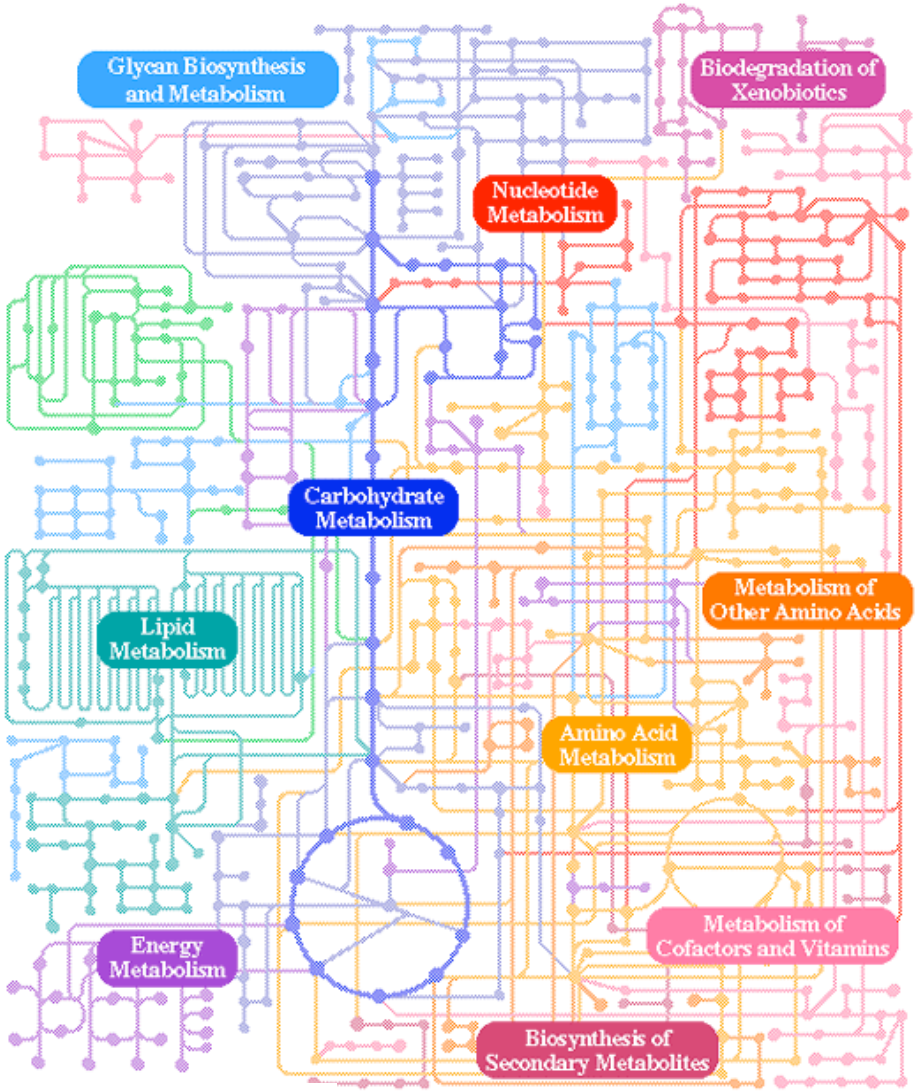
# Chemistry and Introduction to Biochemistry
## Chemical reactivity

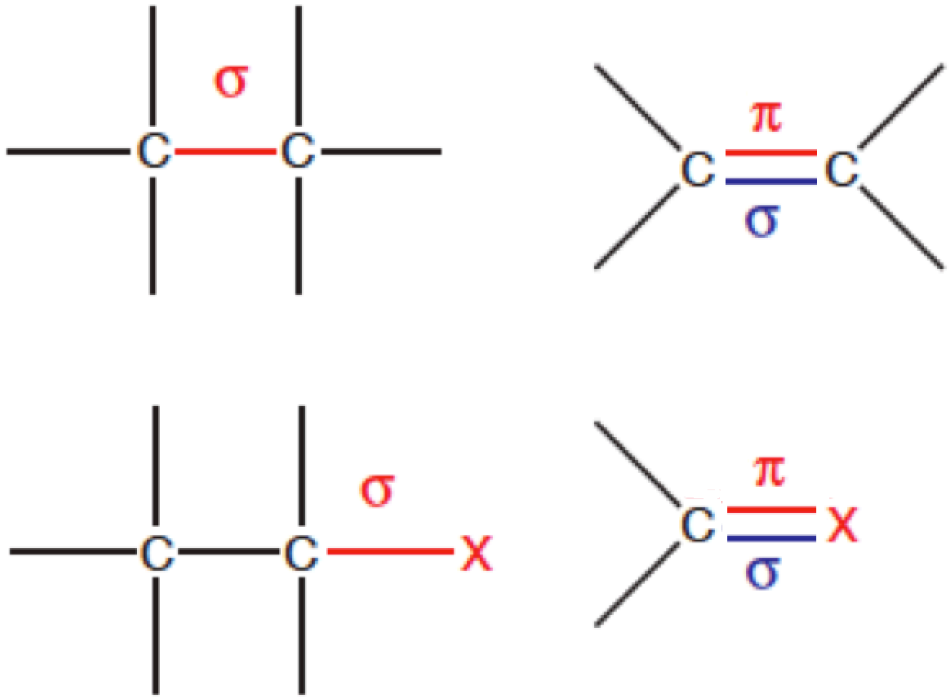


# The reactivity of organic compounds

The reactivity of a molecule is the ability to react and therefore to transform into other compounds.

This chemical behavior is related to the structure of the molecule:

- bond type
- bond polarity
- orbitals and geometry



# Electrophilic and nucleophilic reagents

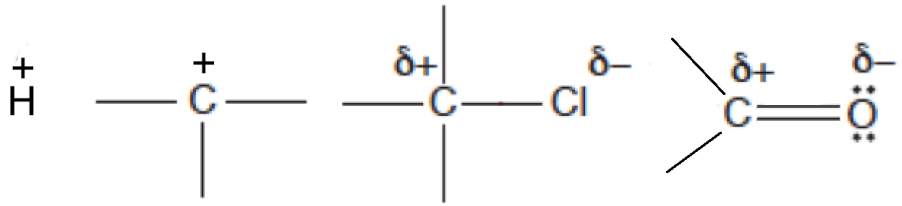
An electrophile (a Lewis acid):

- a chemical species bearing a positive (+) or partially positive (δ+) charge and must be capable of *accepting a pair of electrons* to form a covalent bond

A nucleophile (a Lewis base):

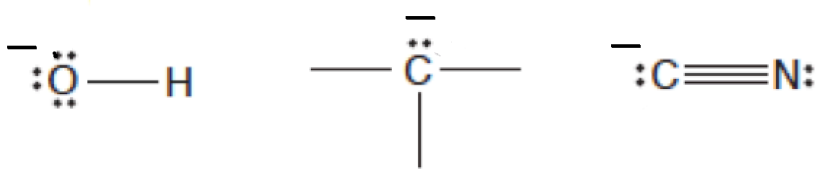
- it is a chemical species that reacts *by donating an electron pair* to another species (electrophile) and forming a covalent bond.

