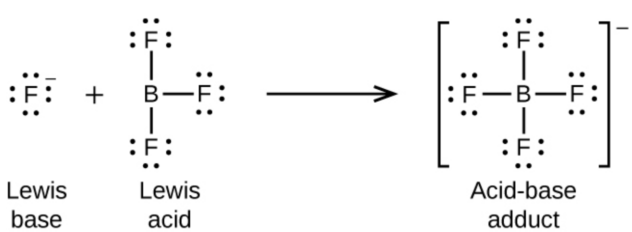
Free Radical Reactions

Types of free radical reactions, free radical substitution mechanism, mechanism at an aromatic substrate, neighboring group assistance.
Reactivity for aliphatic and aromatic substrates at a bridgehead.
Reactivity in attacking radicals. The effect of solvent on reactivity.

Alicyclic halogenation (NBS), oxidation of aldehyde to carboxylic acid, auto-oxidation, coupling of alkynes and arylation of aromatic compounds by diazonium salt. Sandemeyer reaction. Free radical rearrangement. Hunsdiecker reaction.

With rare exceptions, most reactions involve:

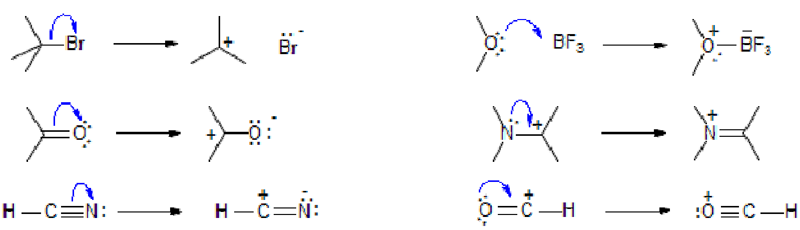
either the formation of bonds between an electron pair donor (Lewis base) and an electron pair acceptor (Lewis acid)



or

the breakage of bonds to generate the same ["heterolytic" cleavage, wherein one bonding partner gets two electrons and the other gets zero].

Bond breaking | Bond making



Arrow starts at a bonding pair of electrons and ends at an atom, creating a sextet atom (or H^+) at the originating atom and new lone pair of electrons at the terminal end.

Arrow starts at a lone pair of electrons and **must** end at a sextet atom (or H^+), creating a new single bond, or converting a single bond to a double bond.

A detour involves

formation of bonds by the combination of single electrons

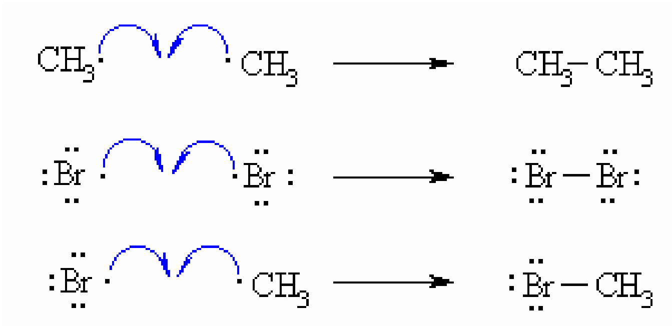
$$A^{\bullet} + B^{\bullet} \longrightarrow A{-}B$$

or bonds break through "homolytic" cleavage [that is, each bonding partner receives an equal number of electrons].

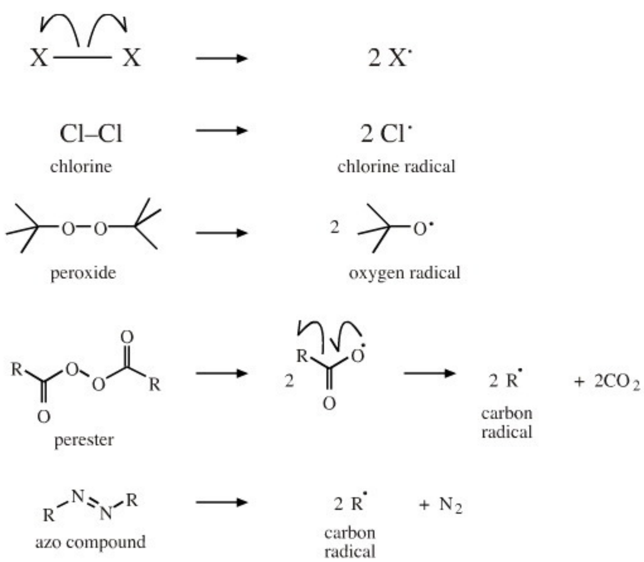
$$A{-}B \longrightarrow A^{\bullet} + B^{\bullet}$$

As we'll see, these reactions are generally referred to as free radicals.

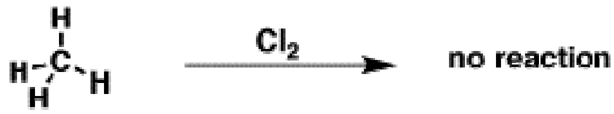
Formation of bonds by the combination of single electrons



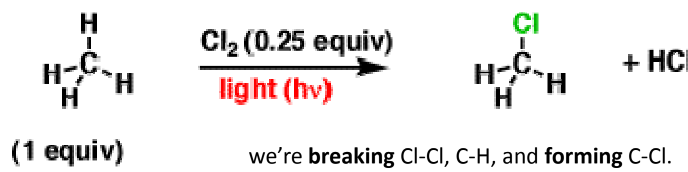
Bonds break through "homolytic" cleavage



It all starts with a simple observation. Lets take an ordinary hydrocarbon gas – methane, when we combine this hydrocarbon with chlorine gas, **in the dark**, nothing happens.



