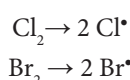


Chemistry of Radicals

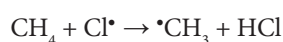
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Free radicals can be defined as chemical species (atom, molecule or ion) which have a single unpaired valence electron. Triplet O₂ and triplet carbene (:CH₂) have two unpaired electrons. Homolytic cleavage of Cl₂ or Br₂ by thermally or photochemically produces two Cl• or Br• radicals.



The presence of an unpaired electron makes the radical **highly reactive** and **less stable**, thus, it can abstract an electron/atom/group from another molecule and becomes stable as shown below (Cl• → HCl).



Free radicals can be positive (e.g., PhOH^{•+}), negative (e.g., naphthalide) or neutral (e.g., Br•). Mass spectrometer produces cation radicals called molecular ions. Reduction of benzophenone, biphenyl and naphthalene with alkali metals generates anion radicals.

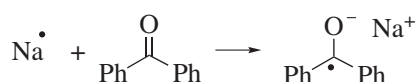


Figure 1: Ketyl anion radical of benzophenone

Stability of free radicals

Electron donating groups can push electrons towards the free radical and stabilize it. Tertiary (3^o) radicals are the most stable.

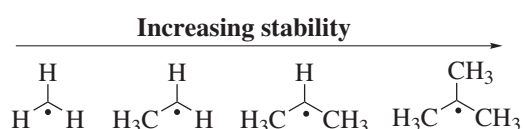


Figure 2: Stability of Me•, 1^o, 2^o & 3^o radicals

The selectivity of C-H bond cleavage is determined by the bond dissociation. The bond dissociation energies of H-CH₃, H-Et, H-CHMe₂ and H-CMe₃ are approximately 440, 425, 415, and 405 kJ per mole.

Free radicals can be further divided into σ- and π-radicals, depending on whether the unpaired electron is located in an σ- or π-orbital. Generally, π-radicals are readily stabilized by conjugation, thus, σ-radicals are less stable than π-radicals.

The allyl and benzylic radicals are examples of conjugative resonance stabilization.

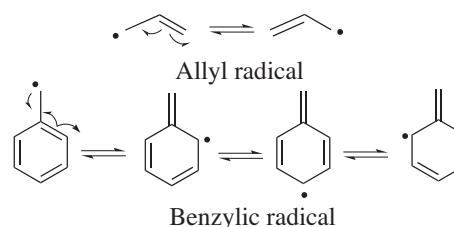


Figure 3: Resonance structures of allyl and benzylic radicals

Stable free radicals

NO is a stable inorganic radical. Generally organic radicals are stabilized by the following factors: hyperconjugation, presence of electronegative atoms such as oxygen and nitrogen, delocalization, and steric hindrance.

2,2,6,6-Tetramethylpiperidine-1 oxyl radical (TEMPO) is a stable radical used in organic oxidation reactions.

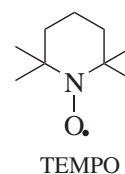


Figure 4: TEMPO: A stable free radical

Types of Free Radicals

Free radicals are classified as Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) (see Table1).

Table 1: Some important ROS and RNS

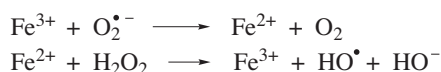
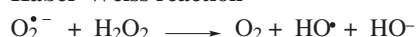
Free radical	Symbol
Reactive oxygen species	
Superoxide anion radical	$O_2^{\cdot-}$
Hydroxyl radical	HO^{\cdot}
Alkoxy radical	RO^{\cdot}
Peroxy radical	ROO^{\cdot}
Reactive nitrogen species	
Nitric oxide radical	NO^{\cdot}
Nitrogen dioxide radical	NO_2^{\cdot}

a) Superoxide anion radical

When a single electron is added to the ground state of the oxygen molecule, it enters into the π -antibonding orbital forming the superoxide anion radical.

b) Hydroxyl radical

The neutral form of the hydroxide ion is the hydroxyl radical. It is very short lived and reacts vigorously with sugars, amino acids, phospholipids and DNA. Hydrogen peroxides (H_2O_2) reacts with metal ions (Fe^{2+} or Cu^{2+}) bound proteins such as ferritin and ceruloplasmin to produce the hydroxyl radical, which is called the Fenton reaction.

