dimer of trityl radical -



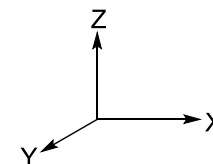
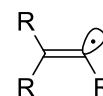
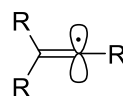
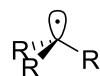
Upon exposure to air, the trityl radical was found to form a peroxide of MF C₃₀H₃₀O₂ which could be reduced to the known alcohol triphenylmethanol.



Reactive Intermediates in Organic Chemistry:

Structure and classification of radicals:

Free radicals are species with an odd, unpaired electron in a non-bonding orbital - many possibilities exist :



The radical centre's hybridization:

 sp^3
 sp^2
 sp
 sp^2
 sp

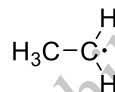
The orbital carrying the unpaired electron:

 sp^3
 p
 p
 sp^2
 sp

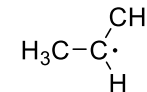
A] Classification depending upon the number of carbons attached to the carbon radical centre:



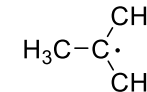
Methyl radical
No C attached to radical centre



1° radical
One C attached to radical centre
(ethyl radical, primary)



2° radical
Two Cs attached to radical centre
(isopropyl radical, secondary)



3° radical
Three Cs attached to radical centre
(*tert*-butyl radical, tertiary)

No. of carbons attached to radical centre:

0

1

2

3

No. of hydrogens attached to radical centre:

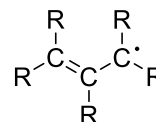
3

2

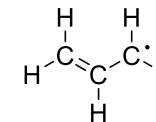
1

0

B] If the carbon carrying the unpaired electron is immediately adjacent to a carbon-carbon double bond, the radical is called an allylic radical. The simplest case (when all R = H) is known as the allyl radical:

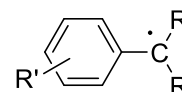


allylic radical
This is also a tertiary radical.

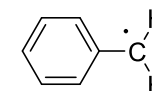


allyl radical
This is also a primary radical.

C] If the radical centre is immediately adjacent to a benzene ring, the radical is termed as benzylic radical. The simplest case is the benzyl carbocation. (R = R' = H)



benzylic radical
This is also a tertiary radical.

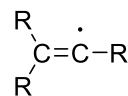


benzyl radical
This is also a primary radical.

Reactive Intermediates in Organic Chemistry:

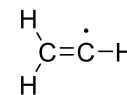
Structure and classification of radicals:

D] If the carbon bearing the unpaired electron is part of an alkene, the radical is a vinylic / alkenyl radical. The simplest case is the vinyl radical, R = H.



vinylic radical, linear

This is also a secondary radical.



vinyl radical

This is also a primary radical.

Note that in this case the carbon radical centre has only two groups attached to it and is linear in shape.

This indicates an sp hybridization.

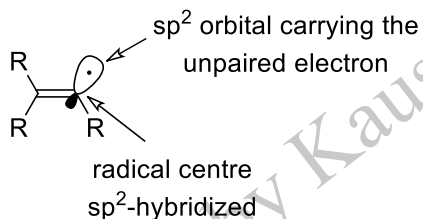
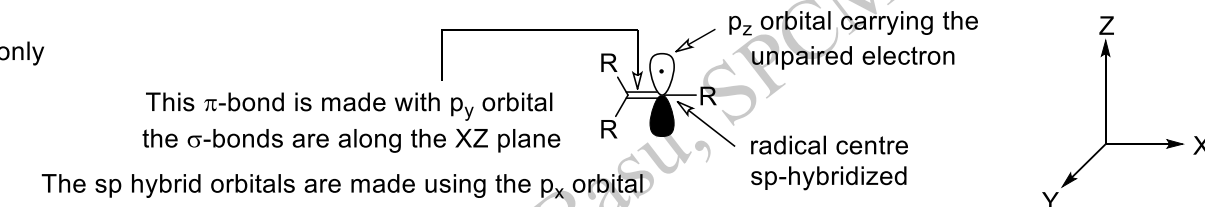
The unpaired electron is in a vacant p orbital.

The alkenyl radical can also be bent in shape:

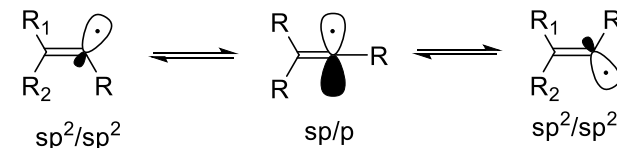
Note that in this case the carbon radical centre has only two groups attached to it and is bent in shape.

This indicates an sp^2 hybridization.

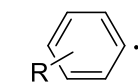
The unpaired electron is in a vacant sp^2 orbital.



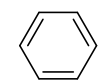
Alkenyl radicals are mostly bent with but they readily invert through the linear structure. This is similar to the inversion of carbanions and tralkylamines.



E] If the carbon bearing the unpaired is part of a benzene ring, the radical is termed as an aryl radical. The simplest case is called the phenyl radical, R = H.



aryl radical

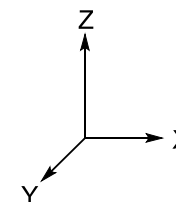
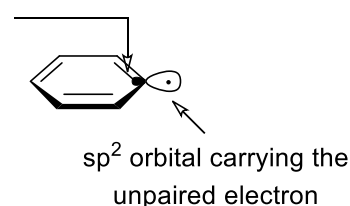
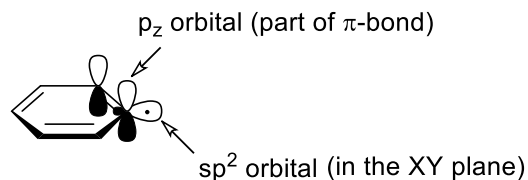


phenyl radical

} both secondary carbocations

The radical centre is sp^2 -hybridised and one of the sp^2 hybrid orbitals is vacant. The p_z orbital is used to form the π -bond with the adjacent ring carbon.

π -bond formed b/w p_z orbitals



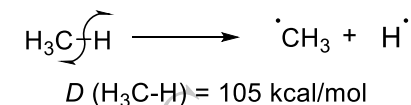
These two orbitals are orthogonal, so they do not overlap with each other.

