Terminology

Lipid Oxidation and Lipid peroxidation

Free Radicals and Reactive oxygen species

Fatty acyl group and methylene group

Hydroperoxides and lipid peroxides

Peroxyl radicals and alkoxyl radicals

Oxidation and reduction

Homolytic and heterolytic fission

Fenton Reaction

Haber-Weiss reaction (Metal-catalyzed Fenton reaction)

Ferryl and perferryl

Heme and non-heme iron

Ischemic conditions

Types of Free Radicals

Reactive Oxygen Species

Peroxyl, alkoxyl rdaicals, and Lipid (alkyl) radicals

Thiyl radicals

Nitric oxide radical

Carbon-centered radicals

Reactive Oxygen Species

Ground-state oxygen ($^3O_2$)

Superoxide anion (O_2^-)

Singlet oxygen ($^1O_2$)

Ozone (O_3)

Hydrogen peroxide (H_2O_2)

Hydroperoxyl radical (HO2.)

Hydroxyl radical ($OH^\cdot$)

Free Radical Half-Life at 37°C

Radical	Symbol	Half-Life Time
Hydroxyl	$.OH$	one nanosecond
Singlet Oxygen	$^1O_2$	one microsecond
Superoxide	$.O_2^-$	one microsecond
Alkoxyl	$.OL$	one microsecond
Peroxyl	$LOO.$	ten milliseconds
Nitric Oxide	$NO.$	few seconds