If visible light can enter the flask, and suddenly our methane is consumed such that carbon-hydrogen bonds are replaced with carbon-chlorine bonds.

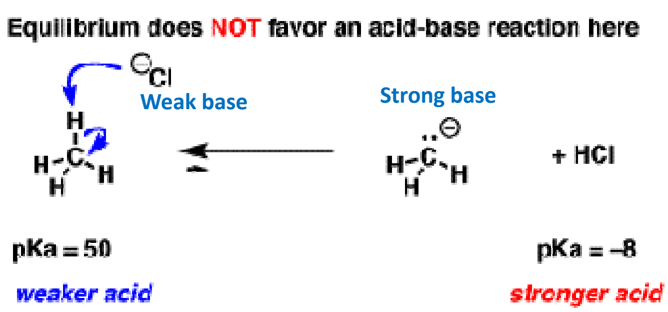


we're **breaking** Cl-Cl, C-H, and **forming** C-Cl.

Now is it an acid-base reaction?

you might say, it's possible that somehow a hydrogen is being pulled off the carbon by a strong base, and then the carbon attacks chlorine.

<u>But does that make sense here</u>?



Why it does not make sense here?

Because we would be going from a very weak acid [CH_4] to a very strong acid [HCl] and likewise a weak base [Cl] to a strong base. This is like trying to get water falls to flow in reverse direction.

Further, if the reaction proceeded through some kind of charged intermediate like Cl^- or CH_3^- , **we would expect that the reaction would proceed more quickly in polar solvents** [that can stabilize charge] as opposed to nonpolar solvents [which do not stabilize charge].

Instead, we find that the rate of the reaction is almost completely independent of solvent polarity.

It proceeds just about as quickly in [nonpolar] carbon tetrachloride as it

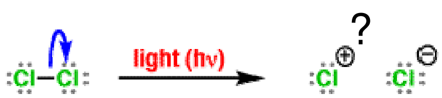
does in a polar solvent such as methanol.

This implies that a neutral species is involved in the reaction (specifically, the rate limiting step of the reaction)

Alright – so how, then, it can be the involvement of a neutral intermediate?

Let's think first about that chlorine-chlorine bond, which is relatively weak. Imagine that by heating it up or by shining light on, it might break somehow. How might it break?

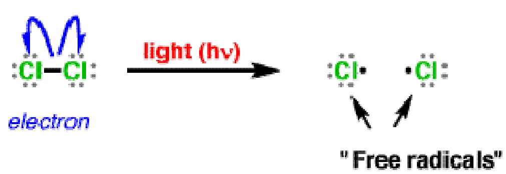
Option #1 would look something like this – "heterolytic" cleavage, where one atom receives both electrons from the bond, while the other does not



However, this leads to polar species (solvent effects tell us this is unlikely)

A second option for Cl–Cl bond breakage: "homolytic" cleavage

Note the "single-barbed" curved arrows, each depicting the movement of 1 electron



Note that each Cl ends up with one electron from the Cl–Cl bond

The resulting species are called "free radicals"

Free radicals

Free radicals may be defined as the species that contain one or more unpaired electrons.

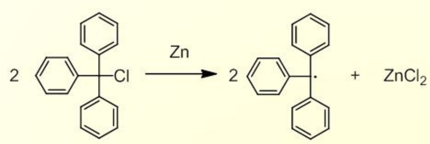
They are generally less stable and react in fraction of seconds with another species.

We would expect such a species to be highly reactive, ***since there will be a strong driving force to form the full octet.***

Free Radicals

Discovery of free radicals

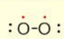
Prof. Gomberg was the first to characterize a free radical in 1900.



Triphenylmethyl **radical** (often called trityl **radical**) is a persistent radical

Properties of free radicals

1. One or more unpaired electrons.



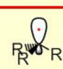
diradical

2. Electron-deficient species.
3. Uncharged molecules.

Shape of free radicals

carbanion, SP^3
Tetrahedron

carbocation, SP^2
Trigonal planar

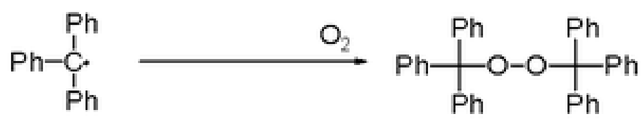


radical
Flattened tetrahedron

Triphenylmethyl radical

Solutions containing the radical are yellow.

When exposed to air the radical rapidly oxidizes to the peroxide and the color of the solution changes from yellow to colorless.