Reactive Intermediates in Organic Chemistry:

Structure and stability of radicals of radicals:

Bond Dissociation Energy (BDE, expressed as D) can be an approximate guide to stability of radicals. Homolysis of chemical bonds generate radicals.

It is expected that greater the stability of the radicals formed, lower is the BDE required to cleave that bond. Therefore, BDE may often serve as a good guide while comparing relative stabilities of the radicals.



Compound	C-centred radical produced	BDE (kcal. mol ⁻¹)
CH ₃ -H	CH ₃ •	105.0
CH ₃ CH ₂ -H	CH ₃ CH ₂ •	100.5
(CH ₃) ₂ CH-H	(CH ₃) ₂ CH•	98.1
(CH ₃) ₃ C-H	(CH ₃) ₃ C•	95.7
CH ₂ =CH-H	CH ₂ =CH•	111.2
CH≡C-H	CH≡C•	132.8

Compound	C-centred radical produced	BDE (kcal. mol ⁻¹)
PhCH ₂ -H	PhCH ₂ •	88.5
CH ₂ =CH-CH ₂ -H	CH ₂ =CH-CH ₂ •	88.2
HOCH ₂ -H	HOCH ₂ •	96
CH ₃ CH ₂ OCH ₂ -H	CH ₃ CH ₂ OCH ₂ •	95
CH ₃ C(O)CH ₂ -H	CH ₃ C(O)CH ₂ •	94
NCCH ₂ -H	NCCH ₂ •	95

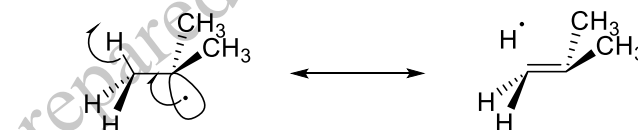
Several trends are noticeable from the given table:

i) Among alkyl radical the BDE decreases $\xrightarrow{\text{methyl, primary alkyl, secondary alkyl, tertiary alkyl}}$
in the following order: $\xrightarrow{\text{BDE decreases}}$

Thus, the stability orders of the radicals are as follows

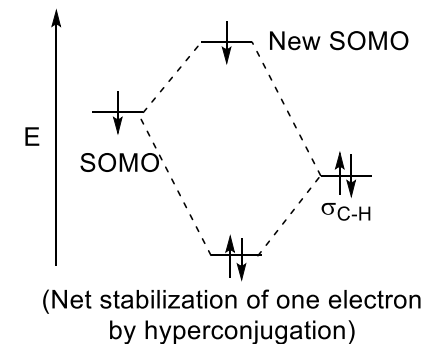
$\xrightarrow{\text{methyl radical, primary alkyl radical, secondary alkyl radical, tertiary alkyl radical}}$
stability of the radical increases

With increasing number of alkyl substitution stability increases. This trend is similar to the order of stability among the carbocations. The reason for this increasing stability is the greater hyperconjugation resulting from the increasing number of alkyl substituents.

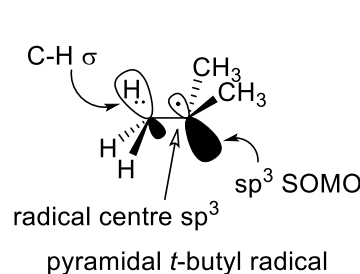


hyperconjugation in *tert*-butyl radical - 9 such Hs

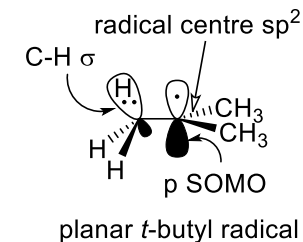
SOMO: Singly-Occupied MO - the orbital holding the unpaired electron



The shape of the alkyl radical is interesting. The methyl radical is planar (sp^2 -hybridized) while with increasing alkyl substitution, the radical becomes pyramidal (radical centre is sp^3 -hybridized). This pyramidalization improves hyperconjugation as overlap between C-H σ orbital and the sp^3 SOMO is better.



is better than

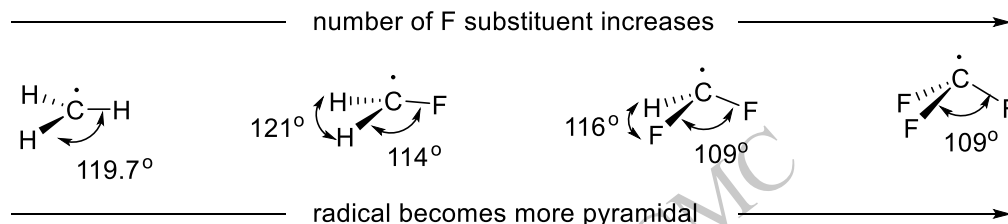


Reactive Intermediates in Organic Chemistry:

Structure and stability of radicals of radicals:

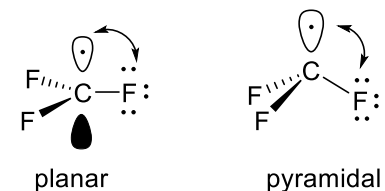
Common alkyl free radicals are near-planar to shallow pyramidal in nature as then these are stabilised through hyperconjugation.

Addition of fluorine and oxygen substituents, in particular, favours more towards the pyramidal structure.

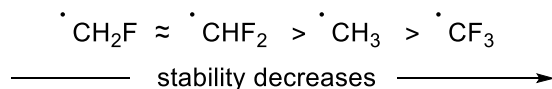


* According to Bent's rule, the more electronegative element has a tendency to use hybrid orbital which has greater p-character. Fluorine being a highly electronegative element tends to prefer sp^3 hybrid orbital which has 75% p-character.

* In planar model there is a repulsive interaction between the singly occupied p-orbital and filled orbitals occupied by the "lone pair" of electrons on the fluorine substituents. This repulsive interaction is lowered in the pyramidal geometry.