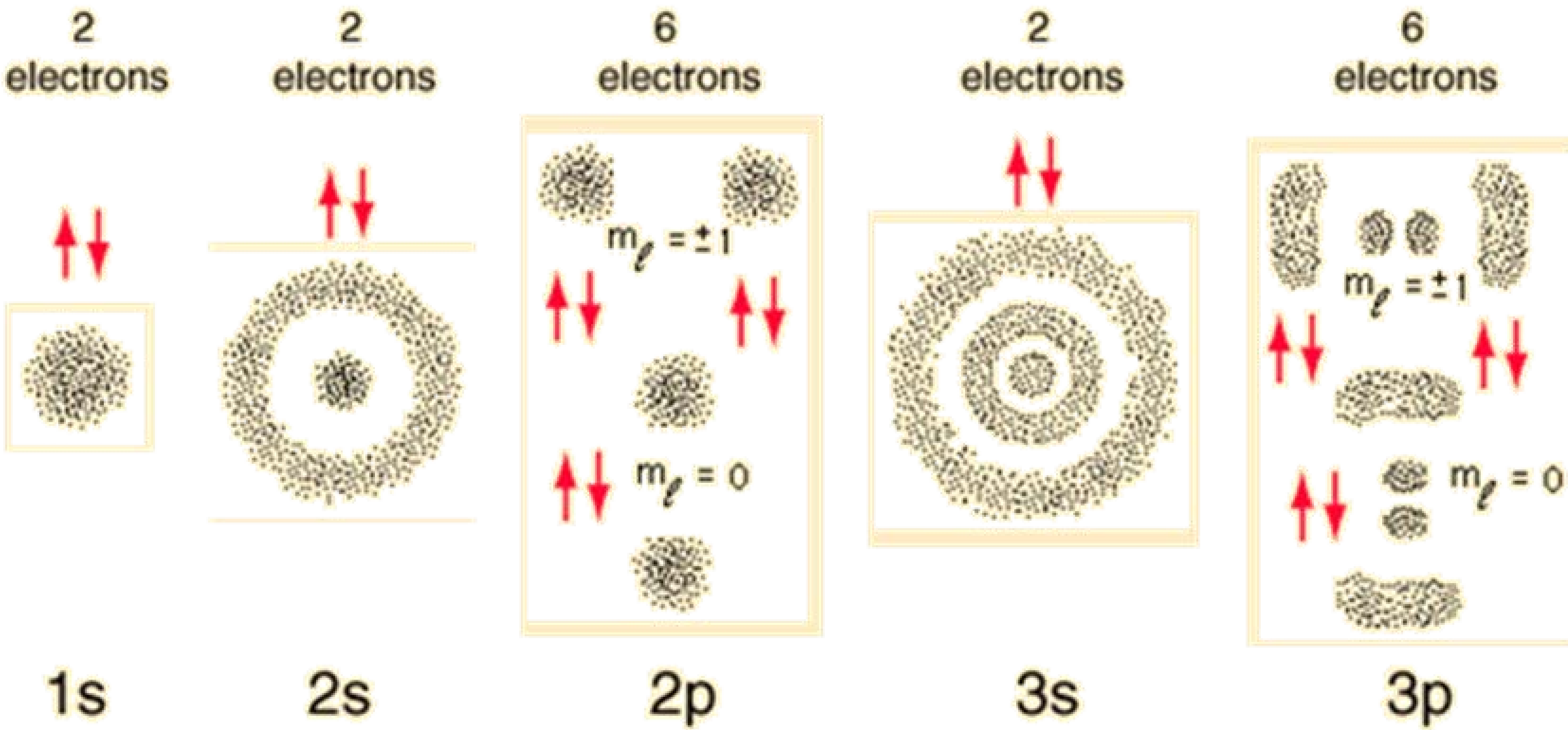
Orbitals

Electrons has some of the properties of a particle, and some of the properties of a wave motion

As a result, the position of an electron at a given time cannot be precisely located, but only the region of space where it is most likely to be.

These regions are referred to as orbitals

Sketches of the electron density for the first three shells



Orbitals available in the principal electron shells

Principal quantum number	Sublevels in main energy electrons level (n sublevel)	number of orbitals (n^2)	number of electrons	number of electrons per main energy per sublevel level ($2n^2$)
1	s	1	2	2
2	s	1	2	8
	p	3	6	
3	s	1	2	18
	p	3	6	
	d	5	10	
4	s	1	2	32
	p	3	6	
	d	5	10	
	f	7	14	

Quantum numbers

Four quantum numbers:

1. Principal quantum number (n):
   Indicates the main energy levels occupied by the electron