Yellow color **Colorless solution**

Whilst simple alkyl radicals are extremely short-lived, trityl radicals survive almost indefinitely. **Such radicals are known as persistent radicals.**

Formation of Free Radicals

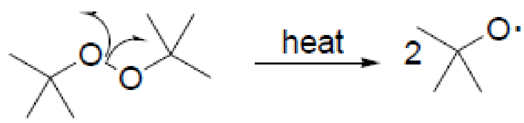
Three general methods are used for the generation of free radicals:

- Thermal Generation
- Photochemical Generation
- Redox Generation

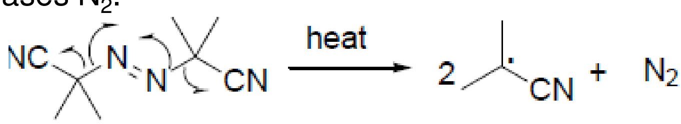
Thermal Generation

Two types of compounds dissociate to give free-radicals at moderate temperature:

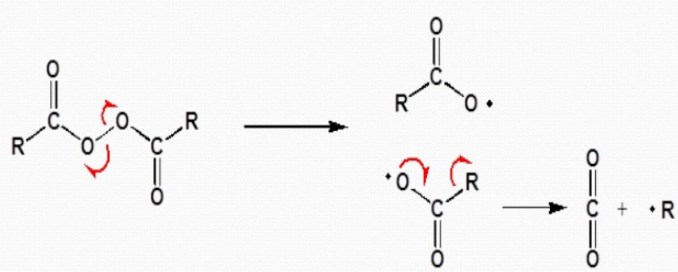
(i) compounds that have an intrinsically weak bond such as **dialkyl peroixides** (DO-O = 155 KJ mol-1),



(i) compounds that, on fragmentation, form strongly bonded products, such as **AIBN** (Azobis-isobutyronitrile) which releases N_2.



Peroxides



When R is alkyl, loss of CO_2 is very fast. Therefore, alkyl peroxides are generally avoided, as they tend to be explosive

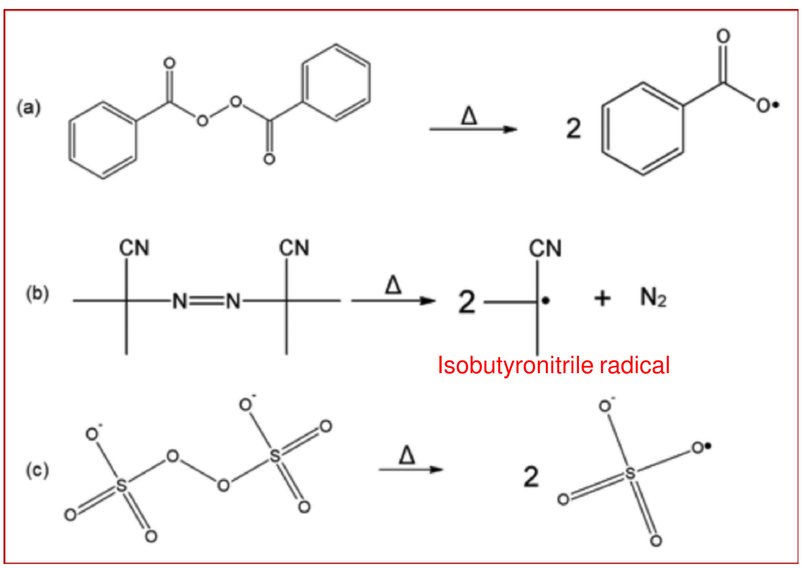
Radical initiator

In chemistry, **radical initiators** are substances that can produce radical species under *mild conditions and promote radical reactions.*

These substances generally possess weak bonds that have small bond dissociation energies.

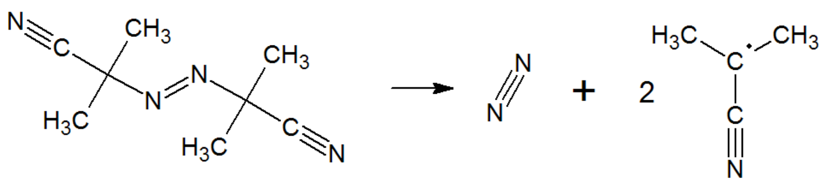
Radical initiators are utilized in industrial processes such as polymer synthesis.

Radical initiators



AIBN as radical initiator

Radical initiators are utilized in industrial processes such as polymer synthesis.

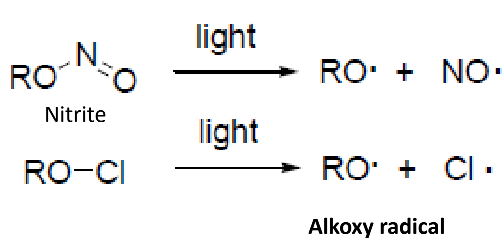


Isobutyronitrile radical

Photochemical Generation

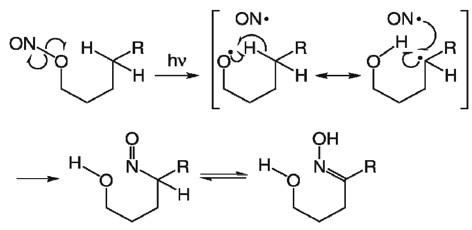
Light can bring the fragmentation of a compound if the wavelength of the light is correspond both to an energy greater than that of the bond to be cleaved, and to an electronic excitation of the molecule concerned.