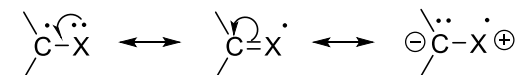


The stability order of these radicals is curious; introduction of F atoms onto the radical centre first stabilizes the radical, but, when three Hs are replaced by three F atoms, the trifluoromethyl radical is even less stable than methyl radical

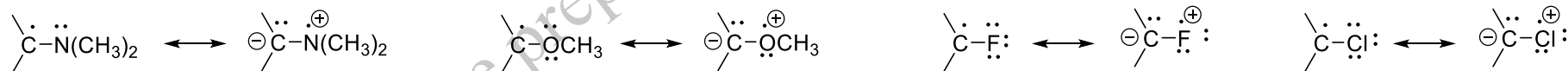


single electron-lone pair repulsion is higher in the planar form

Stabilization of radical centre by F (or any heteroatom with lone pair of e directly attached to radical centre):



The substituent X is a heteroatom with lone pair of electrons and is called a π -donor; examples:



The BDE values of H- CH_2OH and H- $\text{CH}_2\text{OCH}_2\text{CH}_3$ is less than that of H- CH_3 - the stabilizing influence of the π -donor substituents OH and OEt are evident,

Due to better size matching between the orbitals of second row elements, NMe_2 , OMe, F are better stabiliser than Cl here, the latter being a third row element and has size mismatch with orbitals of carbon radical centre.

If introduction of F into the radical centre stabilizes the radical, why is trifluoromethyl radical ($\cdot\text{CF}_3$) less stable than methyl radical ($\cdot\text{CH}_3$)?

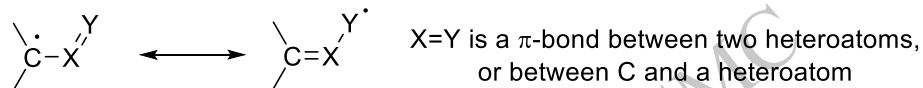
A detailed answer is beyond our scope. A simplistic analysis suggests that the destabilization may be a result of dipolar repulsion between the highly polar C-F bonds. As the number of such bonds increases, the dipolar repulsion between them increases, and becomes so much in trifluoromethyl system that even the stabilizing effect of the three F atoms on radical centre is overridden.

Reactive Intermediates in Organic Chemistry:

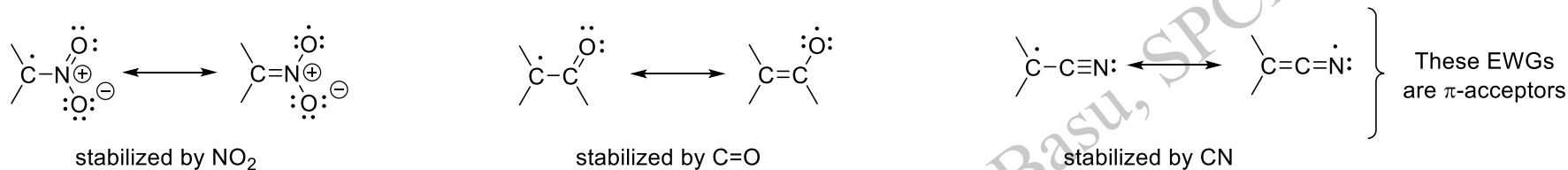
Structure and stability of radicals of radicals:

Radical centres are stabilized by attached ERGs such as σ -donor alkyls or π -donor heteroatoms (O, N, X etc)

Attachment of EWGs also stabilizes radicals in the following way:

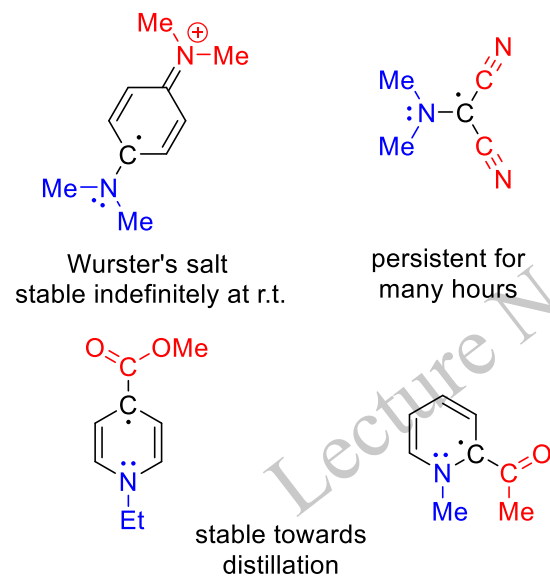


Examples:

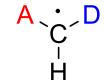
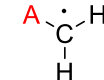


Therefore, radicals are like both carbocations and carboanions. Like carbocations, they are stabilized by ERGs, like carbanions they are stabilized by EWGs. Not entirely unexpected as they are halfway between carbocations and carbanions in terms of number of electrons around carbon.

There is one special type of radical where the radical centre is attached to both a donor (ER) and an acceptor (EW) group. These are known as *captodative radicals* (*capto* from captor signifying the acceptor and *dative* stands for the donor) and they are found to be exceptionally stable.

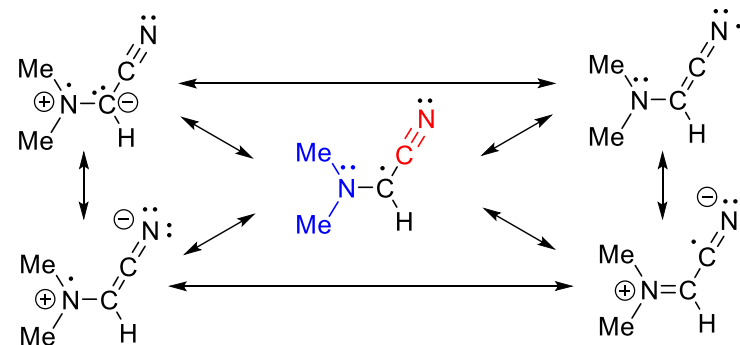


This unusual stability is thought to be due to extended delocalisation where the electron "push" of the donor is assisted by the electron "pull" of the acceptor, i.e.

A is more effective in the  captodative radical than in the  monosubstituted radical.

where A is the acceptor and D is the donor. In this connection, recall the unusually high dipole moment of 4-nitroaniline.

