

Free Radicals, The Cause of Virtually All Disease, Illness and Aging

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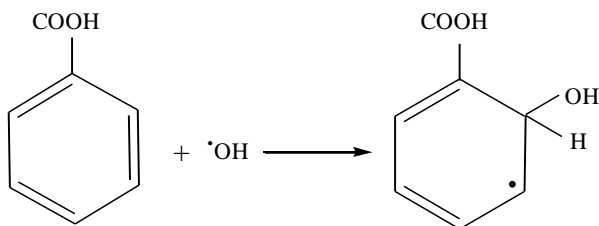
What is free radicals?

An atom or group of atoms that has at least one unpaired electron and is therefore unstable and highly reactive. In animal tissues, free radicals can damage cells and are believed to accelerate the progression of cancer, cardiovascular disease, and age-related diseases.

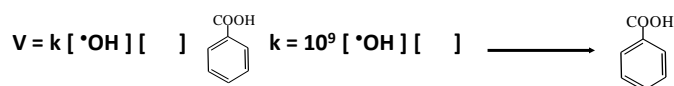
Any species molecules / atom as Gas• with unpaired electron, very reactive, having rate const. $> 10^8 \text{ M}^{-1} \text{ sec}^{-1}$

Different rate constant between OH• and OH⁻

1. Photochemical reaction: $\text{H}_2\text{O}_2 \longrightarrow \cdot\text{OH} + \cdot\text{OH}$



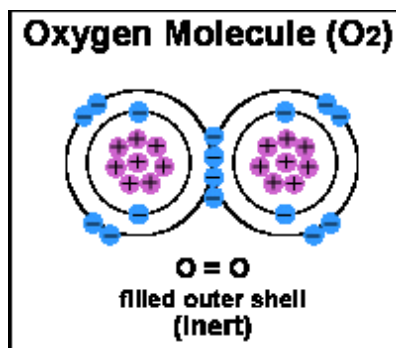
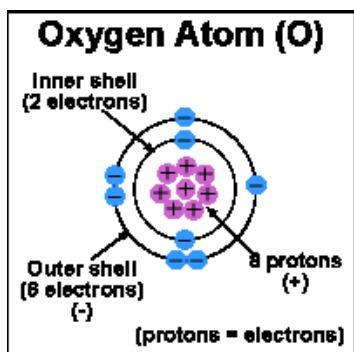
$$k [\text{C}_6\text{H}_5\text{COOH} + \cdot\text{OH}] = 5 \times 10^9 \text{ M}^{-1} \text{ det}^{-1}$$



2. Reaksi Redox : $\text{OH}^- + \text{C}_2\text{H}_5\text{J} \longrightarrow \text{C}_2\text{H}_5\text{OH} + \text{J}^-$

$$v = k [\text{OH}^-] [\text{C}_2\text{H}_5\text{J}] \quad k = 10^{-2} \text{ M}^{-1} \text{ det}^{-1}$$

3



- Gaining or losing electrons to either fill or empty its outer shell
- Sharing its electrons by bonding together with other atoms in order to complete its outer shell

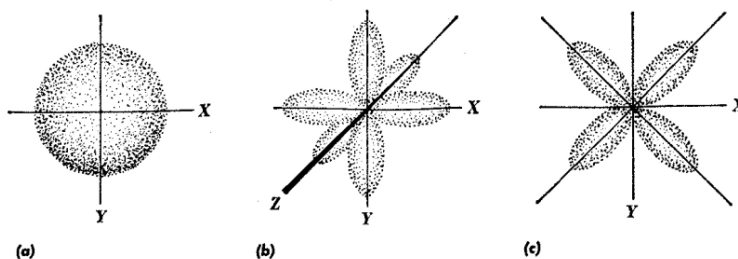
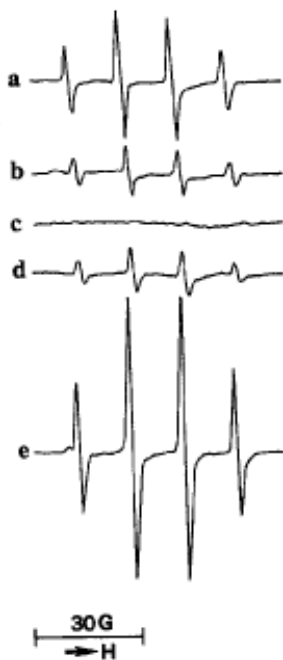
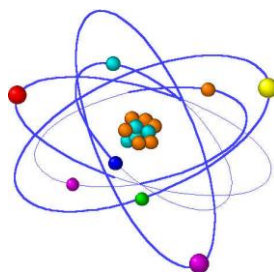