This procedure is suitable for the formation of alkoxy radicals from alkyl nitrite or hypochlorites.



The Barton reaction (Application of Photochemical reaction)

The Barton reaction involves a homolytic RO–NO nitrite cleavage resulting in alkoxy radical



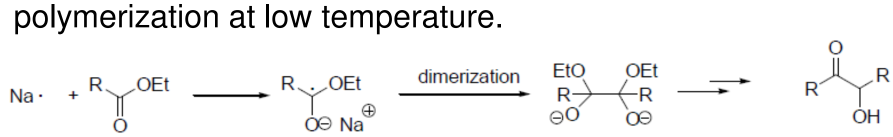
Alkyoxyl radical immediately abstracts a hydrogen atom from the δ-carbon.

In the absence of other radical sources or other proximal reactive groups, the alkyl radical recombines with the nitrosyl radical.

The resultant nitroso compounds undergoes tautomerization to the isolated oxime product.

Redox Generation

Covalent bonds may be broken by electron transfer process either by accepting an electron from a donor or donating an electron to an acceptor. It us used while performing polymerization at low temperature.



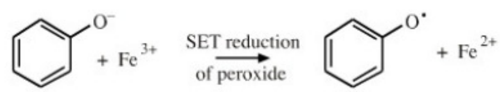
Yet another example

An electron can be removed from an anion, an oxidation process. For example, the phenoxide ion is oxidised by Fe^{3+} to give the phenyl oxygen radical and the Fe^{3+} is co-reduced to Fe^{2+}.

The iron(II) ion, Fe^{2+}, can reduce hydrogen peroxide to hydroxyl radical and hydroxide ion:

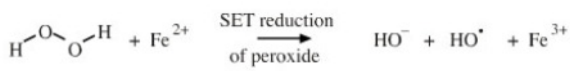
Single Electron Transfer (SET) Oxidation

$$X^{-} \longrightarrow X^{\cdot} + e^{-}$$

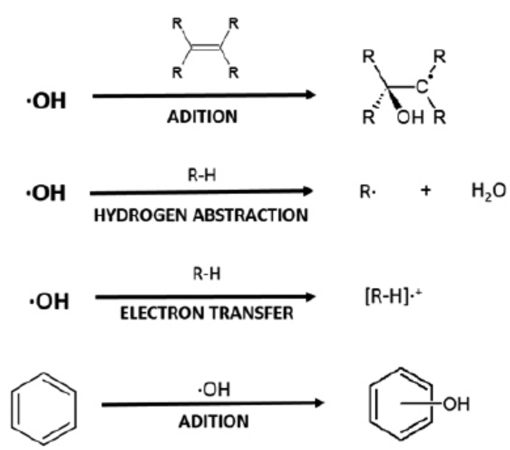


Single Electron Transfer (SET) Reduction

$$X^{+} + e^{-} \longrightarrow X^{\cdot}$$



Application of hydroxy radical



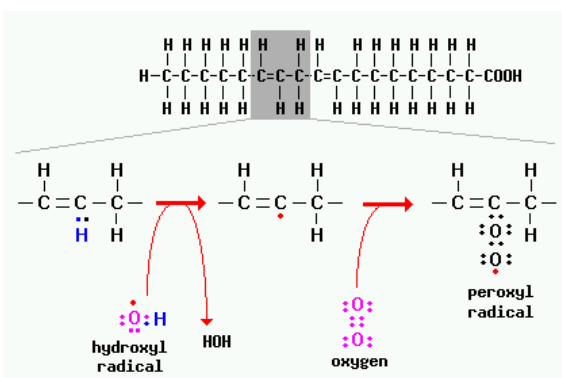
Fenton reagent produces hydroxy radical

Fenton oxidation method

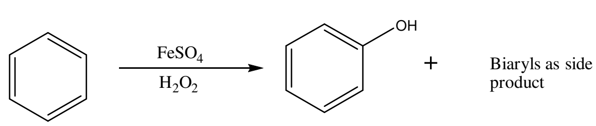
- Fenton's Reagent : Hydrogen Peroxide combined with an Iron catalyst.
- Creates multiple highly reactive powerful oxidizers:
  - Hydroxyl radical: OH^0
  - Peroxide free radical: $HO_2{}^0$

H.J.H. Fenton.*J. Chem. Soc*. 1894, 65, 889.

Application OH radical



Hydroxylation at an aromatic carbon



Types of free radical reactions

Free radicals undergo eight typical reactions:

•atom abstraction (reaction with a *bond),*
•addition to a *bond,*
•*radical–radical combination, disproportionation,*
•*fragmentation,*
•electron transfer,
•addition of a nucleophile, and
•loss of a leaving group.

The first three are by far the most important.

The four most important reaction types involving free radicals are:

•Atom abstraction.

•Free-radical **addition** reactions.

•*radical–radical combination, disproportionation*

•Free radical rearrangement reactions are rare compared to rearrangements involving carbocations and restricted to aryl migrations.