   Values of n are positive integers: n=1 is closest to the nucleus, and lowest in energy
   The number of orbitals possible per energy level is equal to n^2

2. Angular momentum quantum number
   Governs the shape of the orbitals
   number of orbital shapes = n: shapes are designated s,p,d,f

3. Spin quantum number
   Indicates the fundamental spin state of an electron in an orbital
   Two possible values for spin: +½ or -1/2
   A single orbital can contain only 2 electrons, which have opposite spin

Electron configuration

Aufbau Principle: An electron occupies the lowest energy orbital that can receive it.

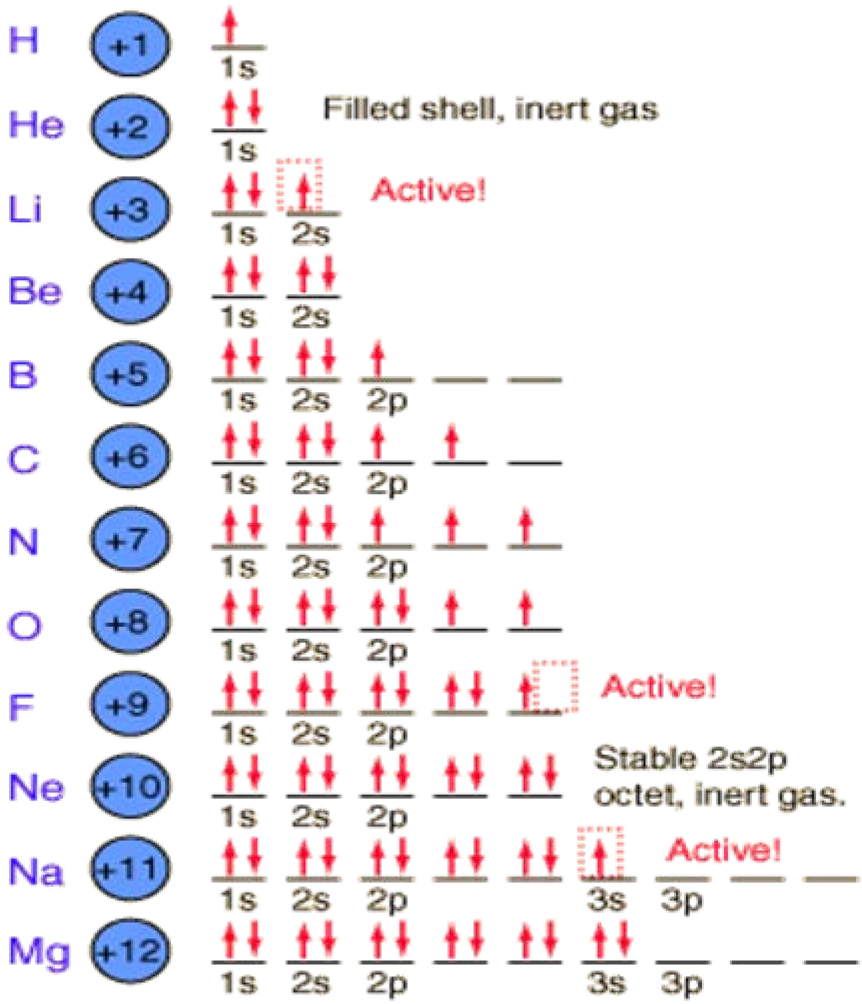
Hund's rule: If orbitals of equal energy are available (e.g., 2p orbitals in the L-shell), each is filled with one electron before any receives two. Also, all electrons in singly occupied orbitals must have the same spin.