electrophiles



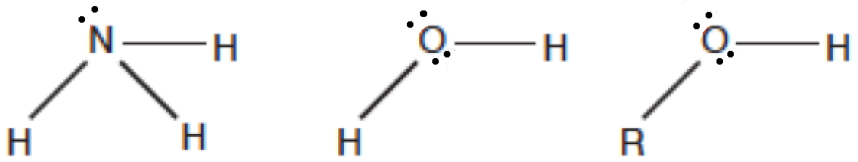

carbocation carbonyl

carbanion




anionic nucleophiles

nucleophiles



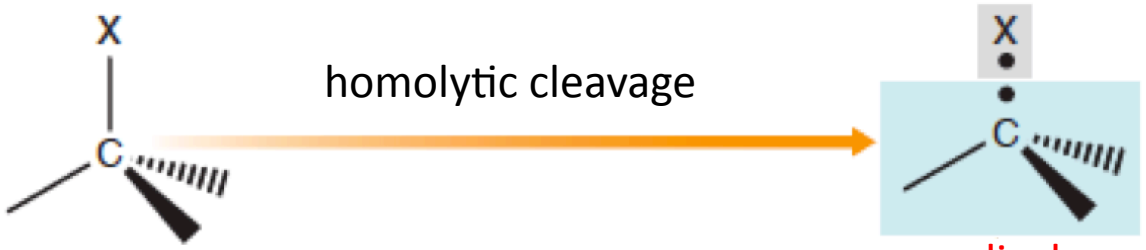

neutral nucleophiles

# Reactivity of organic compounds containing simple bonds σ

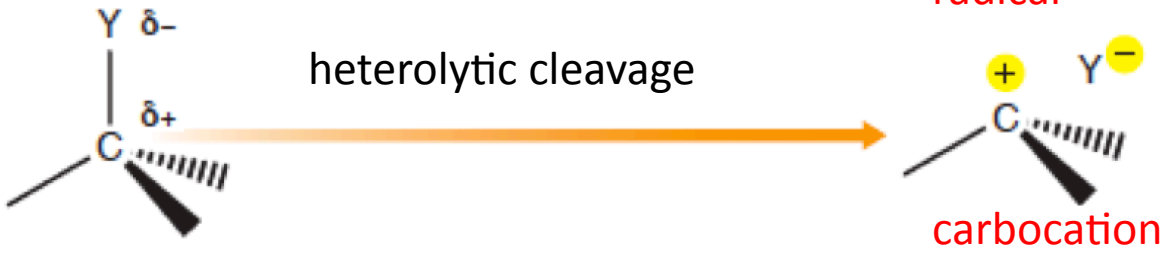
Organic compounds can be characterized by single covalent bonds of σ type in which a C atom is bound to an atom X (Y or Z) that can be C, H or other atom.

It is possible to foresee at least three different types of cleavage of the single bond that unites the C to another atom that depends on the difference of electronegativity between the C and the atom to which it is linked to

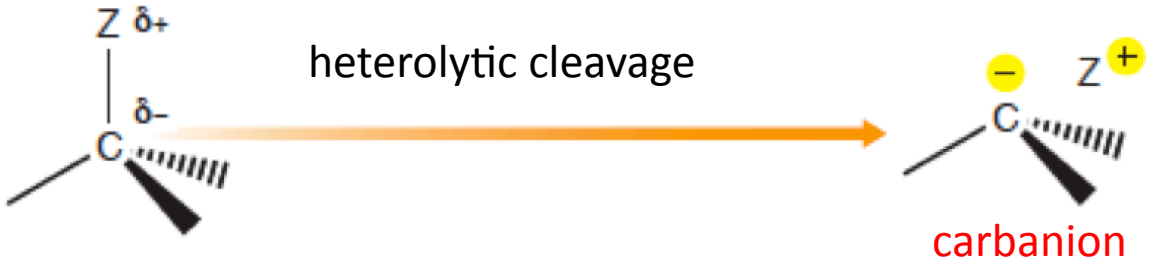
similar electronegativity of C and X




electronegativity of C < Y




electronegativity of C < Z

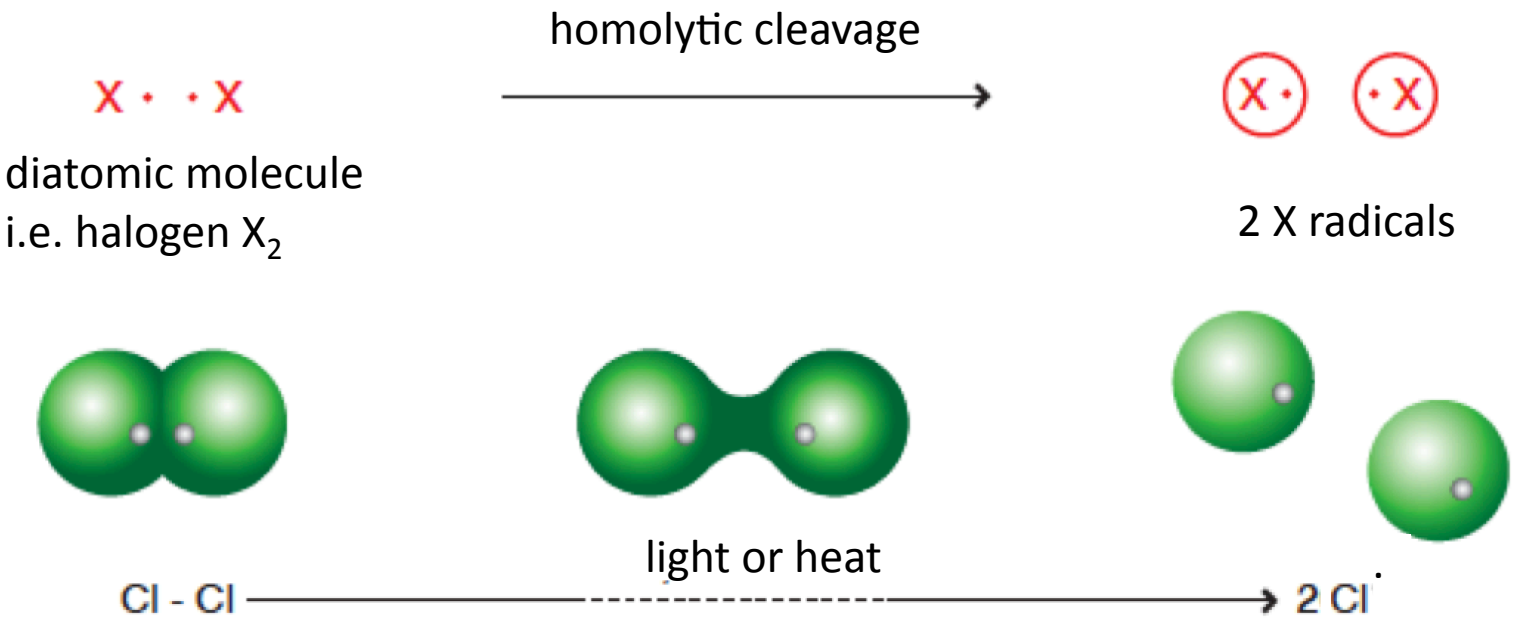


# Radical reactions

• a radical  or free radical can be a very reactive monoatomic or molecular species and is characterized by the presence of an unpaired electron in the most external orbital.

• radicals are unstable because the species needs to acquire an additional electron to achieve electronic stability: a radical tends to reduce, because it is strongly oxidizing

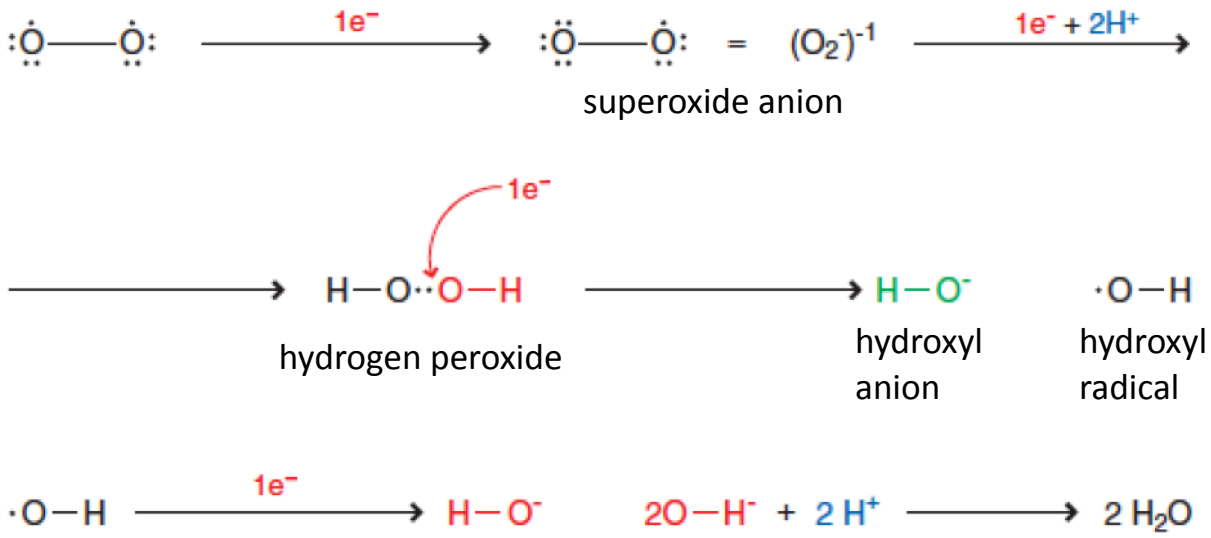
• radicals are also present in living organisms at very low concentrations and are characterized by a very short average life (half-life: < milliseconds)