FIG. 2.1. Electron orbitals: (a) *s* orbitals; (b) *p* orbitals; (c) *d* orbitals.

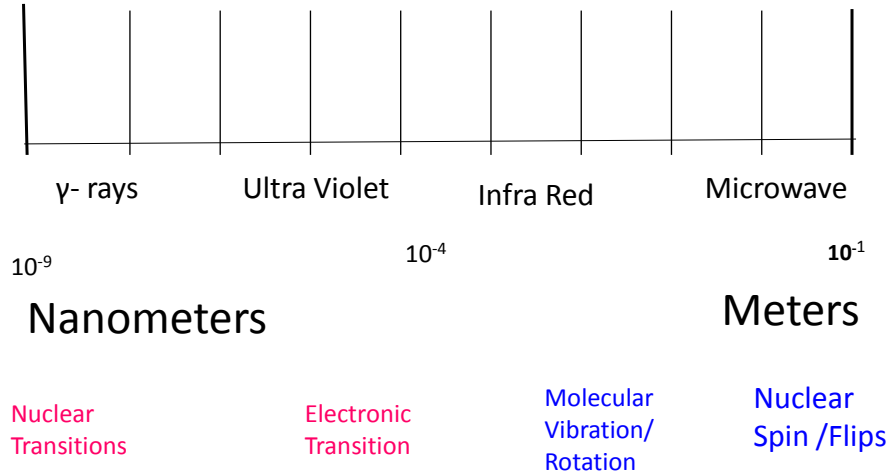


ESR (Electron Spin Resonance) is used to detect short-lived free radical intermediates

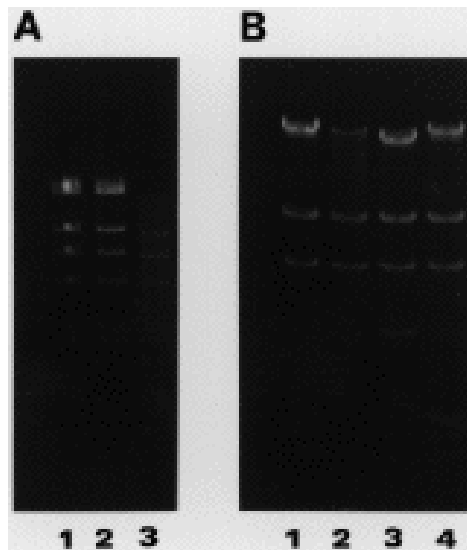
- (A) ESR spectrum recorded 2 min after mixing 100 mM DMPO and freshly fractured silica (150 mg/ml) in a pH 7.4 phosphate-buffered solution.
- (B) Same as (A) but with 5 μ g/ml SOD added.
- (C) Same as (A) but with 5000 units/ml catalase added.
- (D) Same as (A) but with 1 mM deferoxamine added.
- (E) Same as (A) but with 10 mM H_2O_2 added.

Sunlight, X-Rays or other radiation hits the body and creates free radicals inside the body. These are free radicals which, in turn, grab some loose electron from somewhere, and thus create a new free radical.