Illustration of the resonance stabilization in the captodative (2-dimethylamino)propanenitrile radical

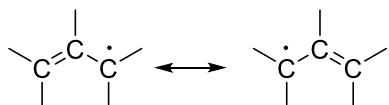


Reactive Intermediates in Organic Chemistry:

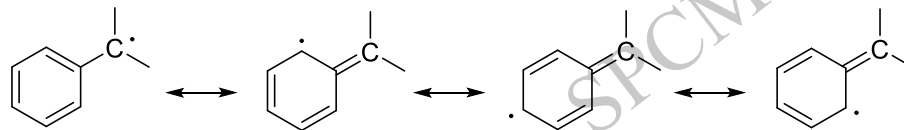
Structure and stability of radicals of radicals:

BDEs for sp^3 -hybridized carbon-hydrogen bonds of propene and toluene are exceptionally low indicating that allyl and benzyl radicals are highly stabilized. This stabilization is the outcome of resonance:

Allylic free radical:

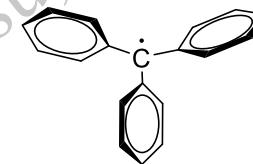


Benzylic free radical:



Gomberg's triphenylmethyl radical (trityl) is expected to be planar on the same grounds but the shape is actually non-planar with a propeller-shape. The angle between phenyl rings is about 35° .

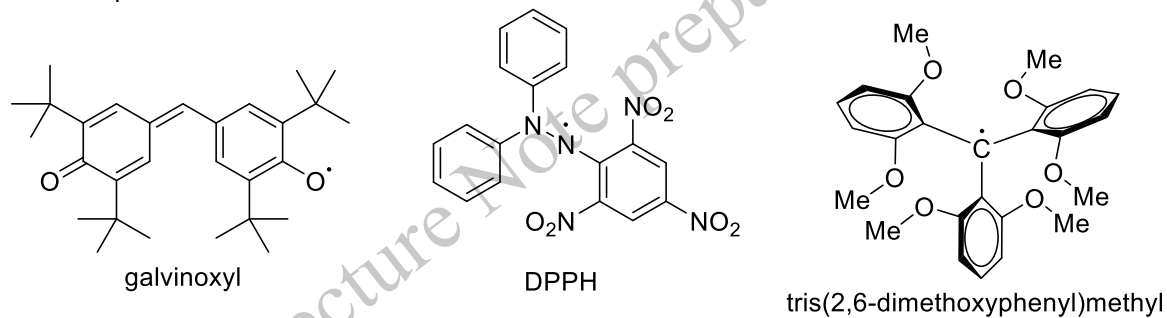
A case of a compromise between a planar conformation with a maximum delocalization of the electrons and a repulsion of the hydrogen atoms localised in the ortho positions of the phenyl groups.



Persistent radicals:

These are long-lived radicals. They may not necessarily be thermodynamically stable but due to some factors, mainly steric, they are unwilling to react with any partner and survive long enough to be observed and isolated.

Gomberg's triphenylmethyl radical which persists indefinitely in benzene solution in strict absence of air was the first persistent radical discovered



Stabilized by - substituent effect and and steric shielding

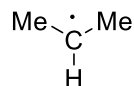
A few more examples are given in the table, their half-life compared to that of methyl radical which is very reactive:

Radical	$t_{1/2}$ at 25°C , 10^{-5} M
$\cdot\text{CH}_3$	20 μs
$(t\text{-Bu})_2\dot{\text{C}}\text{H}$	1 min.
$(t\text{-Bu})_3\dot{\text{C}}$	8.4 min.
	> 110 days
	6 ms

Reactive Intermediates in Organic Chemistry:

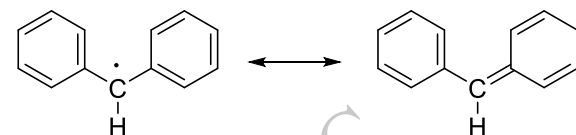
Relative stability of radicals - a few case studies:

I) $\text{Ph}_2\dot{\text{C}}\text{H}$ is less stable than $\text{Me}_2\dot{\text{C}}\text{H}$



isopropyl radical

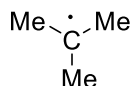
Secondary, 6 hyperconjugative Hs, but no resonance stabilization as seen for the diphenylmethyl radical



diphenylmethyl radical

Secondary, benzylic, resonance stabilization by 2 benzene rings

II) $\text{Me}_3\dot{\text{C}} < \text{PhCH}_2\dot{\text{C}} < \text{H}_2\text{C}=\overset{\text{H}}{\text{C}}\dot{\text{C}}\text{H}_2$



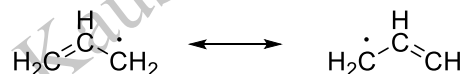
tert-butyl radical

Tertiary, 9 hyperconjugative Hs, but no resonance stabilization as seen for the benzyl or allyl radical

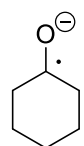


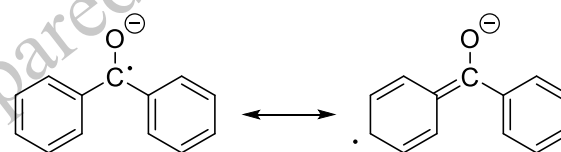
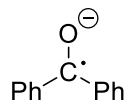
benzyl radical

primary, benzylic, resonance stabilization by benzene ring

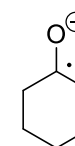


allyl radical - primary - resonance stabilization very effective as canonicals are equivalent

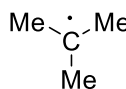
III)  is less stable than

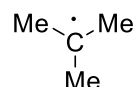
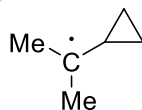


benzophenone radical anion
- resonance stabilized



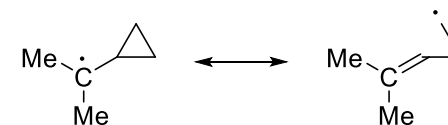
cyclohexanone radical anion
- no resonance stabilization

IV)  is less stable than



tert-butyl radical

Tertiary, 9 hyperconjugative Hs, but no special stabilization from bent bonds like those of cyclopropyl



2-cyclopropylpropan-2-yl radical
Tertiary, 7 hyperconjugative Hs, and special stabilization from the bent bonds of the cyclopropyl moiety

Reactive Intermediates in Organic Chemistry:

Generation and fate of free radicals:

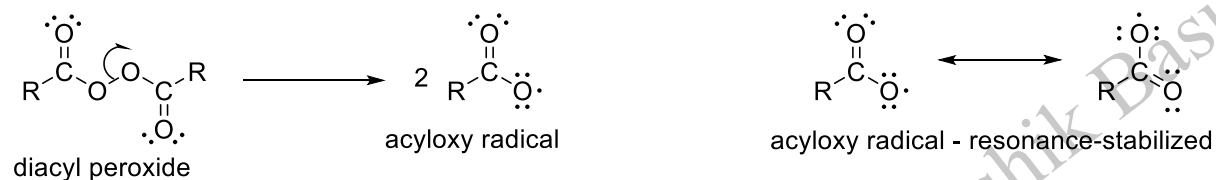
A] Homolysis of covalent bonds generates radicals. Generally, weak (relatively) covalent bonds are targeted.