# Oxygen reaction species (ROS)

Concentrations and $t_{1/2}$ of some ROS

| | | In vivo concentration (mol/L) | $t_{1/2}$ (s) |
|---|---|---|---|
| $O_2^{\bullet -}$ | reductant & oxidant | $10^{-10}$ | $10^{-6}$ |
| $HO_2^{\bullet}$ | intermediate reactivity | $10^{-9}$ | $10^{-6}$ |
| $H_2O_2$ | apolar | $10^{-8}$ | $10^{-5}$ |
| $OH^{\bullet}$ | the most toxic | $10^{-15}$ | $10^{-9}$ |

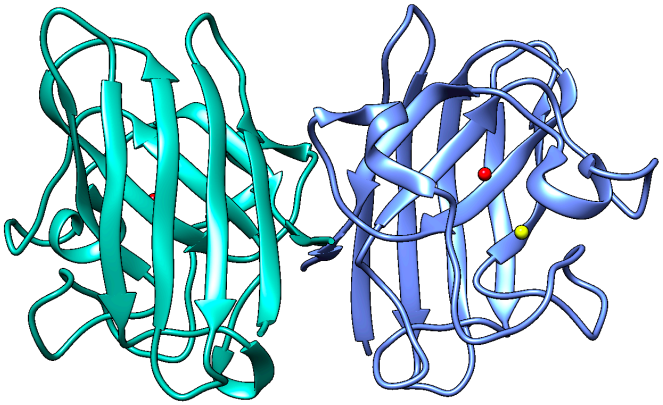



global reaction: $O_2 + 4\ H^+ + 4\ e^- = 2\ H_2O$

# Enzymatic defense systems

superoxide dismutase

$$2\ O_2^- + 2\ H^+ \rightarrow O_2 + H_2O_2$$



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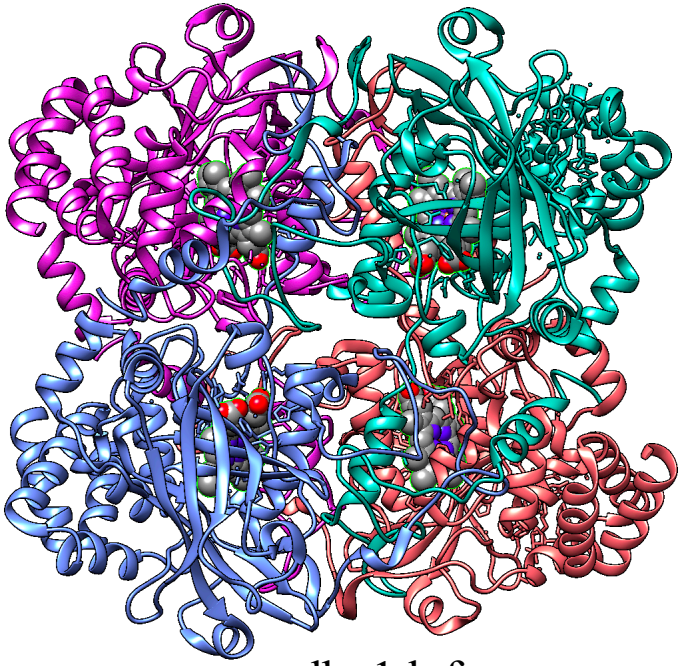
catalase ($H_2O_2$ dismutase)

$$2\ H_2O_2 \rightarrow O_2 + 2\ H_2O$$



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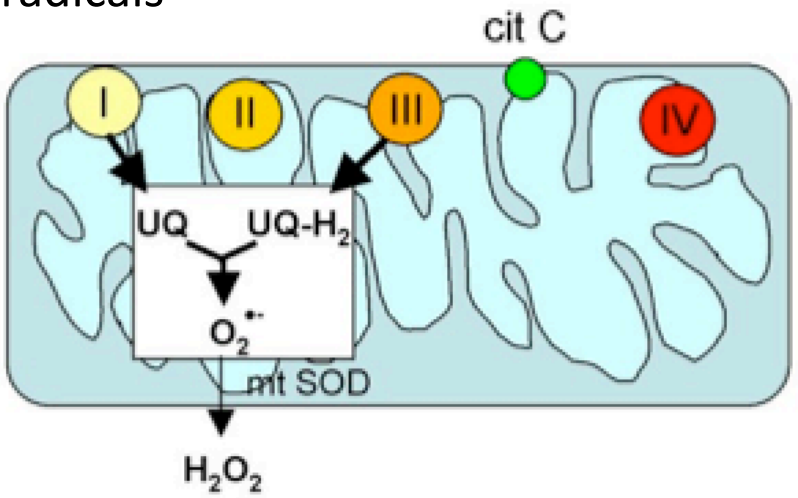
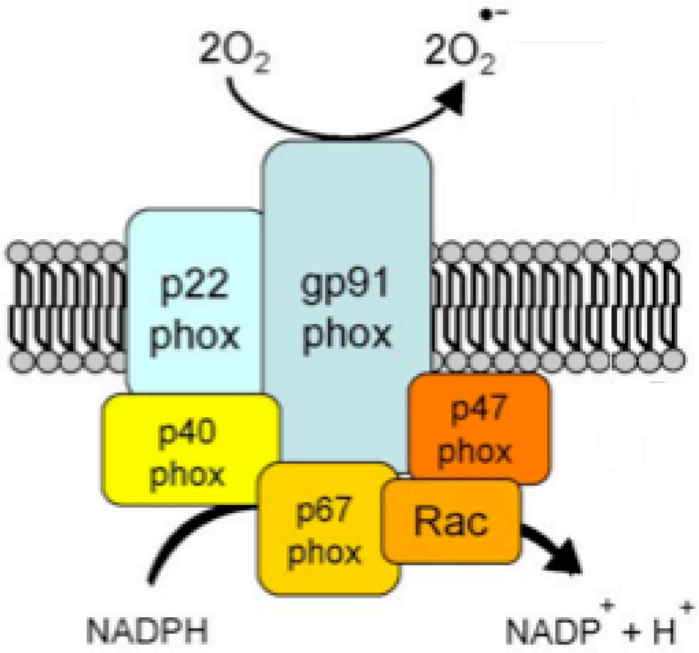
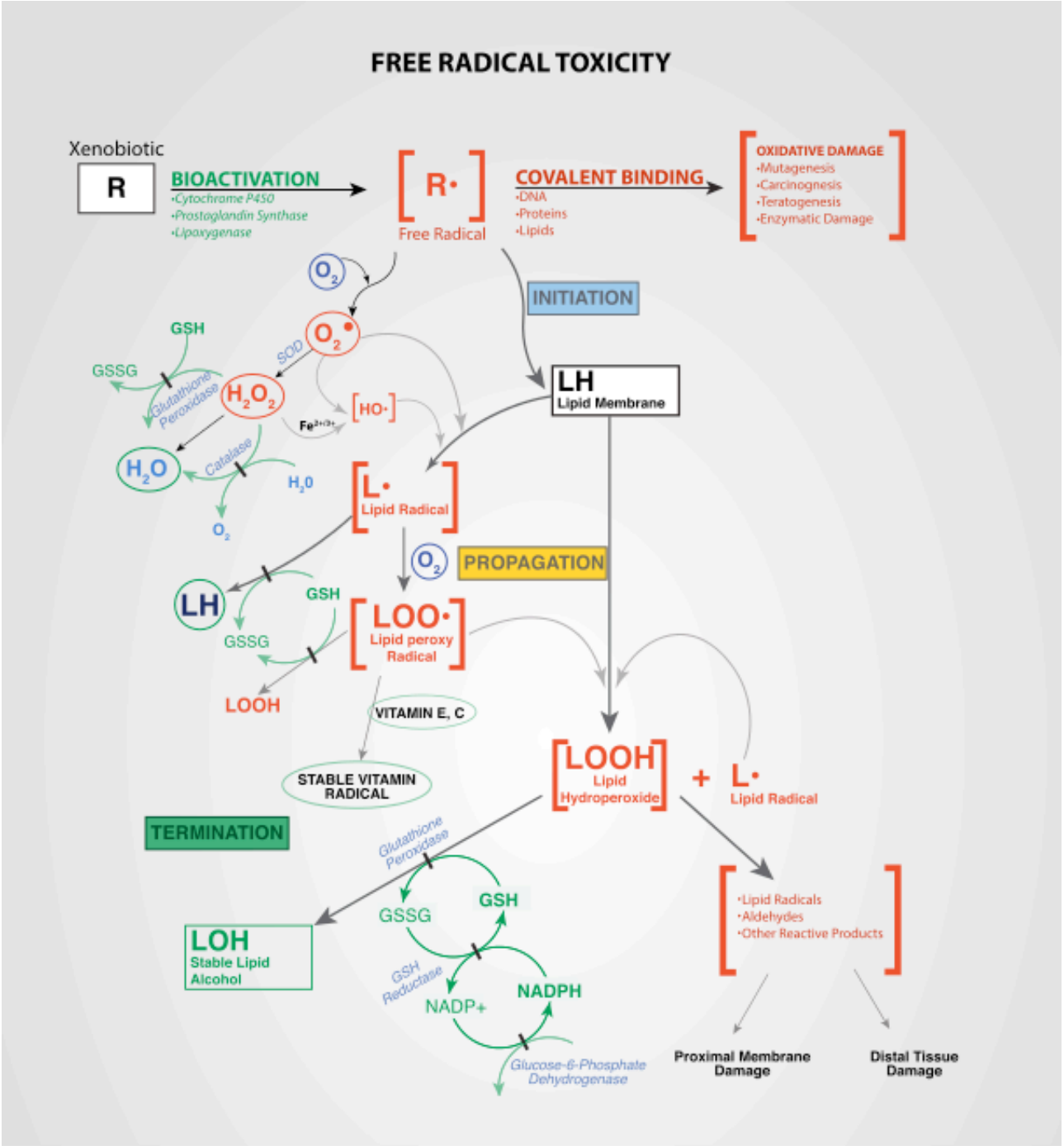
Endogenous production of radicals