Effects of Irradiation to Atoms



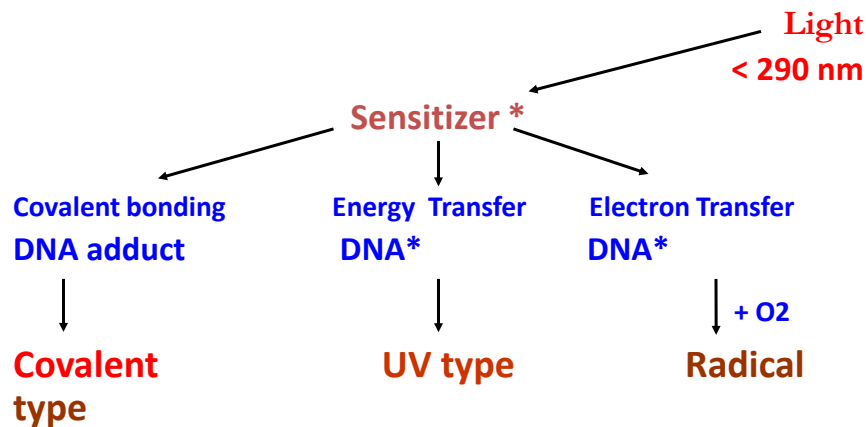
Free Radicals Induced DNA Damage



(A), line 1, untreated control DNA; line 2, 10 mg/ml freshly fractured silica with Hind III digested DNA in a pH 7.4 phosphate-buffered solution; line 3, same as line 2 but with 1.5% H_2O_2 added. The samples were incubated for 24 hr.

(B) line 1, untreated control DNA; line 2, 10 mg/ml freshly fractured silica with Hind III digested DNA in a pH 7.4 phosphate-buffered solution; line 3, same as line 2 but incubation was carried out under argon; line 4, same as line 2 but with 7500 units/ml catalase added. The samples were incubated for 3 weeks (Xianglin Shi, et al., 1994)

UV C enable induce organic sensitizer to become radicals and damaging DNA (Epe, 2001)



Sensitizer : Organic compound including many antibiotic and Hg sensitizer, Amalgam filling

Sensitizer

Sensitizer : Molecules which easily absorb UV <290nm, able to keep or transfer to DNA or others

B. Epe : Organic Compound Antibiotic,
G. Zahar: Hg, Mercury sensitizer

- Sensitizer**
- Two electron $6s^2$, having high speed, absorbing UVC, when match $-(\text{Hg } \bullet+)_2 + e^-$ ("relativistic effect")
- $$\text{Hg (liquid)} \rightleftharpoons \text{Hg}^* \text{ (Vapor)}$$

$$\text{Hg (Vapor)} \xrightarrow{<290} \text{Hg } \bullet+ \xrightarrow{\text{(Associated)}} (\text{Hg}^{++} \text{Hg } \bullet+) + e^-$$
- Hg manufacturing Radicals

$$\text{Hg } \bullet+ + \text{DNA} \longrightarrow \text{Hg} + \text{DNA } \bullet \longrightarrow \text{Radicals}$$
- Hg / amalgamated, having *spherical character*

How inflammatory Free Radicals are formed?

In the living system, free radicals formed when there is weak bonds split.

Free radicals are very unstable and react quickly with other compounds, trying to capture the needed electron to gain stability.

Generally, free radicals attack the nearest stable molecule, "stealing" its electron. When the "attacked" molecule loses its electron, it becomes a free radical itself, beginning a chain reaction.

Once the process is started, it can cascade, finally resulting in the disruption of a living cell.

The factors induce inflammatory free radicals

Environmental factors

Some free radicals arise normally during metabolism. However, environmental factors such as pollution, radiation, cigarette smoke and herbicides can also spawn free radicals.

Immune system disorder

The body's immune systems cells purposefully create free radicals to neutralize viruses and bacteria, but overwhelming production occurred when there is system disorder

Insufficient antioxidant.

Normally, the body can handle free radicals, but if antioxidants are unavailable, or if the free-radical production becomes excessive, damage can occur.

Aging

In particular importance is that free radical damage accumulates with age.

Dr. Denham Harman
The Father of Free Radical Medicine,
a Professor Emeritus of Medicine and Biochemistry at the
University of Nebraska

Even though the free radicals are acknowledged as the basic cause of disease, but since we don't have any drugs to treat free radicals with, we then continue to administer drugs which are, themselves, often sources of more free radicals.