Compounds that contain relatively weak covalent bonds, i.e. with BDE typically ~25 to 40 kcal/mol can undergo homolysis at a convenient rate at temperatures below 150 °C. These are often used in radical reactions to generate the radical species. These are known as radical initiators.

Examples of radical initiators:

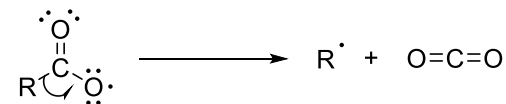
Organic peroxides are good radical initiators. They contain an O-O bond which has a BDE 30 to 35 kcal/mol. O-O bonds are weak due to interelectronic repulsion

Diacyl peroxides:

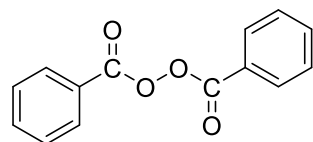


The acyloxy radical may decarboxylate and lead to alkyl (R = alkyl) or aryl (R = aryl) free radicals

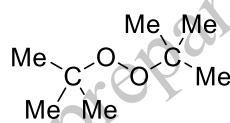
Decarboxylation is fast for R = alkyl, and slow for R = aryl (why, do you think?)



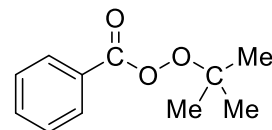
A few dialkyl or diaryl peroxides are also important radical initiators.



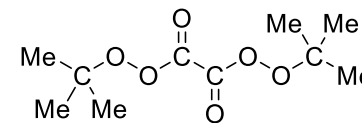
dibenzoyl peroxide



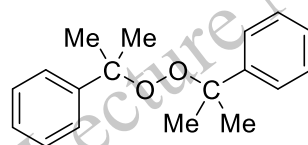
di-*t*-butyl peroxide



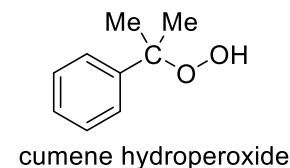
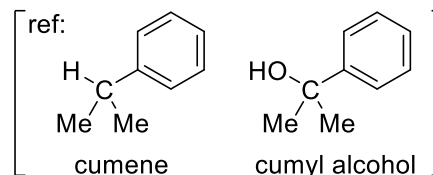
tert-butyl benzoyl peroxide



di-*tert*-butyl peroxyoxalate



dicumyl peroxide

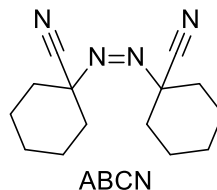
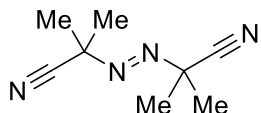


Reactive Intermediates in Organic Chemistry:

Generation and fate of free radicals:

Peroxides have an unfortunate tendency of exploding suddenly. Thus, a better alternative is using azo compounds (R-N=N-R). These dissociate on heating, with loss of nitrogen, to give radicals at temperatures which depend upon the nature of R.

2,2'-azobisisobutyronitrile (AIBN) is frequently used as an initiator in radical reactions. Another example is 1,1'-Azobis(cyclohexanecarbonitrile) (ABCN)

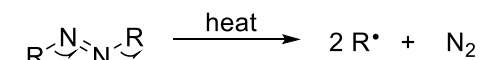


AIBN - half-life of ~ 1 hour at 80 °C, i.e. it undergoes homolysis more easily than benzoylperoxide.

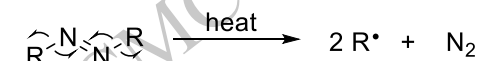
The ease of decomposition and radical generation from the azo compound depends upon the nature of R. Greater the stability of \dot{R} is, lower is the temperature required for homolysis. The following table summarises the activation energy and relative rates for a few azoalkanes:

Relative rates of decomposition of azoalkanes at 300 °C				
Azoalkane	Radicals produced	E_{act} (kcal.mol ⁻¹)	Relative rate	
$H_3C-N=N-CH_3$	$\dot{C}H_3$	52	1	decomposition easier
$Et-N=N-Et$	$H_3C-\dot{C}H_2$	50	5	
$i-Pr-N=N-i-Pr$	$H_3C-\dot{C}H-CH_3$	47.5	60	
$t-Bu-N=N-t-Bu$	$(CH_3)_3\dot{C}$	44	130	
$PhH_2C-N=N-CH_2Ph$	$Ph-\dot{C}H_2$	37.5	700	

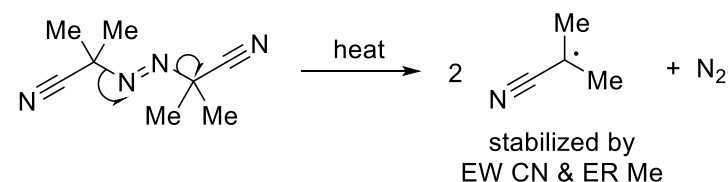
stability increases ↓



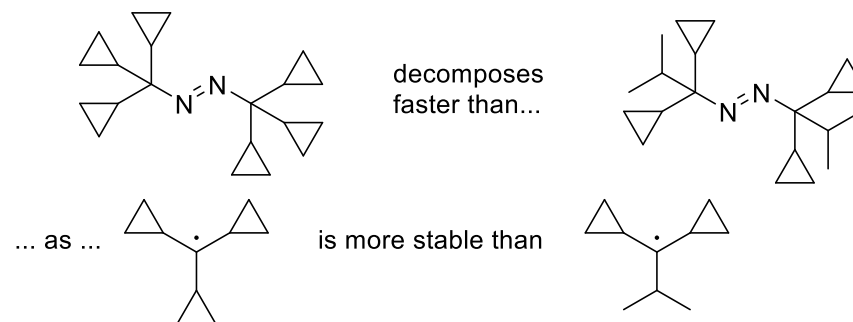
Alternative representation:



Clearly, homolysis is easier for azoalkanes which break down to afford comparatively stable radicals. This is why AIBN decomposes so readily, as the resulting radicals are stabilized by captodative effect.