Fenton reaction**Haber-Weiss reaction****Figure 5:** Fenton and Haber-Weiss reactions

HO^{\cdot} is also formed from the Haber-Weiss reaction where superoxide anion radical reacts with hydrogen peroxide.

c) Alkoxy and hydroperoxy radicals

Alkoxy radicals are good oxidizing agents. Protonation of the superoxide anion radical gives the hydroperoxy radical (HOO^{\cdot}). It has the ability to initiate fatty acid peroxidation and tumor development.

d) Nitric oxide radical

Nitric oxide radical (NO^{\cdot}) reacts with molecular oxygen

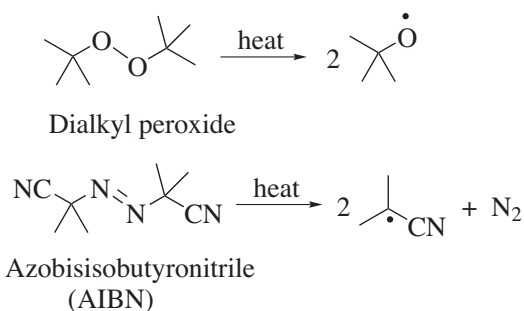
to produce NO_2^{\cdot} . It is highly soluble in organic solvents and less soluble in water; it has the ability to diffuse through cytoplasm and plasma membranes.

Formation of radicals

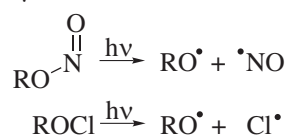
Heat, light, electrical discharges, electrolysis and redox reactions are known to produce radicals.

1. Thermal generation

Compounds that have intrinsically weak bonds dissociate to give free radicals at moderate temperatures.

**Figure 6:** Thermal generation of radicals**2. Photochemical generation**

Fragmentation of compounds occurs if the light energy is sufficient enough to cleave a bond and electronically excite the molecule. Alkoxy radicals can be easily formed photochemically.

**Figure 7:** Photochemical generation of radicals

Norrish type I and II reactions are examples for reactions involving the photochemical generation of radicals. In Norrish type I, the cleavage of **alpha** bond of a ketone takes place, whereas, in Norrish type II, the transfer of **gamma** (γ) hydrogen to the carbonyl oxygen takes place, forming 1,4-hydroxy biradical.

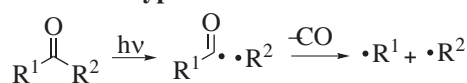
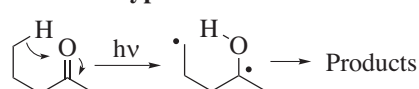
Norrish type I**Norrish type II****Figure 8:** Examples for Norrish type I and II cleavages

Figure 9 shows the photochemistry of (1), which undergoes both Norrish type I and II reactions.

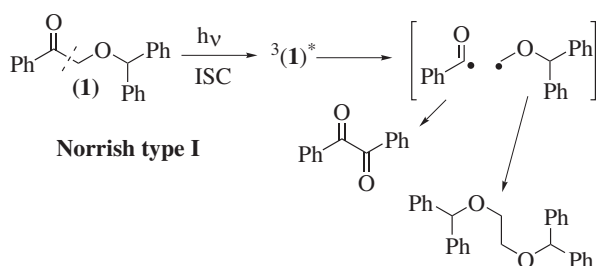


Figure 9: Norrish type I and II cleavages of (1)

3. Redox generation

Covalent bonds may be broken by electron transfer process either by **accepting** an electron from a donor (*via* reduction, Fig. 10) or **donating** an electron to an acceptor (*via* oxidation, Fig. 11).

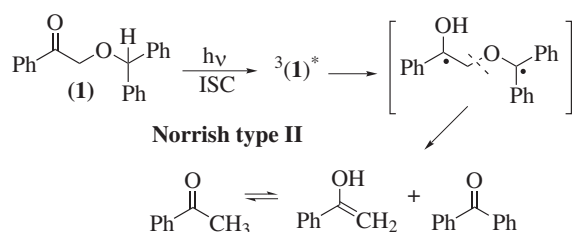


Figure 10: Reduction of EtOAc with Na

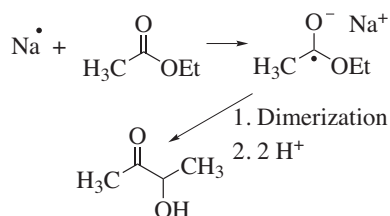


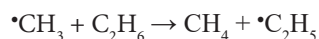
Figure 11: Oxidation of 2,6-dimethylphenol with Fe³⁺ ions

Reactions of Radicals

Abstraction, addition, combination, disproportionation and rearrangement are the common reactions of free radicals.

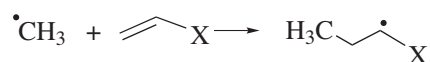
1. Abstraction

Free radicals proceed with reactions by abstraction of another atom/group. The bond dissociation energy and the polar effects determine the selectivity of radicals towards C-H bonds. As the bond dissociation energy decreases the rate of abstraction increases.



2. Addition

Free radicals undergo a selective addition reaction to carbon-carbon double bonds. Usually, the addition of radicals takes place according to the anti-Markovnikov rule where the substituent is added to the less substituted carbon atom.