Abstraction

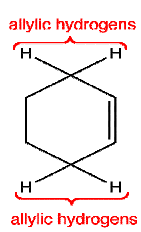
Free radicals proceed reactions with saturated organic molecules by *abstracting an atom from carbon.*

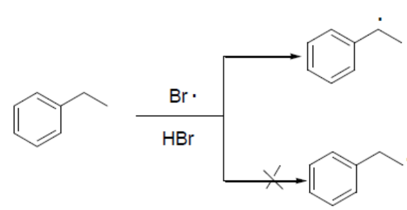
The selectivity of the free radicals towards C-H bonds of different types is determined by bond dissociation energy and polar effects.

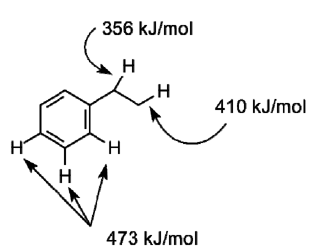
The rate of the abstraction process increases as bond dissociation energy decreases. For examples:

Bond:	H−CH_3	H−CH_2Me	H−$CHMe_2$	H−CMe_3
Bond Dissociation Energy ($KJmol^{-1}$)	426	401	385	372
Reactivity Order::	H−CH_3 <	H−CH_2Me <	H−$CHMe_2$ <	H−CMe_3

Allylic and benzylic C-H bonds are weaker than those of saturated systems and exhibit greater reactivity and selectivity with free radicals.







vinylic	$H_2C{=}CH{-}H$	DH° = 452 kJ / mol
primary	$CH_3CH_2{-}H$	DH° = 410 kJ / mol
secondary	$(CH_3)_2CH{-}H$	DH° = 396 kJ / mol
tertiary	$(CH_3)_3C{-}H$	DH° = 389 kJ / mol
allylic	$H_2C{=}CH{-}CH_2{-}H$	DH° = 364 kJ / mol

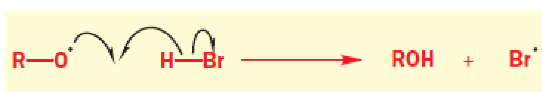
In general in an *atom abstraction reaction*,

a radical X attacks a Y–Z bond to give a new closed-shell species X–Y and a new radical Z.

One of the electrons in the old *bond goes to form a bond to X, and the other one ends up on Z.*

The transferred atom, Y, is usually H or halogen, but not always.

$$X^{\bullet} + Y\text{-}H \longrightarrow XH + Y^{\bullet}$$



These radicals are formed by the action of the alkoxy radicals on HBr—a process known as **radical abstraction.**

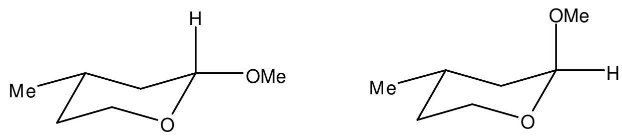
The peroxy radical RO• 'abstracts' H• from the HBr to give ROH, leaving behind a new radical Br•.

Stereoelectronic effects in the abstraction of hydrogen:

Such effects are important where a hydrogen is abstracted from a Carbon adjacent to C-O or C-N bond.

In such cases hydrogen is abstracted from C-H bonds that have a relatively small dihedral angle (~30º) with the unshared orbitals of the O or N much easily than those with a large angle (~90º).

For example, the hydrogen in **I** can be abstracted about 8 times faster than the hydrogen in **II**



I

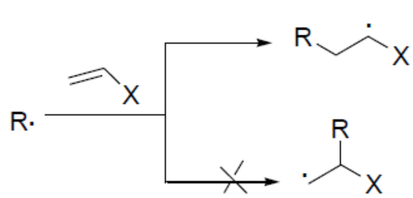
II

Addition

Free radicals undergo addition to carbon-carbon double bonds.

The reaction is generally selective.

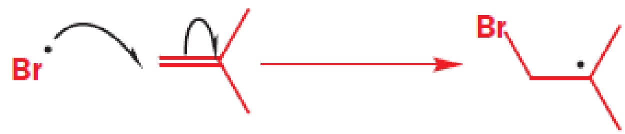
For example, addition to CH2=CHX takes place exclusively at the methyl group, irrespective of the nature of X.



Alkynes also exhibit similar reactivity with free radicals.

The Br• radical adds to the alkene to give a new, carbon-centred radical.

radical addition



Key features:

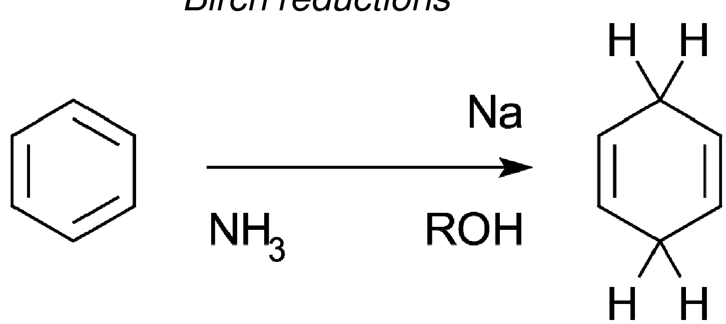
Addition of a radical to a spin-paired molecule always generates a new radical.