In the same token,



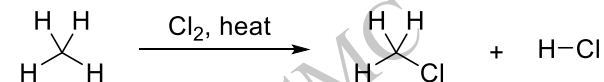
Reactive Intermediates in Organic Chemistry:

Generation and fate of free radicals:

B) Generation of radicals from other radicals: The propagation steps of radical reaction:

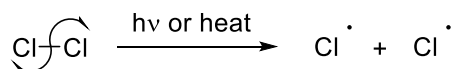
Abstraction of one atom from a covalent bond by a radical can generate a new radical.

For example, free radical bromination of alkane such a methane produces methyl chloride:



The reaction is believed to proceed in three stages:

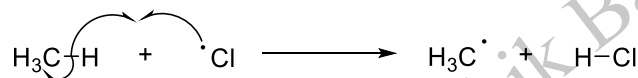
Initiation:



This is one of the steps where radical is generated

Propagation:

propagation step-1 (hydrogen abstraction)

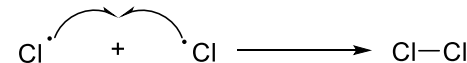
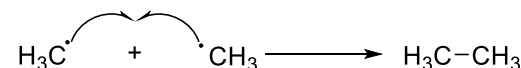
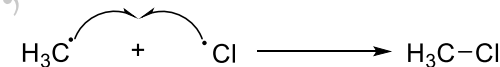


propagation step-2 (chlorine abstraction)



This is the other steps where other radicals are generated by atom abstraction by a precursor radical. These are known as the propagation steps.

Termination:

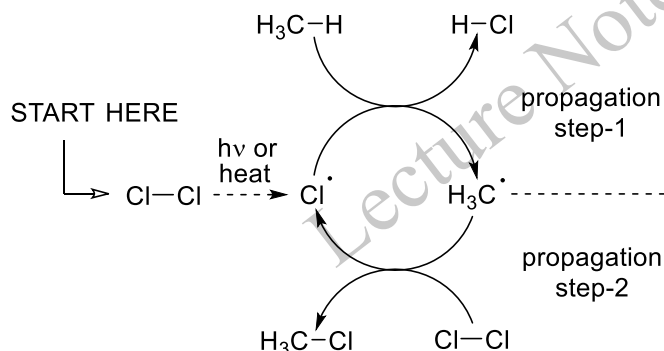


Termination steps destroys radicals. These take over when the concentration of one of the reactants, CH₄ or Cl₂ become very low.

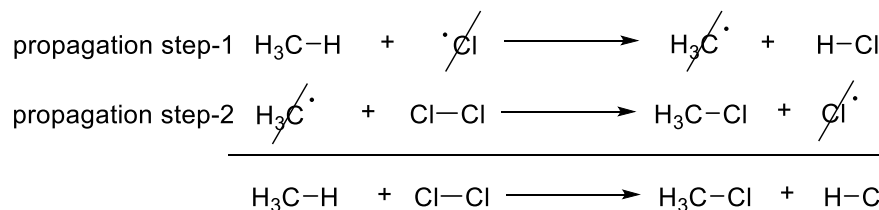
Propagation steps:

In each of these steps, one radical is consumed while another one is produced, and more importantly, the one radical that is formed has to be used as a reactant in one of the subsequent propagation steps. This way, a cyclic mechanism starts to operate and there remains no further need for the initiation to occur.

The cyclic nature of the mechanism is illustrated below:



Also note that propagation step-1 accounts for one of the products, HCl, and step-2 produces the other, methyl chloride. If we sum up the two propagation steps, we have the overall reaction:



This now provides us with a new, refined definition for propagation steps. Specifically, **the sum of the propagation steps gives the net chemical reaction**. All other steps must be either initiation or termination, not propagation.

Generation and fate of free radicals:

B) Generation of radicals from other radicals: The propagation steps of radical reaction:

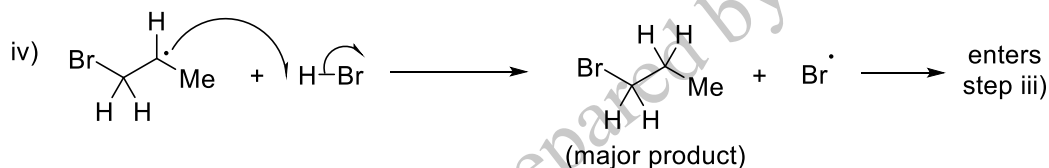
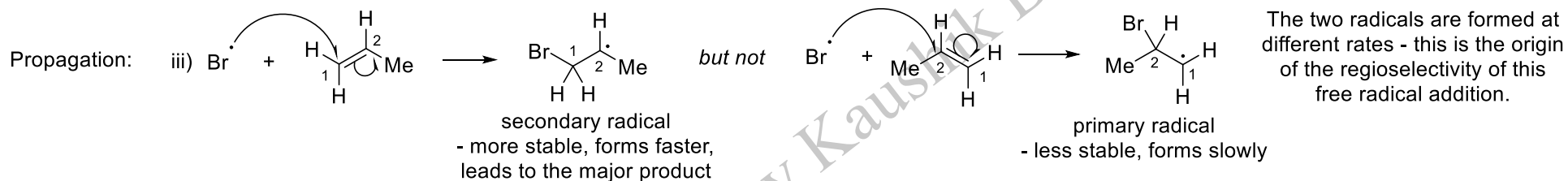
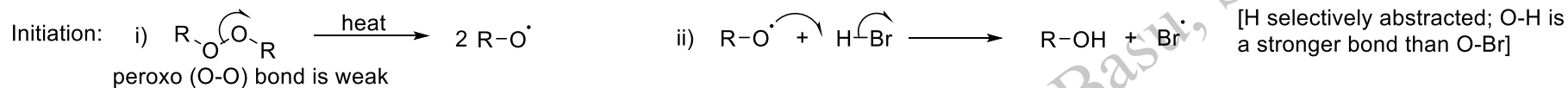
Addition to a multiple bond : Another type of propagation reaction