Pauli's exclusion principle: an atomic orbital cannot contain more than two electrons.

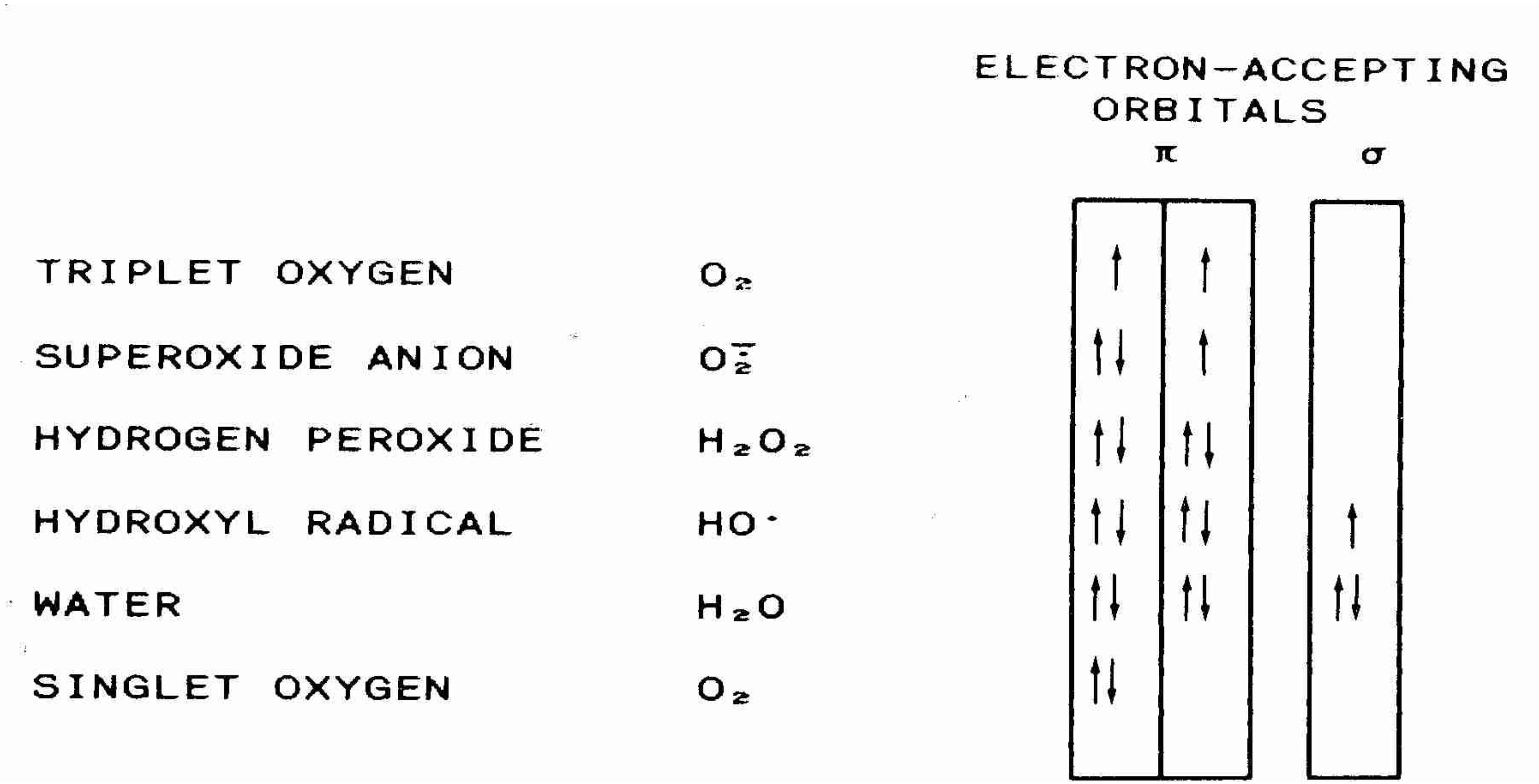
The order of electron filling

1s 2s 2p 3s 3p 4s 3d 4p 5s 4d 5p 6s 4f 5d 6p 7s 5f

Electron Configuration of Atoms

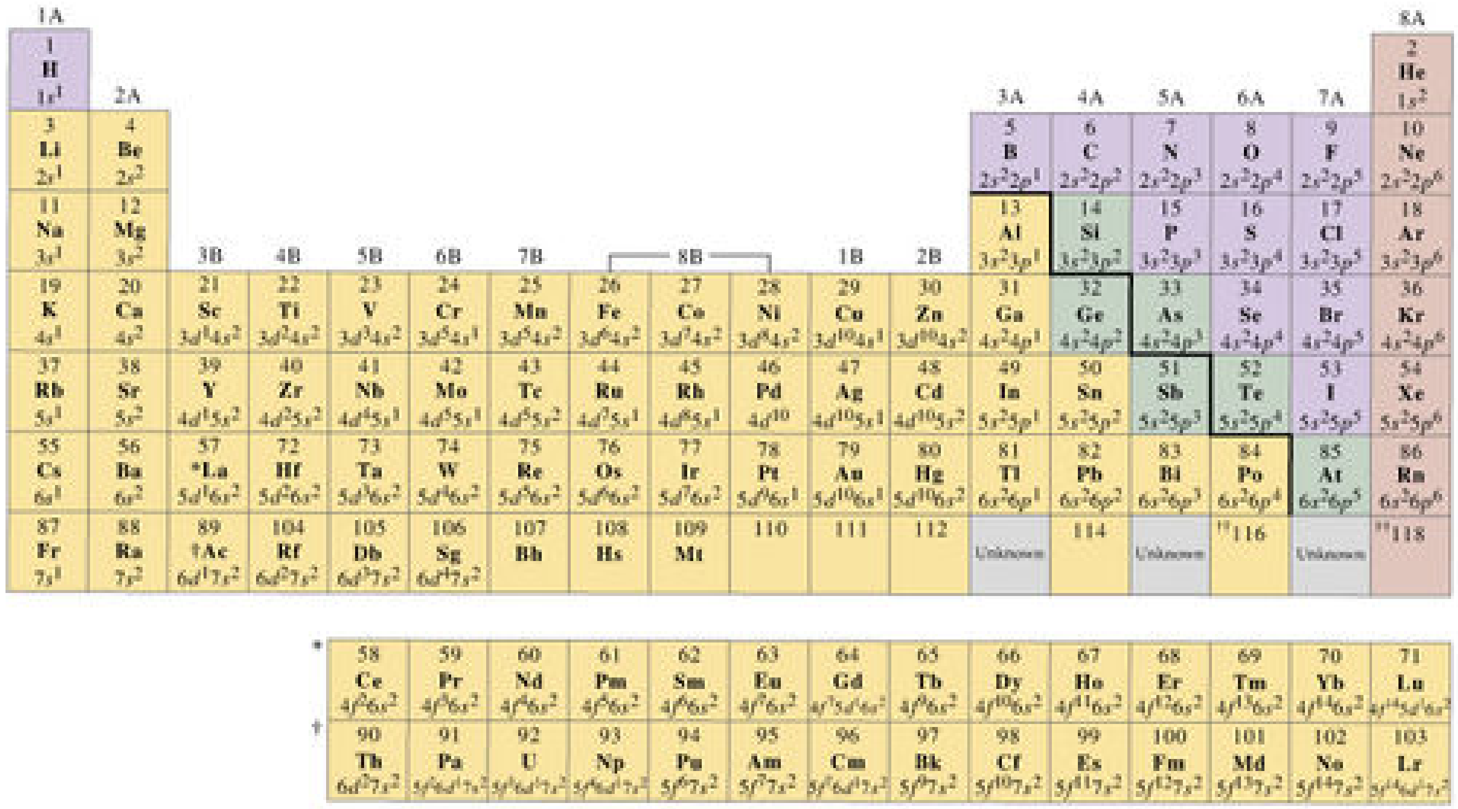


Electron States of ROS



Transition metal

Some of the d-block elements with their inner shell of electrons is not complete (the electrons in the fourth shell are filled, but all the d-orbitals of the third sell are not yet full)

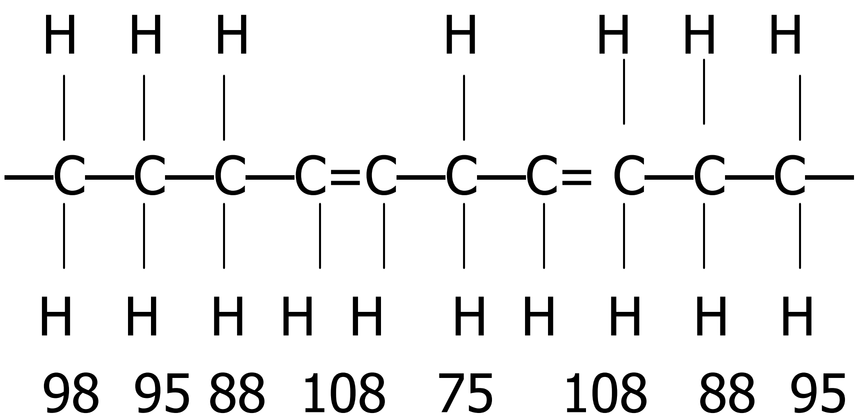


Bond Energy and Lipid Oxidation

Bond Strength (kcal/mol)

H-O-H, 119; RO-H, 104-105; ROO-H, ~90; Ar-H, 112; ArO-H, 85; NH_2-H, 107, RS-H, ~90; ArS-H, ~84

Bond energies in kcal/mol of C-H bonds in polyunsaturated fatty acids



Unsaturated fatty acids

Oleic acid: $CH_3(CH_2)_7\mathbf{CH{=}CH}(CH_2)_7COOH$

Alpha-linolenic acid:

$CH_3CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}(CH_2)_7COOH$

Linoleic acid: $CH_3(CH_2)_4\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}(CH_2)_7COOH$

Arachidonic acid

$CH_3(CH_2)_4\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}(CH_2)_3COOH$

Eicosapentaenoic acid

$CH_3CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}$
$(CH_2)_5COOH$

Docosahexaenoic acid

$CH_3CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH}$
$\mathbf{{=}CH}(CH_2)_3COOH$

Enzymatic peroxidation

Cyclooxygenase and lipoxygenase catalyze the reactions between oxygen and polyunsaturated fatty acids

The main function of enzymes are generating superoxide, which serves as a reducing agent for ferric iron complexes in microsomes

Enzymic lipid peroxidation in skeletal muscle microsomes is dependent on NADH or NADPH and requires ADP and Fe(II) or Fe(III) for maximum rate.

Iron(II) and its complexes stimulate membrane peroxidation more than does iron(III)

Photo-oxidation

A quicker reaction than autoxidation

Singlet oxygen is involved

In the presence of sensitizers: chlorophyll, porphyrins, myoglobin, riboflavin, bilirubin, erythrosine, rose bengal, methylene blue...