The candidate for drug scavenging free radicals should be compounds rich of electron enable to capture electron which do not become source of more free radicals

Antioxidants May Prevent Against Free Radical Damage

Antioxidants neutralize free radicals by donating one of their own electrons, ending the electron-"stealing" reaction. The antioxidant nutrients themselves don't become free radicals by donating an electron because they are stable in either form

Vitamin E and C is the most abundant fat-soluble and water-soluble antioxidant in the body. Acts primarily in cellular fluid for water soluble radicals.

Problem: These soluble antioxidants are inadequate to act as scavenger for gaseous free radicals which have very high speed half life ($0.000000001 \text{ Mol}^{-1}\text{Sec}^{-1}$)

Free radicals :

Non Metals Gas • : \bullet H; \bullet OH; \bullet NO; $\text{NO}_2\bullet$; $\text{HO}_2\bullet$; \bullet OONO

Metal Gas • : $\text{Hg}^{\bullet+}$ (rad ion mercurio), Hg-metal (amalgam)

Radicals : Compound with unpaired electron, very reactive, not stable, solid a liquid phase.

Biradical: Radical-radical intermolecular interaction depends on the distance of the unpaired electrons between the radical compounds

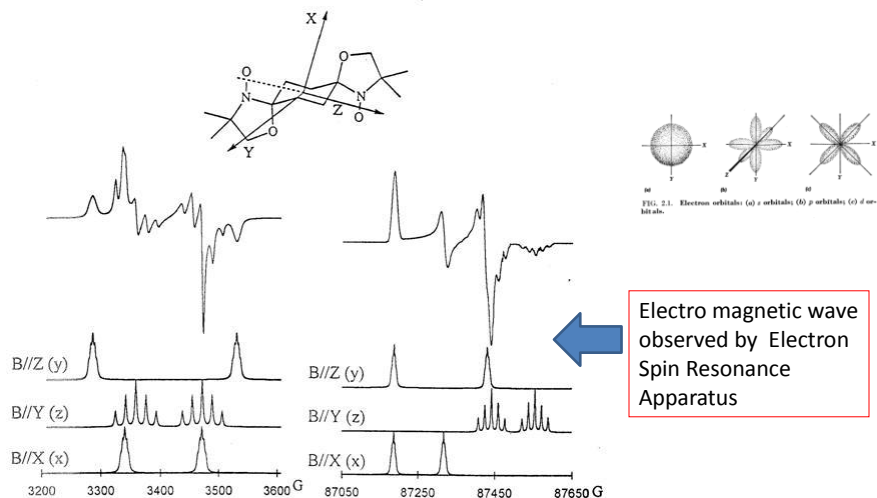


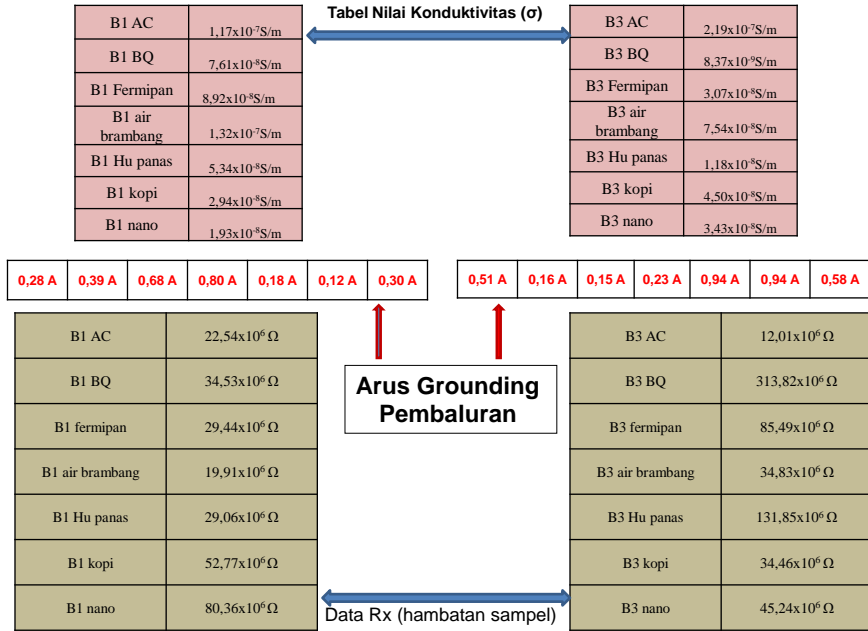
Can be used to construct complex molecules able to scavenge fast gaseous free radicals