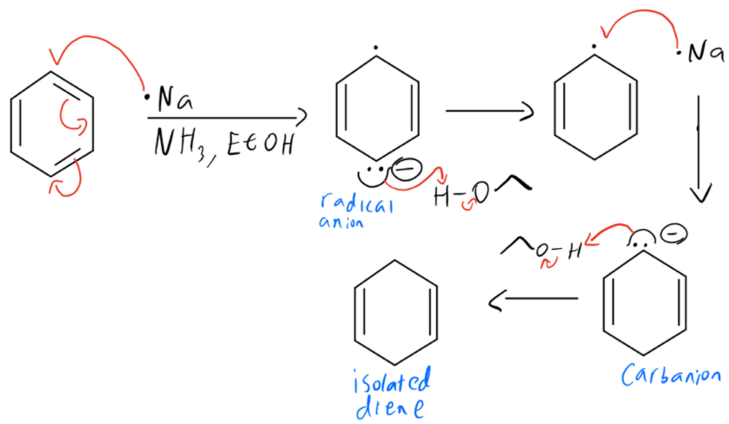
Radical addition is therefore a second type of radical-forming reaction.

The simplest radical addition reactions occur when a single electron is added to a spin-paired molecule. This process is a reduction.

Birch reductions use the single electron formed when a group I metal (sodium, usually) is dissolved in liquid ammonia to reduce organic compounds.

Birch reductions





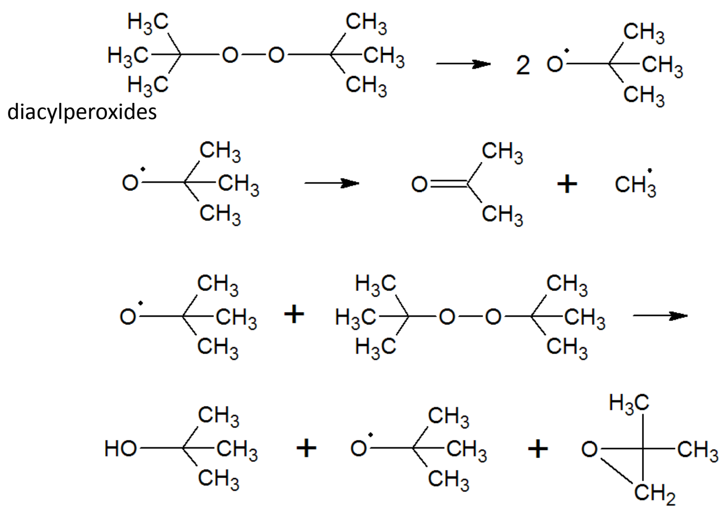
Combination and Disproportionation

Two free radicals can combine by dimerization or disproportionation.

$$2Br\cdot \longrightarrow Br_2$$
$$2CH_3\cdot \longrightarrow H_3C{-}CH_3$$
$$CH_3\cdot + Br\cdot \longrightarrow H_3C{-}Br$$

These reactions are generally fast, some having negligible activation energies.

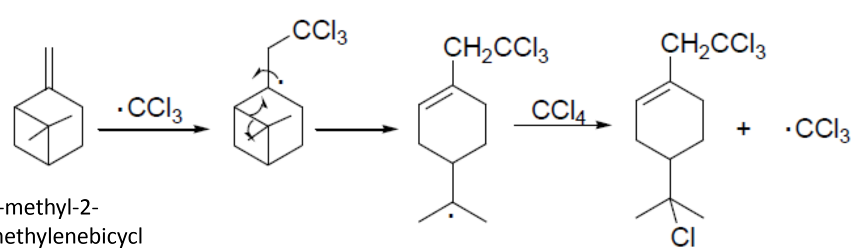
Disproportionation yields acetone and a methyl radical whereas hydrogen abstraction leads to t-butyl alcohol and, in some cases, to iso-butylene oxide, ..



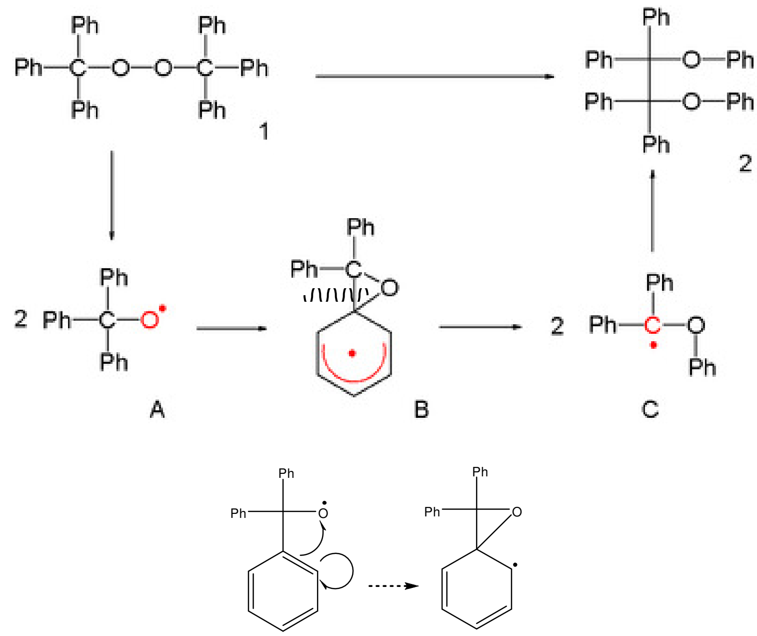
diacylperoxides

Rearrangement

Free radicals are known to rearrange in certain circumstances. For example, the addition of free radical leads to rearrangement due to relief of strain in the cyclic system.