mitochondria

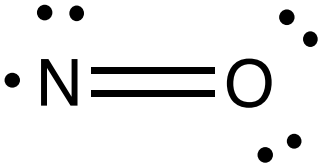



phagocytic cells:
NADPH oxidase



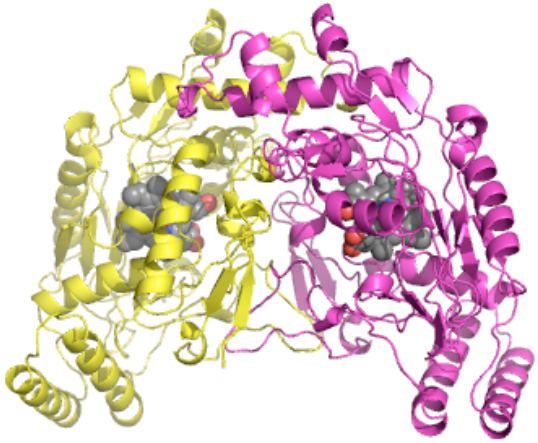

FREE RADICAL TOXICITY
Xenobiotic
R
BIOACTIVATION
•Cytochrome P450
•Prostaglandin Synthase
•Lipoxygenase
R•
Free Radical
COVALENT BINDING
•DNA
•Proteins
•Lipids
OXIDATIVE DAMAGE
•Mutagenesis
•Carcinogenesis
•Teratogenesis
•Enzymatic Damage
INITIATION
LH
Lipid Membrane
GSH
GSSG
Glutathione Peroxidase
SOD
H2O2
HO•
Fe2+/3+
H2O
Catalase
H2O
O2
L•
Lipid Radical
PROPAGATION
LOO•
Lipid peroxy Radical
LOOH
VITAMIN E, C
STABLE VITAMIN RADICAL
LOOH
Lipid Hydroperoxide
+
L•
Lipid Radical
TERMINATION
Glutathione Peroxidase
LOH
Stable Lipid Alcohol
GSSG
GSH
GSH Reductase
NADP+
NADPH
Glucose-6-Phosphate Dehydrogenase
•Lipid Radicals
•Aldehydes
•Other Reactive Products
Proximal Membrane Damage
Distal Tissue Damage

# An important radical: nitric oxide (NO)



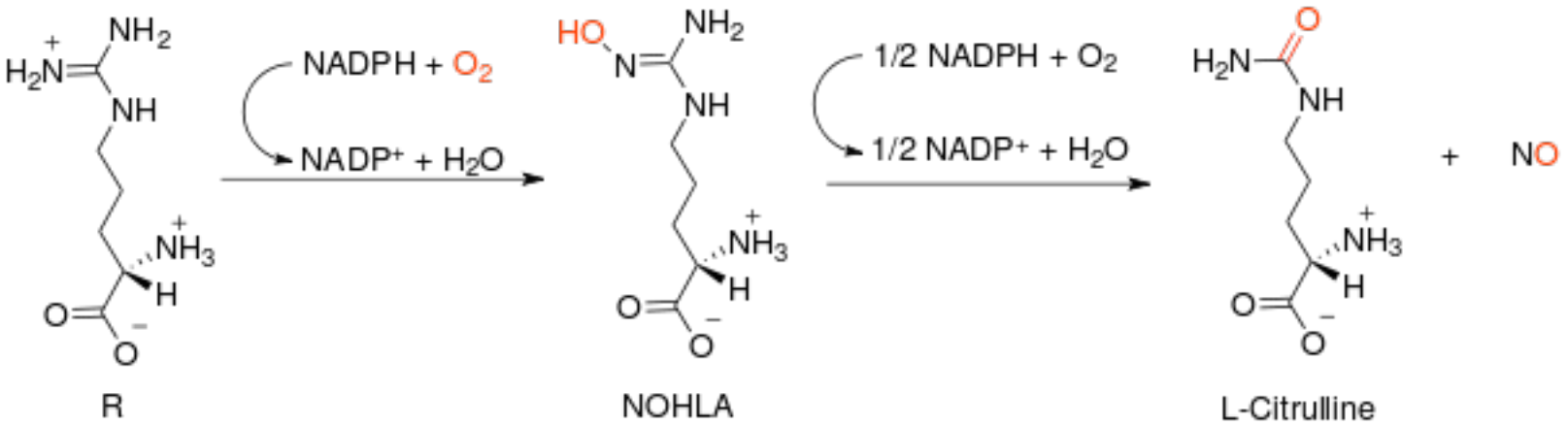

NO is an important cellular signaling molecule:

- modulates vascular tone
- insulin secretion
- peristalsis
- angiogenesis
- neural development.