For example, addition of HBr under the influence of peroxides:



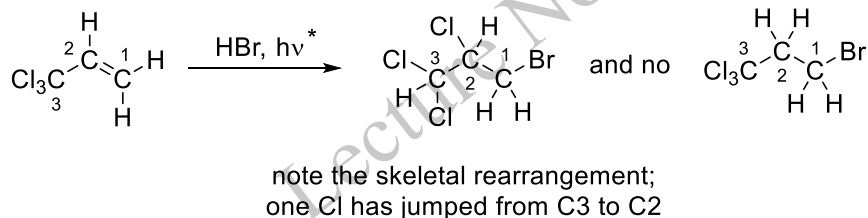
HBr is added across the double bond with the so-called anti-Markovnikov regioselectivity, Br attaches to the less substituted C1 and H to the more substituted C2

These reactions also proceed by the three stages, like other radical reactions.

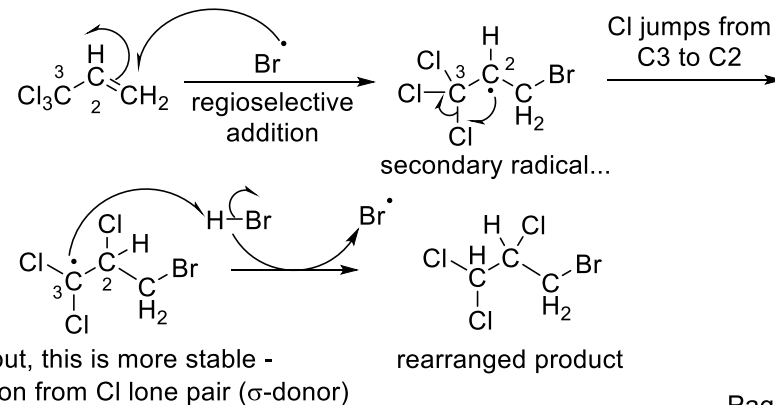


Termination: The chain can be terminated in several ways (think of some!). These will take over once the concentration of HBr and/or propene gets too low.

Rearrangement in free radical hydrobromination:



Mechanism:

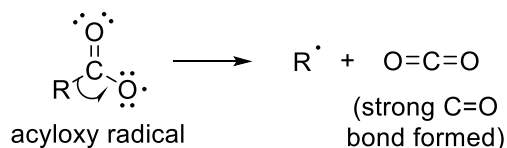


* no peroxide, free radical mechanism triggered photochemically

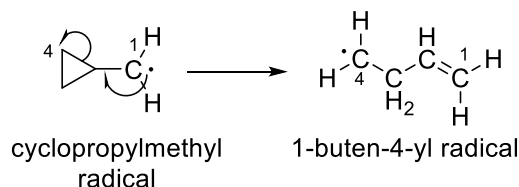
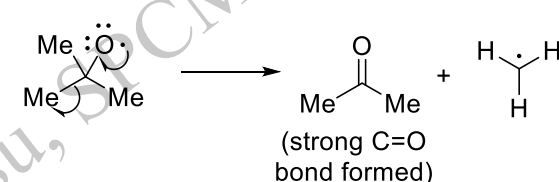
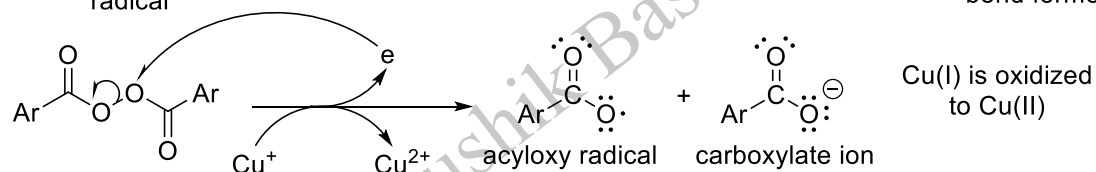
Generation and fate of free radicals:

C] Generation of radicals from other radicals: Fragmentation:

The reverse reaction (thematically) of radical addition - already have seen one example - there are more.

 decarboxylation of acyloxy radical to form
alkyl / aryl radicals


ring opening of cyclopropylmethyl radical


 fragmentation of *t*-alkoxy radical to alkyl radical

 D] Generation of radicals through redox reaction:
via Single Electron Transfers (SET), can involve
metal ions -


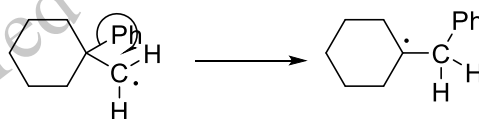
Fates of free radicals:

A] Addition to multiple bonds - already discussed - see free radical addition of HBr to propene;