6-methyl-2-methylenebicyclo[3.1.1]heptane

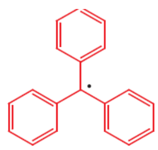


Reactivity in attacking radicals

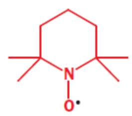
Most radicals are extremely reactive…….. but a few radicals are very unreactive

Unpaired electrons are desperate to be paired up again. This means that radicals usually have a very short lifetime; they don't survive long before undergoing a chemical reaction.

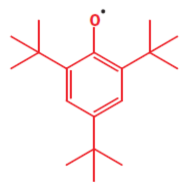
Whilst simple alkyl radicals are extremely short-lived, some other radicals survive almost indefinitely.
<u>Such radicals are known as persistent radicals</u>.



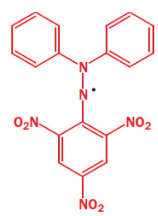
triphenylmethyl radical – stable in solution in equilibrium with its dimer



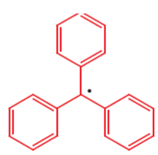
TEMPO
TEtraMethylPiperidine *N*-Oxide
m.p. 36–38°C



dark blue solid
m.p. 97°C



violet crystals



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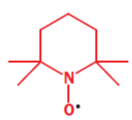

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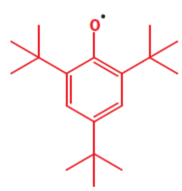

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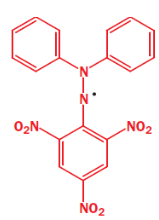
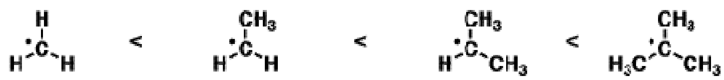


violet crystals

There are two reasons why some radicals are more persistent than others:
(1) steric hindrance and
(2) electronic stabilization.

In the four extreme cases above, their exceptional stability is conferred by a mixture of these two effects.

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



Methyl radical	Primary radical	Secondary radical	Tertiary radical
Least stable			Most stable

same factors which stabilize free radicals are also the same factors which stabilize carbocations!

Short lived radicals (R*)

- Are difficult to handle, most important and are highly reactive
- Their stability will be in the order:
  $R_3C^* > R_2CH^* > RCH_2^* > CH_3^*$
- The sequence shows that stability increases due to increase in hyper-conjugation and decrease due to relief of steric strain as the series traversed
- Radical forms having allylic or benzylic are more stable through delocalization of pi electrons e.g

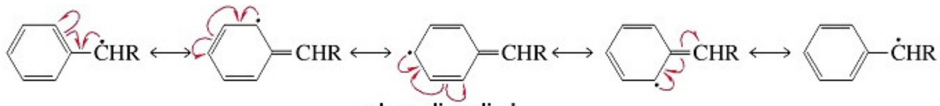
$$CH_2=CH-{}^*CH_2 \longleftrightarrow {}^*CH_2-CH=CH_2$$

Stability of radicals

Radicals forms having benzylic/allylic are more stable through declocalization of pi electrons.

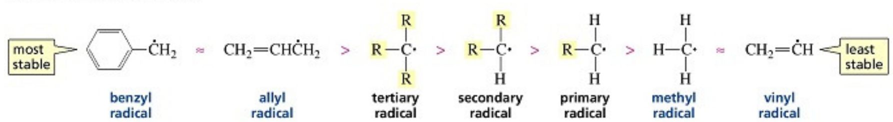
$$R\dot{C}H-CH=CH_2 \longleftrightarrow RCH=CH-\dot{C}H_2$$

an allylic radical



a benzylic radical

relative stabilities of radicals



- Free radical electron movement is quite different from electron movement in ionic reactions
- For example, free radicals don’t undergo rearrangement

This carbocation will rearrange to produce a more stable tertiary carbocation

This radical will <u>not</u> rearrange to produce a more stable tertiary radical

Radical Substitution Mechanism

The Characteristics of Free radical Reactions

Free radical reactions may be broadly classified into two groups. In the first, the product formation occurs from the combination of two radicals.

$$2CH_3\cdot \longrightarrow H_3C\text{-}CH_3$$

In the second class, the product formation results from the reaction of a *radical with a molecule* by chain process.

Initiation

$$Cl_2 \xrightarrow{\text{light}} 2Cl\cdot$$

Propogation

$$Cl\cdot + CH_4 \longrightarrow HCl + \cdot CH_3$$

$$\cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + \cdot Cl$$

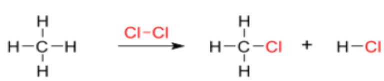
Termination

$$2Cl\cdot \longrightarrow Cl_2$$

$$2CH_3\cdot \longrightarrow C_2H_6$$

$$\cdot CH_3 + Cl\cdot \longrightarrow CH_3Cl$$

The net reaction is:



or $CH_4 + Cl_2 \xrightarrow{uv\ light} CH_3Cl + HCl$

•In the case of methane or ethane, all the hydrogen atoms are equivalent and thus have an equal chance of being replaced.