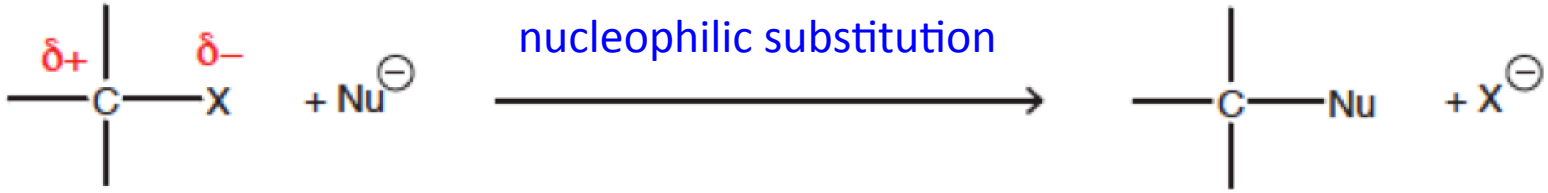
Nitric oxide synthase

2 L-arginine + 3 NADPH + $H^+$ + 4 $O_2$ ⇌ 2 citrulline +2 NO + 4 $H_2O$ + 3 $NADP^+$

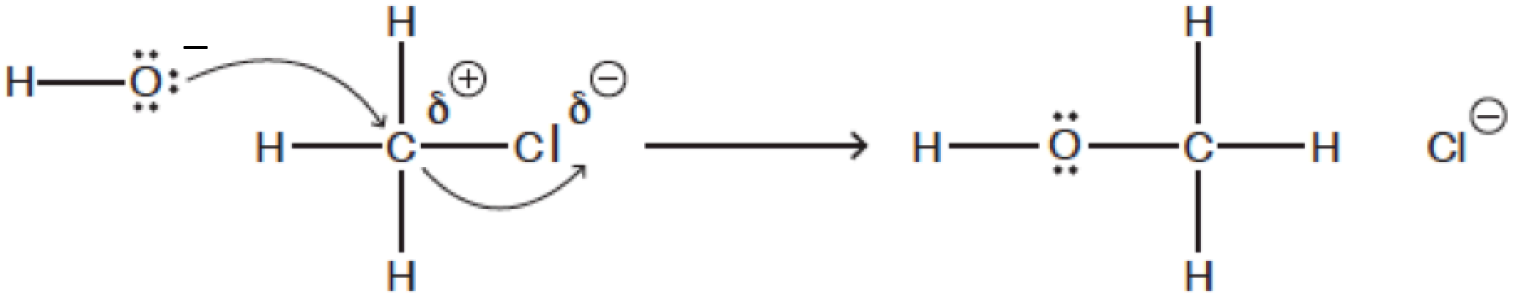


# Nucleophilic substitution reactions

A reaction in which a C atom in a molecule is bound to a more electronegative X group (hence with a polarized covalent bond) can react with a nucleophile Nu, and expel the X group (leaving group).