Inhibited by carotenoids: through an interference with the formation of singlet oxygen from the oxygen molecule

Tocopherols inhibit photo oxidation by quenching the previously formed singlet oxygen

Homolytic and heterolytic fission

Homolytic fission:

A**:**B -----> A**.** + B**.**

H_2O -----> HO**.** + H**.**

Heterolytic fission:

A:B -----> A**:**- + B^+

H_2O -----> HO^- + H^+

Function of Iron – Fenton Reaction

Fe^{2+}-dependent decomposition of H_2O_2 (Fenton reaction)

$Fe^{2+} + H_2O_2$ -----> Fe^{3+} + .OH + OH^-

$Fe^{2+} + H_2O_2$ -----> ferryl? -----> Fe^{3+} + .OH + OH^-

Sources of iron for the Fenton reaction *in vivo*: released iron from injured tissues by cell damages through toxin and other mechanisms

Haber-Weiss Reaction

$Fe^{3+} + O_2^- \text{----->} Fe^{2+} + O_2$

$\underline{Fe^{2+} + H_2O_2 \text{----->} Fe^{3+} + \mathbf{.}OH + OH^-}$

Net $O_2^- + H_2O_2 \text{----->} O_2 + \mathbf{.}OH + OH^-$

(metal-catalyzed Haber-Weiss reaction or superoxide-driven Fention reaction)

MECHANISMS OF FATTY ACID OXIDATION

Process of Lipid Oxidation - Autoxidation

Initiation

RH + (reactive oxygen species) $\cdot OH$ -->$R\cdot$ + H_2O

Propagation

$R\cdot + O_2$ ------> $ROO\cdot$

$ROO\cdot$ + RH ------> $R\cdot$ + ROOH

ROOH -------> $RO\cdot + HO^-$

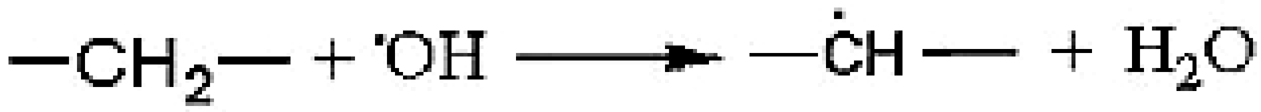
Termination

$R\cdot + R\cdot$ ------> RR

$R\cdot + ROO\cdot$ ------> ROOR

$ROO\cdot + ROO\cdot$ ------> $ROOR + O_2$

Initiation



The attack of a ROS able to abstract a hydrogen atom from a methylene group (- CH_2-).

Generates easily free radicals from polyunsaturated fatty acids.

.OH is the most efficient ROS to do that attack

Energy requirement for radical production by rupture of a CH bond is about 80 kcal