• This leads to what is known as a *statistical product distribution*.

• For propane and higher alkanes, the hydrogen atoms which form part of CH_2 (or CH) groups are preferentially replaced.

The **initiation phase**

•The **initiation phase** describes the step that initially creates a radical species.

•In most cases, this is a homolytic cleavage event, and takes place very rarely due to the high energy barriers involved.

•Often the influence of heat, UV radiation, or a metal-containing catalyst is necessary to overcome the energy barrier.

•Peroxides including hydrogen peroxides, dialkyl, diacyl and alkyl-acyl peroxides and peracids are widely used to induce free radicals.

•Organic compounds with low energy bonds such as azo compounds are also used to induce free radicals..

•Molecules that are cleaved by light are chlorine, bromine and various ketones.

The **propagation phase**

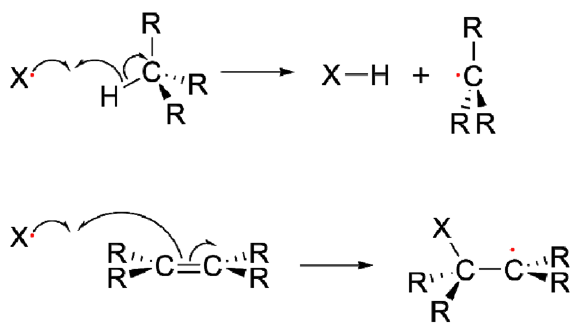
The **propagation phase** describes the 'chain' part of chain reactions.

Once a reactive free radical is generated, it can react with stable molecules to form new free radicals.

These new free radicals go on to generate yet more free radicals, and so on.

Propagation steps often involve

hydrogen abstraction
or
addition of the radical to double bonds



Chain termination

Chain termination occurs when two free radical species react with each other to form a stable, non-radical adduct.

In fact it involves the destruction of free radicals.

General characteristics of free radical reactions

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase.
2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents except that nonpolar solvents may suppress competing ionic reactions.
3. They are initiated by typical free radical sources such as light, peroxides or peracids.

4. The rates are decreased or the reactions are suppressed entirely by substances that scavenge free radicals. E.g. nitric oxide, molecular oxygen or benzoquinone and are called inhibitors.

Free radical substitution mechanism

In a free-radical substitution reaction

$$R{-}X \longrightarrow R{-}Y \qquad (1)$$

there must first be a cleavage of the substrate RX so that R• radicals are produced. This can happen by a spontaneous cleavage

$$R{-}X \longrightarrow R\bullet + X\bullet \qquad (2)$$

or it can be caused by light or heat, or, more often, there is no actual cleavage, but R• is produced by an *abstraction*

$$R{-}X + W\bullet \longrightarrow R\bullet + W{-}X \qquad (3)$$

W• is produced by adding a compound, such as a peroxide, that spontaneously forms free radicals. Such a compound is called an *initiator*. Once R• is formed, it can go to product in two ways, by abstraction

$$R\bullet + Y{-}W \longrightarrow R{-}Y + W\bullet \qquad (4)$$

or by coupling with another radical

$$R\bullet + Y\bullet \longrightarrow R{-}Y \qquad (5)$$

Reactivity for aliphatic substrates during halogenation

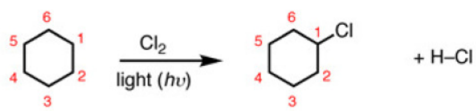
Controlled by three factors:

- Stability of aliphatic radicals formed
- Bond strength or bond dissociation energy of C-H bonds
- Reactivity of halogens (or their ability to abstract hydrogen

Two simple examples.

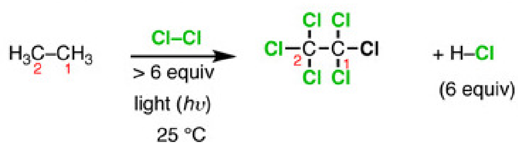
Broken	Formed
C_1–H	C_1–Cl
Cl–Cl	H–Cl

hopefully you can see that putting a Cl on C_1 or C_2 leads to the same product



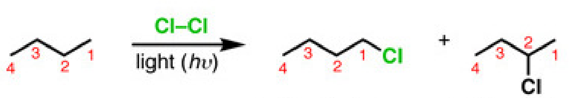
Broken	Formed
C_1–H	C_1–Cl
Cl–Cl	H–Cl

Excess chlorine leads to increased substitution of H by Cl.



Broken	Formed
C_1–H (3)	C_1–Cl (3)
C_2–H (3)	C_2–Cl (3)
Cl–Cl (6)	H–Cl (6)

So what happens if we use something a little different – like butane, for instance?



1-chlorobutane *2-chlorobutane*

Broken	Formed
C–H	C–Cl
Cl–Cl	H–Cl

ratio: ~3:2

two possible products – 1-chlorobutane and 2-chlorobutane – and they're formed in about a 3:2 ratio.

Not coincidentally, this is also the ratio of CH_3 hydrogens (there are 6) to CH_2 hydrogens (4).