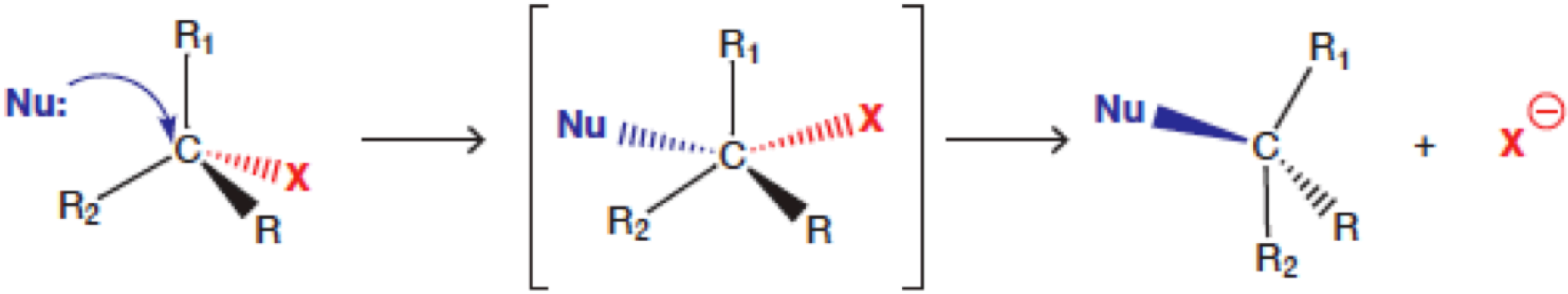

in the C-X bond, X is more electronegative than C



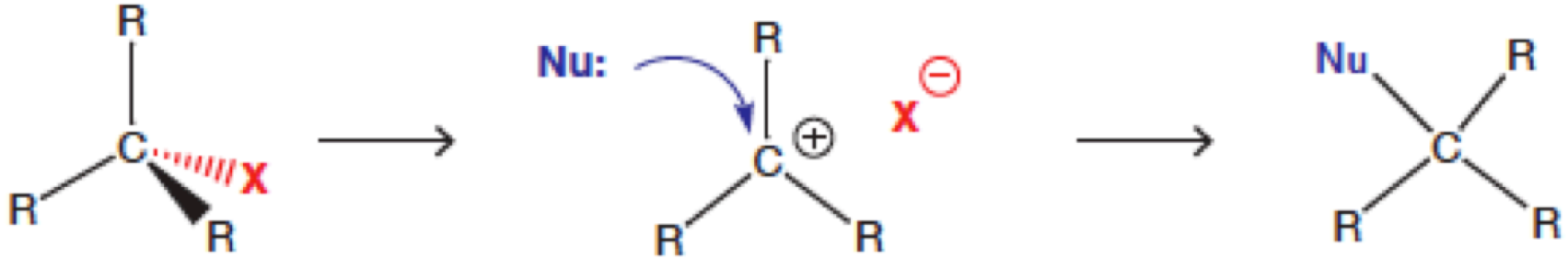

chloromethane methanol

# Mechanisms

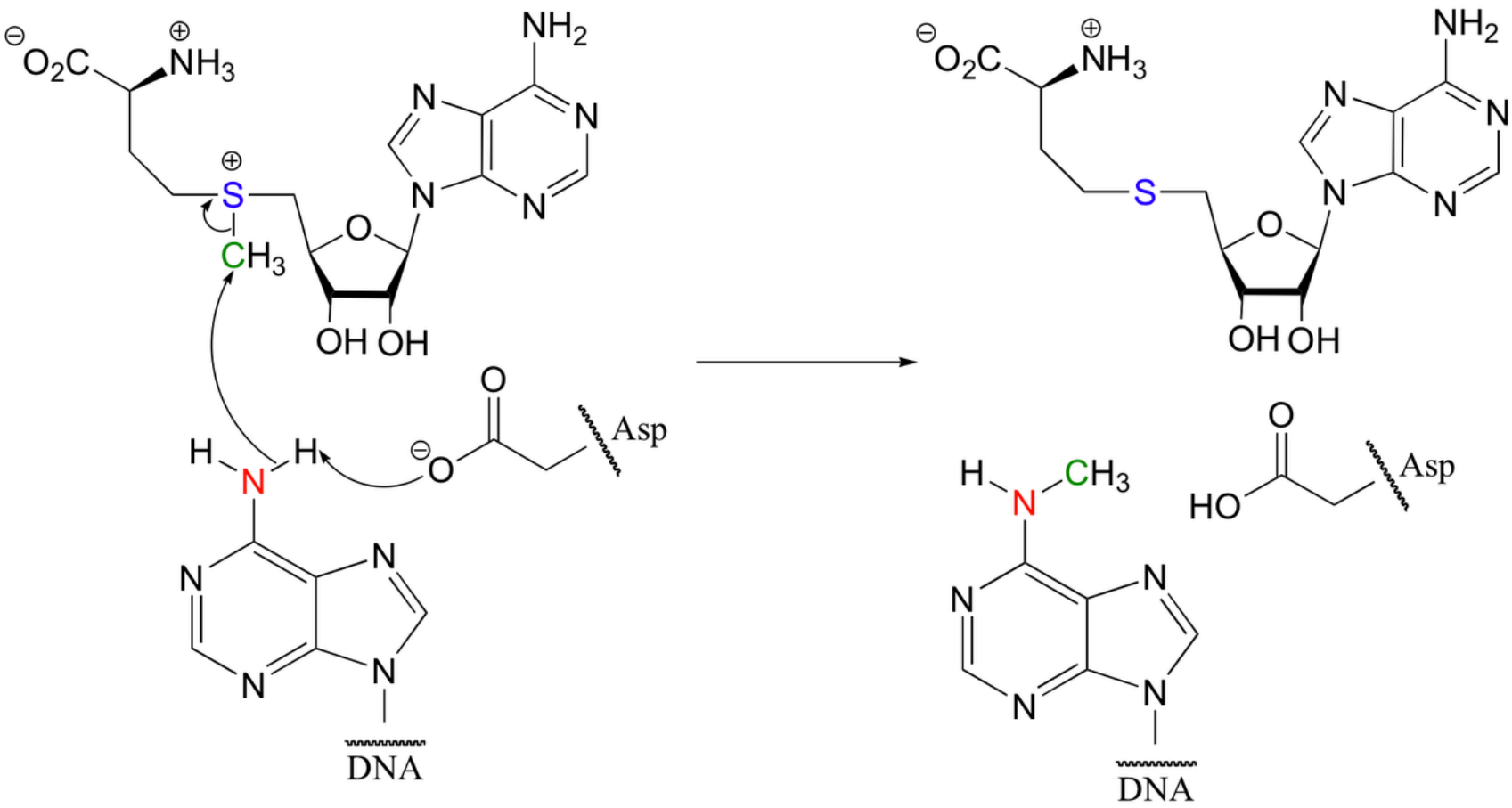
## $S_N2$




## $S_N1$



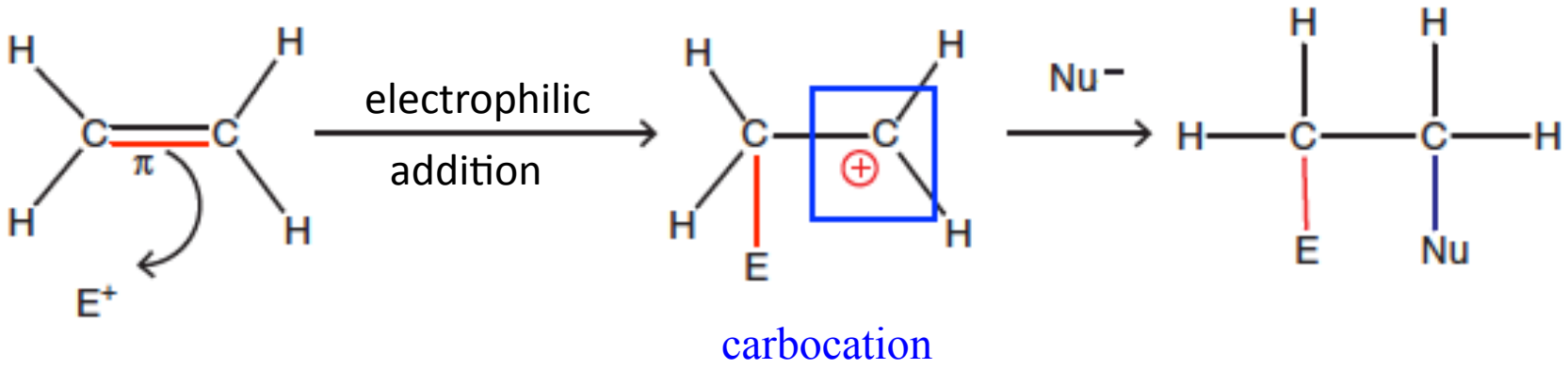
Some of the most important examples of $S_N2$ reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes.



# Reactivity of π-bond containing compounds: electrophilic addition

Alkenes are unsaturated hydrocarbons characterized by the presence of at least one double bond in the molecule: the two C-linked atoms are hybridized $sp^2$ and the two bonds are of a different chemical nature (σ and π)

Alkenes are planar and rotation around the double bond is not possible.
The two π electrons are accessible both in the upper and lower half-space one with respect to the plane of the molecule: they are thus easily attacked by electrophiles.

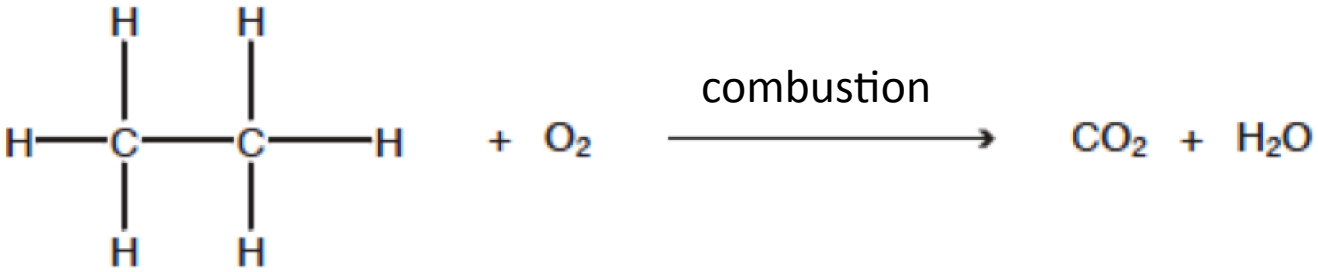



carbocation

# Reactions of the main classes of organic compounds

## Reactions of the alkanes

combustion




ethane

$2\ C_2H_6 + 7\ O_2 = 4\ CO_2 + 6\ H_2O$

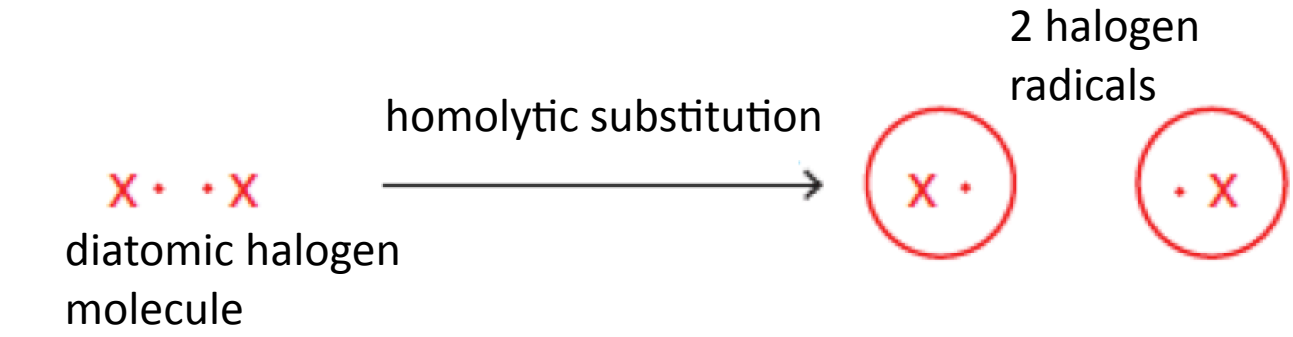
balanced reaction

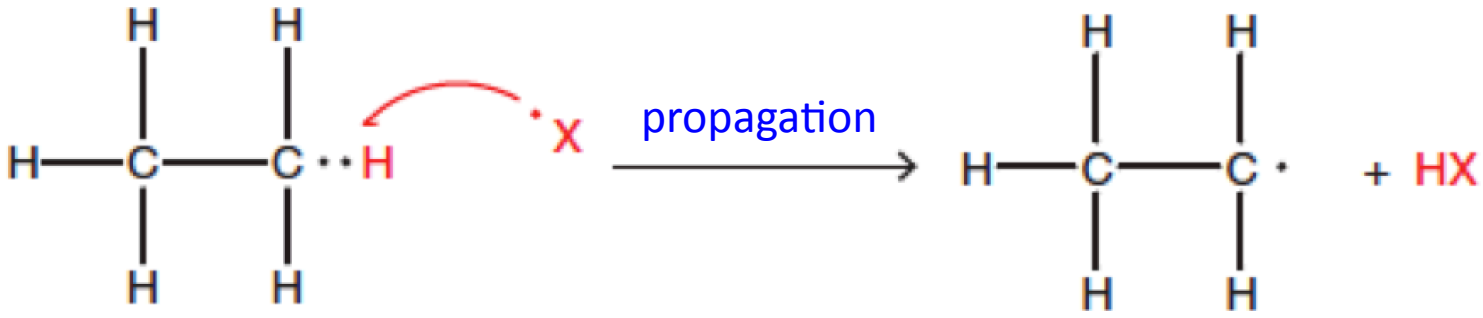
The combustion reaction of a generic alkane $C_nH_{2n+2}$ is as follows:

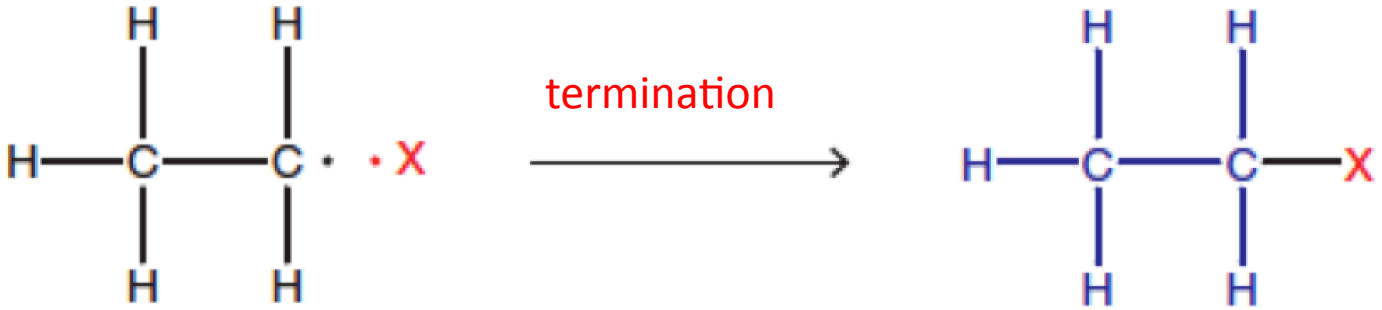
$$C_nH_{2n+2} + [(3n+1)/2]\ O_2 = n\ CO_2 + (n+1)\ H_2O$$

# Reactions of the alkanes

## Radical substitution

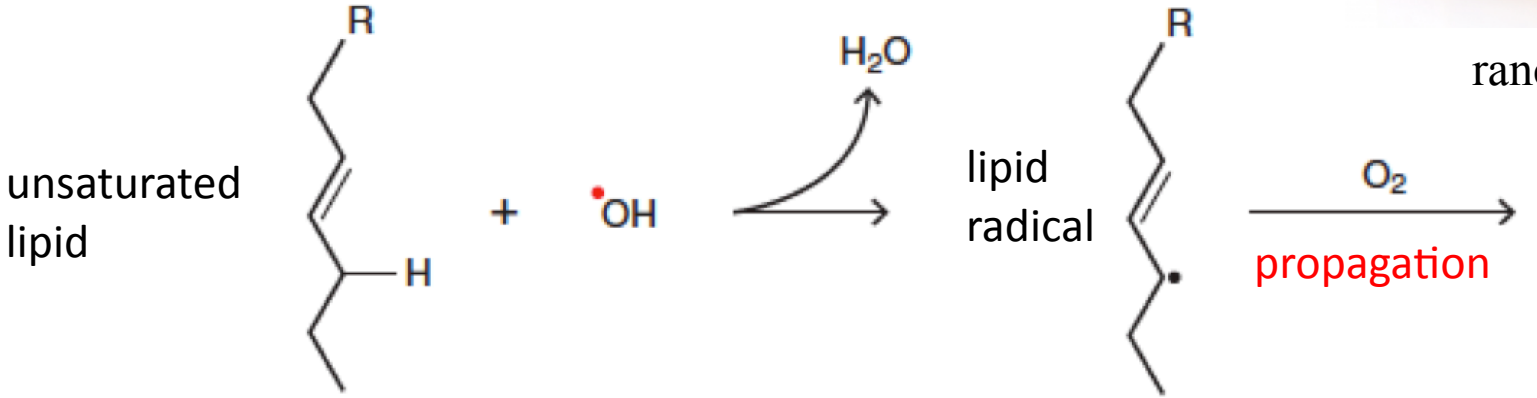


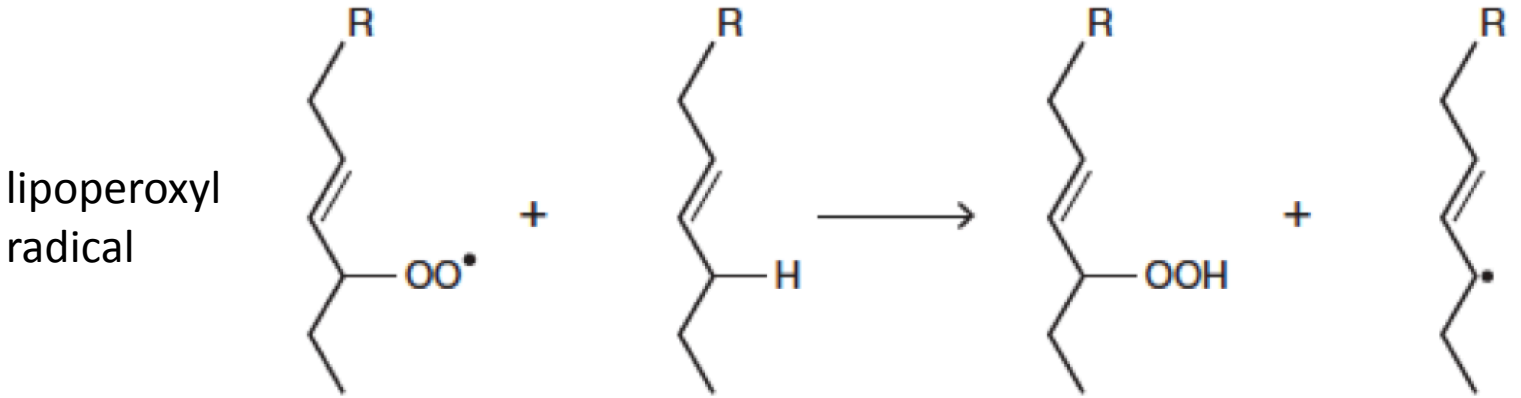



# Lipid peroxidation and ROS

rancid butter

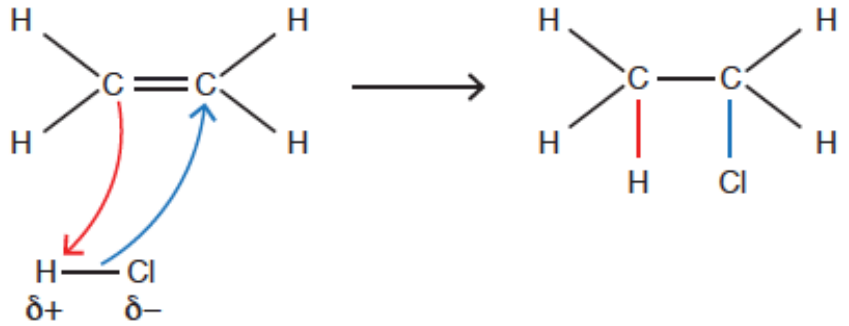


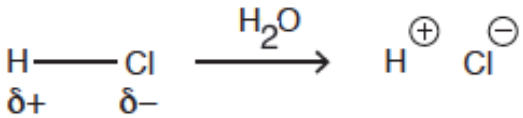

lipoperoxide radical

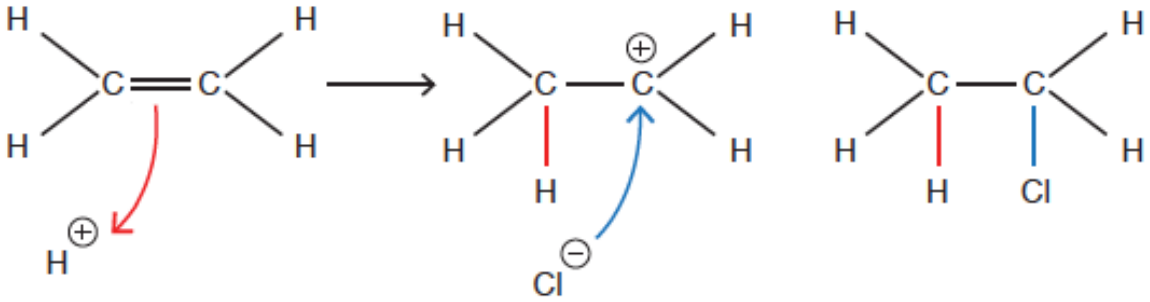
# Alkenes reactions: electrophilic addition reaction

The typical reaction that highlights the reactivity of an alkene is a sum reaction of the type A + B = C, defined as an electrophilic addition reaction since it starts with an electrophile attack to the double bond.