15

Why biradical potential for electron stealing?

They have enough characters of magnetic force generated from it's Triplet states

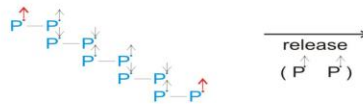




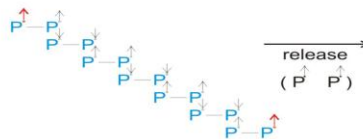
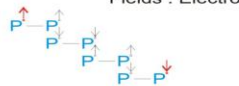
There are : 1) Electromagnetic fields
2) Gravitation fields

Association Of Paramagnetic complex in "cage"

Structure of $(P^{\uparrow} - P^{\uparrow})_{2n+1}$



Structure $(P^{\uparrow} - P^{\downarrow})$
Ended : Diamagnetic
Fields : Electron

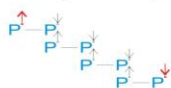


Ended : Paramagnetic
Fields : Gravitation

Ended : Diamagnetic
Fields : Electromagnetic

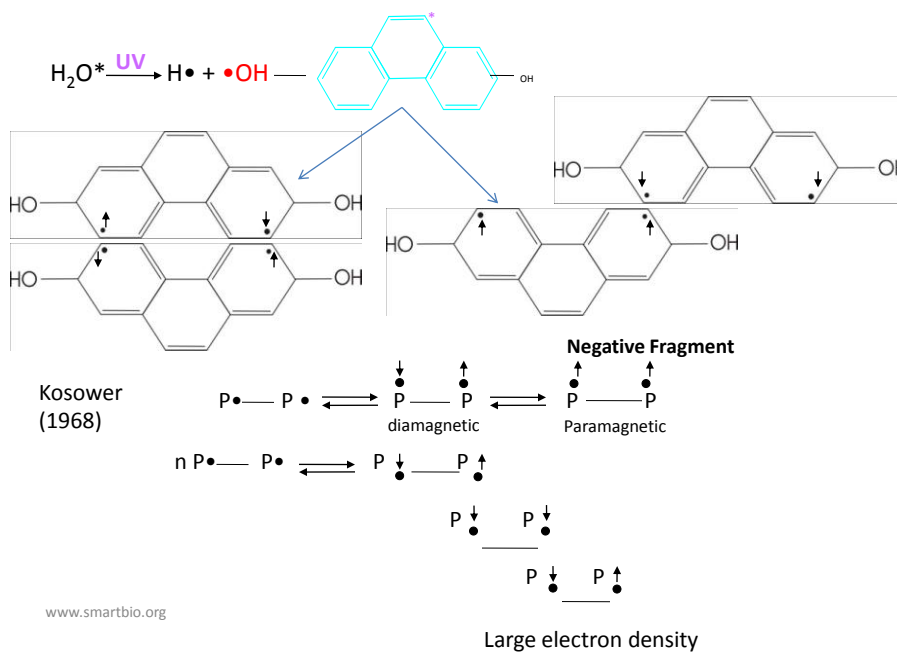
Association Of Diamagnetic complex in "cage" (Bubble)