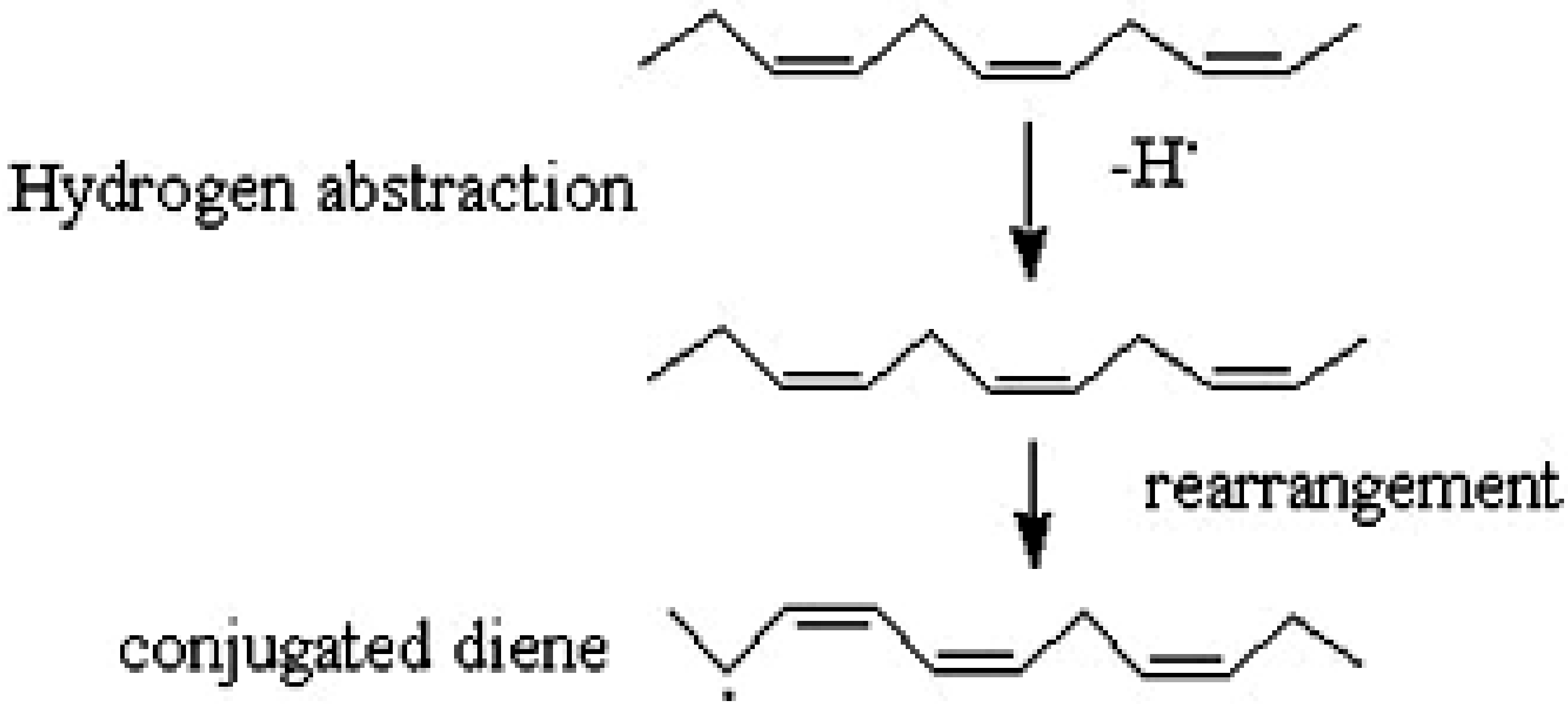
Initiation - continued

The presence of a double bond in the fatty acid weakens the C-H bonds on the carbon atom adjacent to the double bond and so makes H-removal easier

Metal activation, enzyme catalysis or photooxidation: Less energy is required

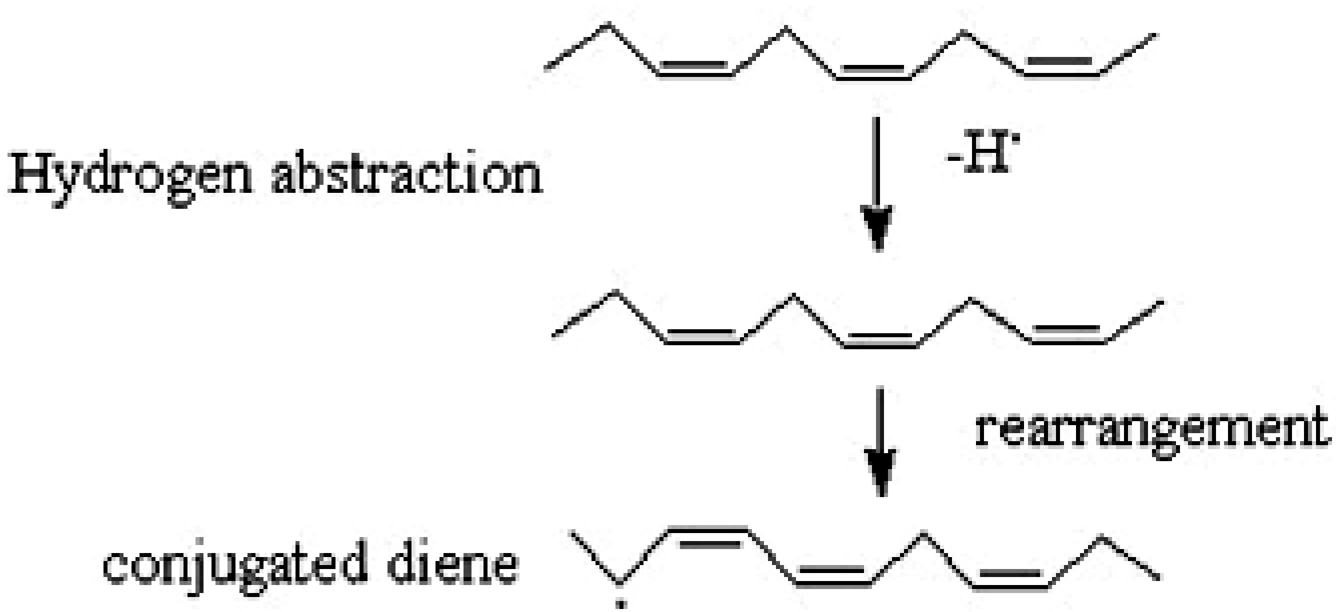
Inhibited by tocopherols, mannitol and formate