Some unstable radicals break down into a spin-paired molecule and a new radical, for example, benzoyloxy radical (PhCO₂•) eliminates a phenyl radical (Ph•) and CO₂. This can be viewed as the reverse of radical addition.

3. Combination and disproportionation

Two free radicals can combine by dimerization or disproportionation as shown below.

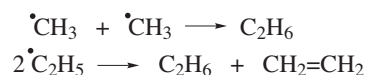


Figure 12: Dimerization and disproportionation reactions

4. Rearrangement

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

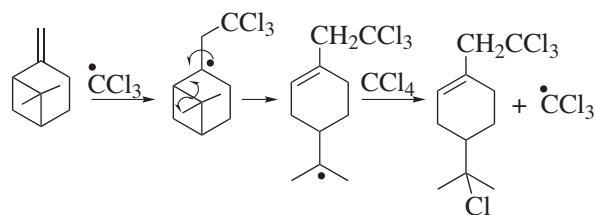


Figure 13: Rearrangement of a strain system

Unlike carbocations, radicals seldom rearrange to become more stable.

Some Applications

1. Chlorination of alkanes

Molecular chlorine and bromine form radicals by thermal or photochemical methods. Chlorination and bromination of alkanes takes place in both gas and liquid phase. Chlorination of methane is carried out thermally at rather high temperatures (250 - 300 °C) by the homolytic cleavage of the Cl-Cl bond (initiation

step).

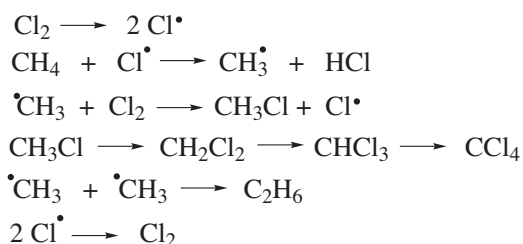


Figure 14: Chlorination of methane

Homolytic dissociation of Br_2 can be achieved at room temperature by irradiation. Conversion of cyclohexane to cyclohexyl chloride is shown in Figure 15.

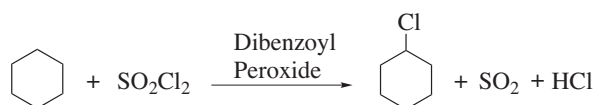


Figure 15: Chlorination of cyclohexane

2. Polymerization of alkenes

Free radical polymerization proceeds with three fundamental steps: initiation, propagation and termination.

The initiation step involves in the generation of active radical species (R^\bullet). The most common radical initiators are benzoyl peroxide and AIBN. The active radical species (R^\bullet) reacts with a monomer (M) to give RM^\bullet . This initiation step is considered to be the rate limiting step. In propagation, the polymer chain grows by successive addition of monomers to give $\text{R}(\text{M})_{n-1}\text{M}^\bullet$. The quenching of the active radicals ends the propagation process. The termination can occur in different ways; *via* combination or abstraction of H^\bullet or another radical (R'^\bullet) to produce $\text{R}(\text{M})_{2n}\text{R}$ or $\text{R}(\text{M})_n\text{H}$ or $\text{R}(\text{M})_n\text{R}'$. The termination can also take place via a disproportionation process.

3. Coupling of alkynes

The coupling reaction of mono-substituted acetylenes is catalyzed by $\text{Cu}(\text{II})$ ions in the presence of pyridine to give diynes as shown in Figure 16. This is called Glaser coupling, which is also similar to Hay coupling of acetylenes.

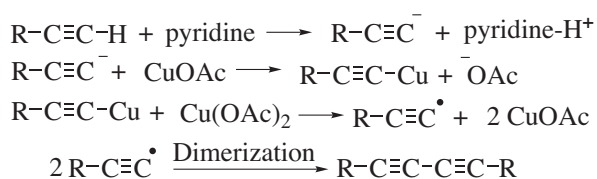


Figure 16: Coupling of acetylenes

4. Hunsdiecker Reaction

The silver salts of carboxylic acids react with halogens forming unstable intermediates which readily undergoes thermal decarboxylation to form alkyl halides.

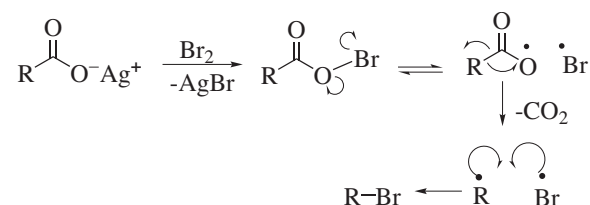


Figure 17: Conversion of RCO_2H to RBr

Similar silver-catalyzed decarboxylative bromination of aliphatic carboxylic acids is given Figure 18.