gas phase

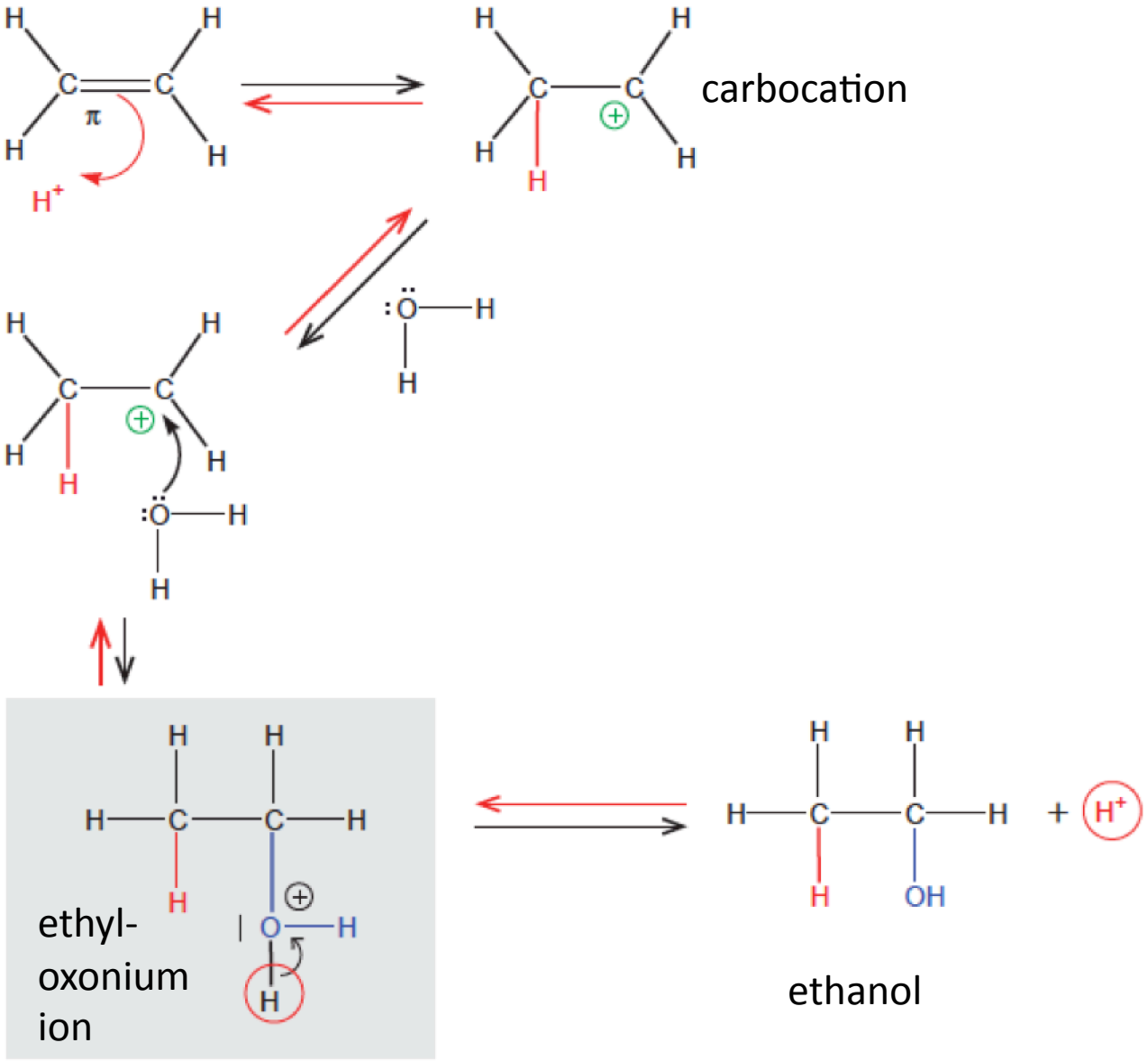


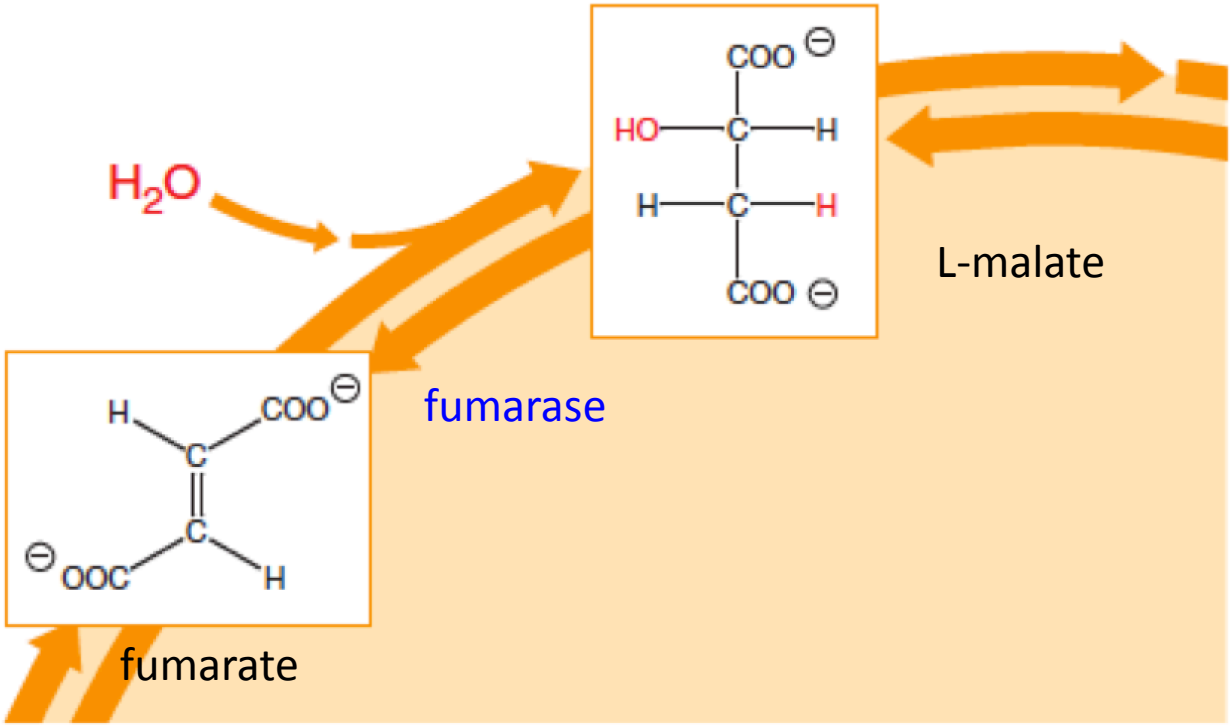

in water

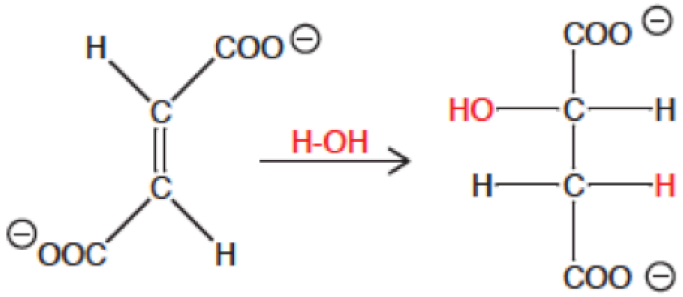
The carbocation is such a strong elettrophile to attract the very poor nucleophile chloride

# Alkenes reactions: water addition reaction

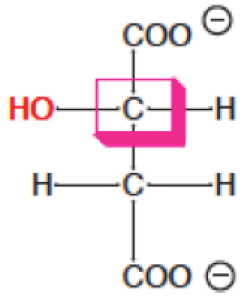


# An hydration reaction in the Krebs cycle

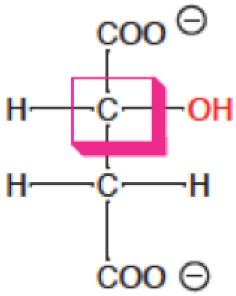



fumarate L-malate



L-malate



D-malate