$(P^{\uparrow} - P^{\downarrow})_{2n+1}$



Resulted Diamagnetic ends
Fields : Electromagnetic

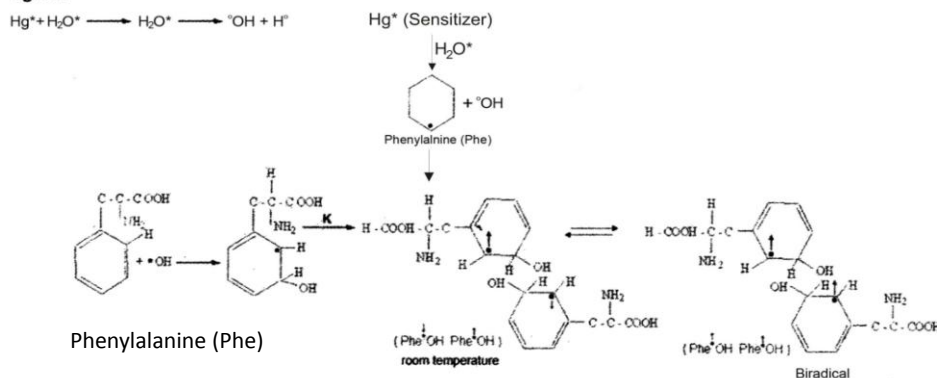
Tar is Aromatic Phenantren structures rich of electron moving on its surface



G. Zahar (1982-1993)

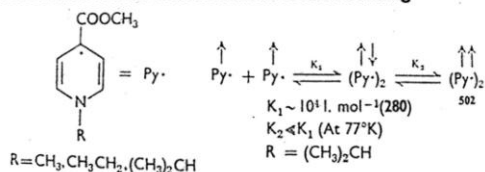
Biradical product of Gamma Irradiated X – Aromatic in tridest solution

Figure :



Biradical

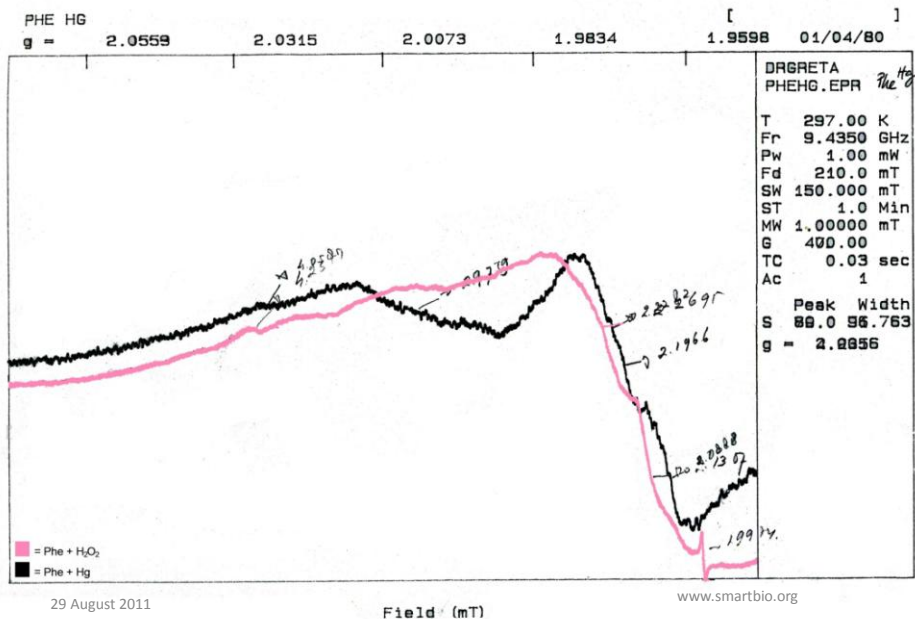
Biradical : Self association radical-radical without covalen bonding



(Edward M. Kosower (1967): "An Introduction to Physical Organic Chemistry")