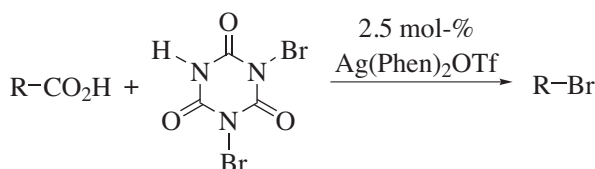


Figure 18: Decarboxylative Bromination

Role of free radicals in biology

Free radicals are produced in cells as by products, particularly due to oxidative phosphorylation in mitochondria. Superoxide anion radical is one of the most common radical which is formed by auto-oxidation, enzymatic and non-enzymatic electron transfer processes.

Homolysis of chemical bonds accompanied by the formation of other bonds leads to forming free radicals in the cells. Both ROS and RNS are produced from endogenous sources (mitochondria, peroxisomes, endoplasmic reticulum, phagocytic cells) and exogenous sources (pollution, alcohol, tobacco smoke, heavy metals, transition metals, industrial solvents, and pesticides, certain drugs like halothane, paracetamol and radiation). Excess production of oxygenated free radicals leads to oxidative stress which damages the integrity of many biomolecules including lipids, proteins and DNA. Oxidative stress results in various human diseases: respiratory, cardiovascular, diabetes mellitus, cataracts and rheumatoid arthritis.

Radical inhibitors

Radical inhibitors are compounds capable of stopping

the propagation step thereby terminating the radical chain reaction, e.g., hydroquinone (HQ), 4-*tert*-butylcatechol (TBC), 4-methoxyphenol, 2,6-di-*tert*-butyl-4-methylphenol (BHT), etc.

Alkyl Metal Complexes

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An alkyl-metal complex has at least one Metal Carbon (M-C) σ - or π -bond. Grignard reagent (RMgX) and LiR are the most common alkyl-metal reagents used in organic synthesis. ZnEt₂ and EtZnI are the first metal alkyls prepared by Edward Frankland in 1848.

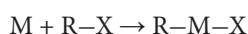
Synthetic routes to metal alkyls (M-R)

There are many ways to synthesize metal-alkyls. Here, the appropriate aliphatic, alkenyl, alkynyl, and aryl groups are considered as alkyl groups (R).

1. By reacting a metal directly with RX

This can be considered as an oxidative addition of an organic halide to a zerovalent metal.

With divalent metals

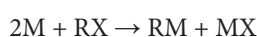


Some examples are given below.

- Mg + PhI \longrightarrow PhMgI (Grignard reagent)
- Zn + EtI \longrightarrow EtZnI
- Hg + CH₂=CHCH₂I \longrightarrow CH₂=CHCH₂HgI
- Ca + MeI \longrightarrow MeCaI

Note that structures of some of these reagents are not *monomeric*.

With monovalent metals

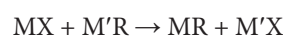


The order of the reactivity of organic halides is as follows.



2. via Transmetallation

Alkylating agents (containing transferable alkyl groups) can be used to prepare other organometallic compounds as shown below.



Magnesium, lithium, aluminium and mercury alkyls are some of the common alkylating agents. This transfer of an alkyl group from one metal to another is known as **transmetallation**.

Some reactions are given below.

- [PtBr₂(PPh₃)₂] + 2 EtMgBr \longrightarrow [PtEt₂(PPh₃)₂]
- TiCl₃ + 3 LiMe \longrightarrow TiMe₃ + 3 LiCl
- [Cp(OC)₂RuBr] + HgPh₂ \longrightarrow [Cp(OC)₂RuPh] + PhHgBr
- [Cp(OC)₂RuBr] + LiMe \longrightarrow [Cp(OC)₂RuMe] + LiBr
- [Cp₂TiCl₂] + 2 LiMe \longrightarrow [Cp₂TiMe₂] + 2 LiCl
- [Cp₂TiCl₂] + AlMe₃ \longrightarrow [Cp₂TiCl(Me)] + AlClMe₂
- WCl₆ + 6 AlMe₃ \longrightarrow [WMe₆] + 6 AlClMe₂

AlR₃ usually transfer only **one alkyl** group.

The nucleophilicity of the R⁻ varies as given below.



3. via Oxidative addition

Alkyl and aryl halides add to coordinatively unsaturated transition metal centres to form metal-carbon bonds. Some examples are given below.

- [IrCl(PPh₃)₃] + MeI \longrightarrow [IrCl(I)(Me)(PPh₃)₃]
- [Fe(CO)₅] + MeC(=O)CH₂Br \longrightarrow [(MeCOCH₂)FeBr(CO)₄]
- [Pd(PPh₃)₄] + CH₂=CHBr \longrightarrow *trans*-[PdCl(CH=CH₂)(PPh₃)₂]

Oxidative addition of a C-H bond of a coordinated ligand generates a metallacycle with a M-C bond.

4. via Reacting with an electrophile

Some complexes have *nucleophilic* (π -basic) metal