Degree of unsaturation in Fatty Acids



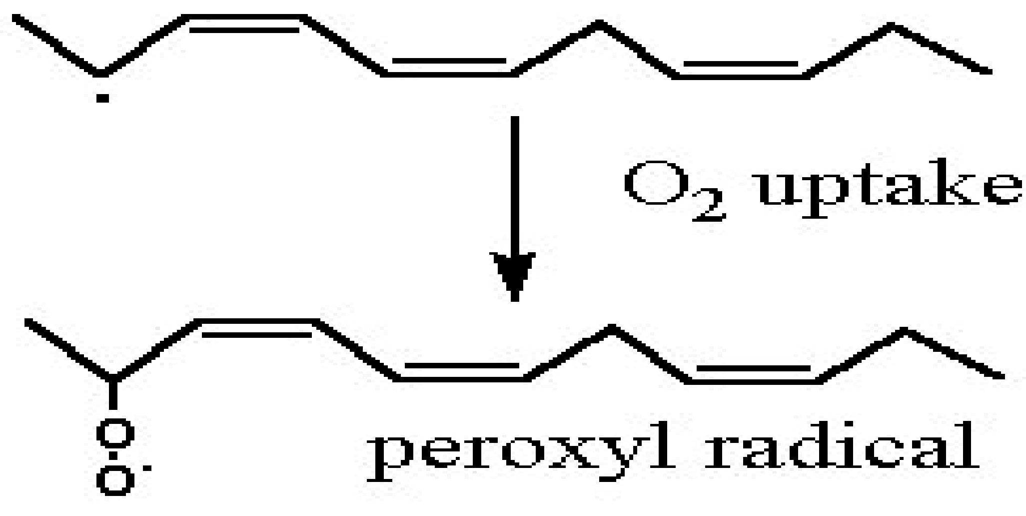
Propagation

1. Diene Conjugation



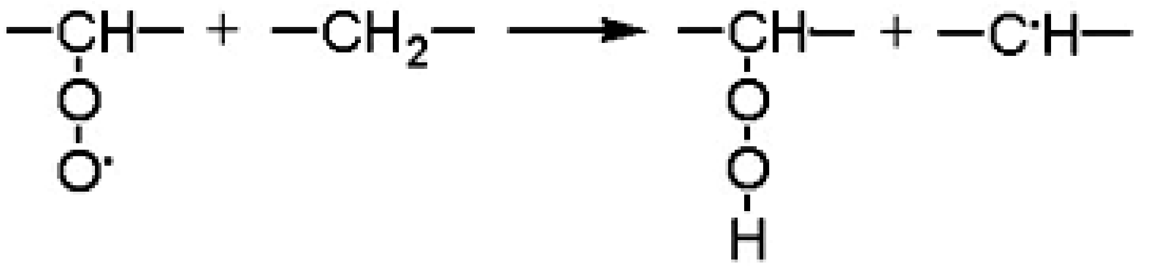
Propagation - Continued

2. Oxygen uptake



Propagation - Continued

3. Autoxidation



ROOH + Fe^{2+}-complex ---→ Fe^{3+}-complex ---→ RO. + OH^-

ROOH + Fe^{3+}-complex ---→ ROO. + H^+ + Fe^{2+}-complex

Termination

Formation of hydroperoxides: ften achieved by reaction of a peroxyl radical with a-tocopherol: chain breaking

Radical-Radical reactions

R· + R· ------> RR

R· + ROO· ------> ROOR

ROO· + ROO· ------> ROOR + O_2