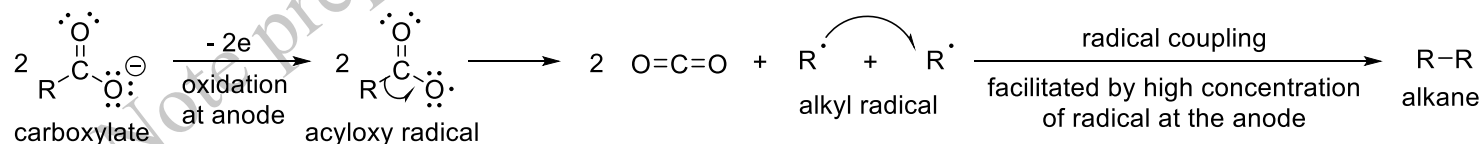
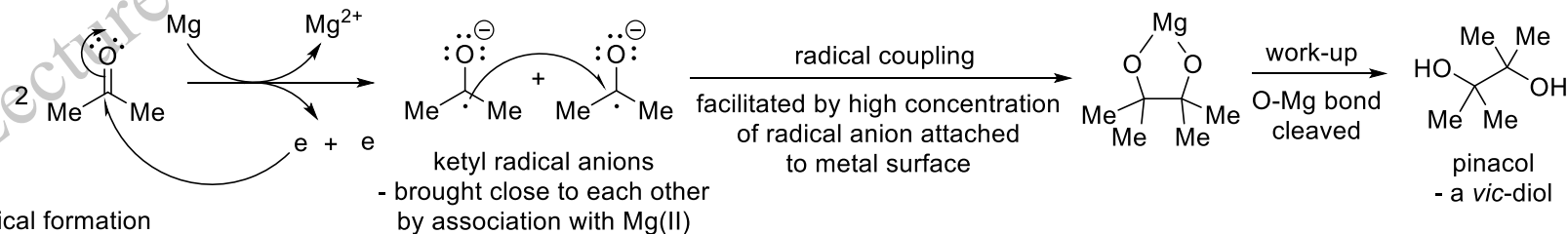
B] Abstraction of (most commonly) H - already discussed - see chlorination of methane;

C] Fragmentation - already discussed - see above!

D] Rearrangement - already discussed - here's one more example



E] Radical coupling - the so-called termination step:

 Kolbe's electrolytic synthesis
of alkanes from carboxylates:

 Formation of pinacol
from acetone by reductive
coupling of the ketone:

 Both examples involve radical formation
through redox reactions.

Reactive Intermediates in Organic Chemistry:

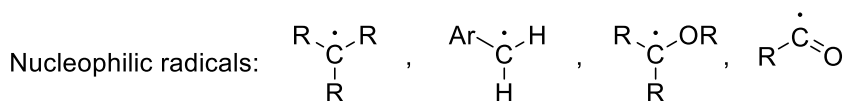
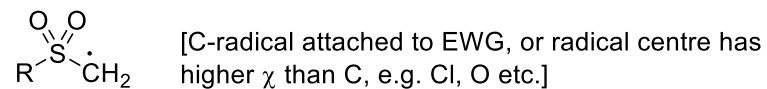
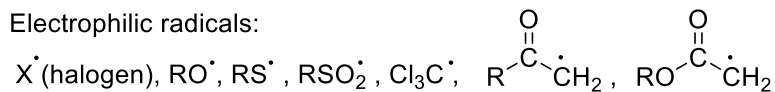
Electronic nature of radicals - electrophilic and nucleophilic radicals

The substituents attached to radical centre markedly influence the stability of that radical.

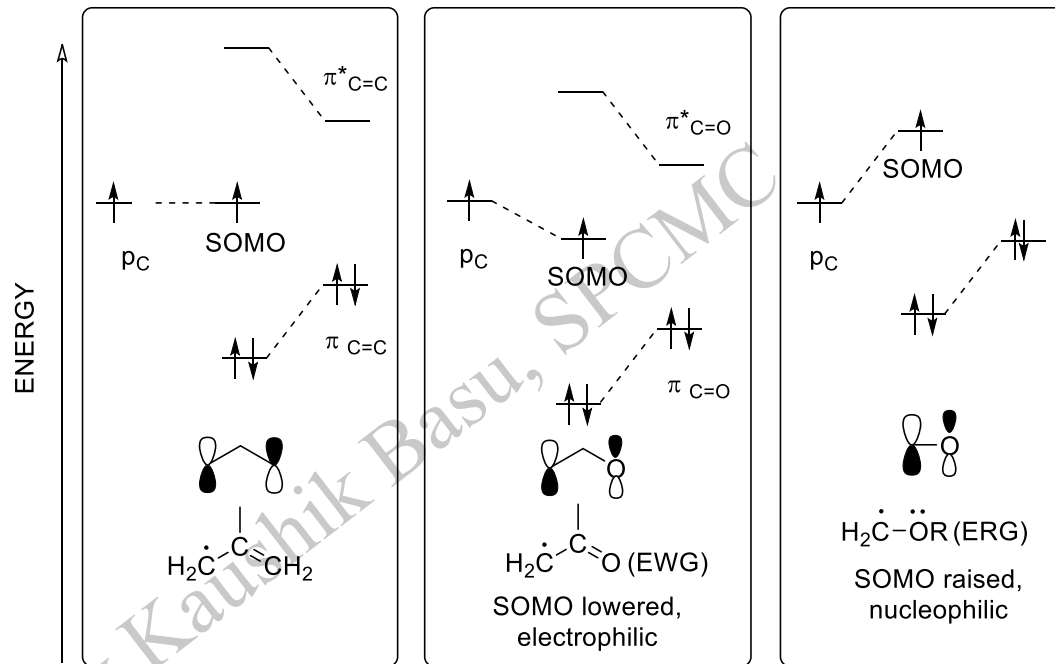
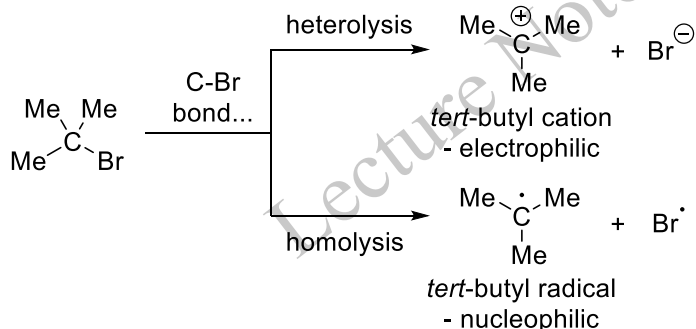
These substituents also alter the reactivity of the radicals profoundly.

Donor substituents raise the SOMO energy which makes the radical nucleophilic, while acceptor groups lower the SOMO energy and the radical becomes electrophilic.

Electrophilic radicals:



Point to note that while carbocations resulting from heterolytic cleavage of C-X bonds of organohalides is electrophile while a homolysis of the same bond leads to carbon-centred radical which is of opposite polarity, i.e., nucleophilic



Addition of radical to C=C is guided by philicity of both alkene and the radical. As the olefin becomes less and less electrophilic by varying the structure of R, reaction rate with electrophilic radicals speeds up while reaction with nucleophilic radicals slows down.