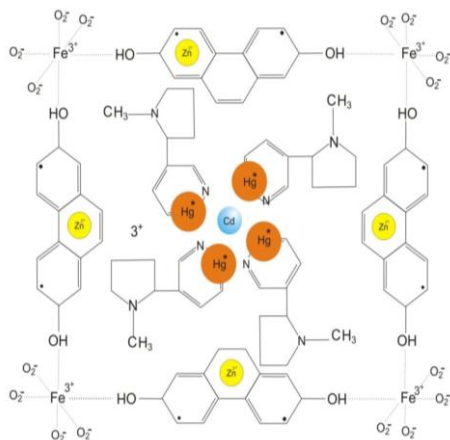
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Polymerized phenylalanine scavenge free radicals in the smoke



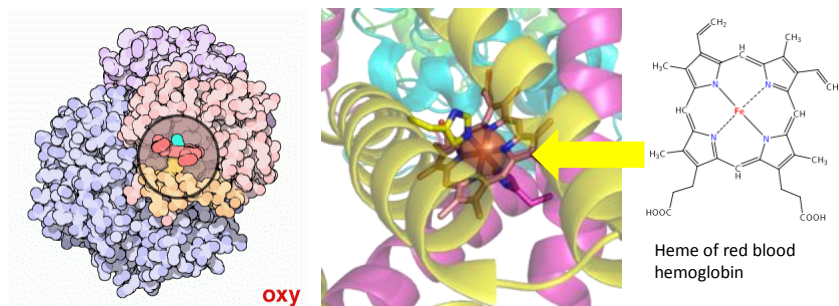
The nanostructures of tobacco smoke

Characterized by the *intra spin-spin interaction of the conjugated di-HO•-Phenanthrenedieryl* with very mobile electron in their surface. This complex structure can act as scavenger enable to catch and deliver single electron



Fe acting to move free electron as mercurio defend

Divine Nanostructure

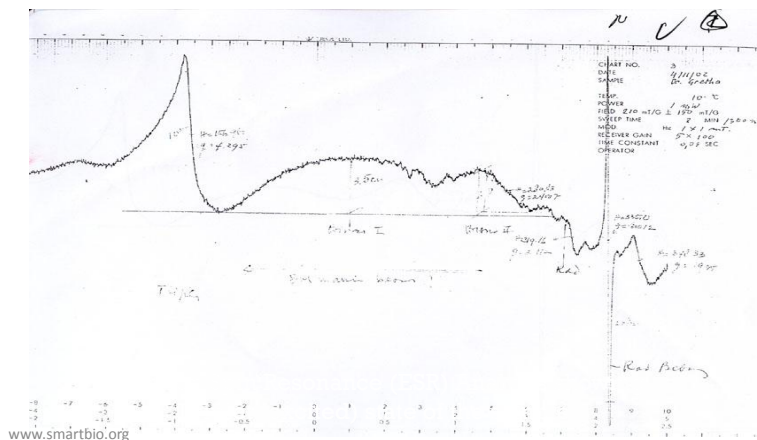


Iron's oxidation state in oxyhemoglobin

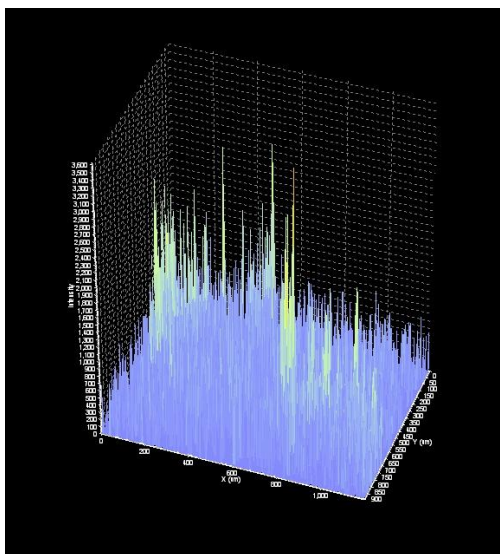
Assigning oxygenated hemoglobin's oxidation state is difficult because oxyhemoglobin (Hb-O₂), by experimental measurement, is diamagnetic (no net unpaired electrons), yet the low-energy electron configurations in both oxygen and iron are paramagnetic (suggesting at least one unpaired electron in the complex).

The ESR observation showed that nanostructure molecular blocks (particulates) of tobacco smoke with triplet state

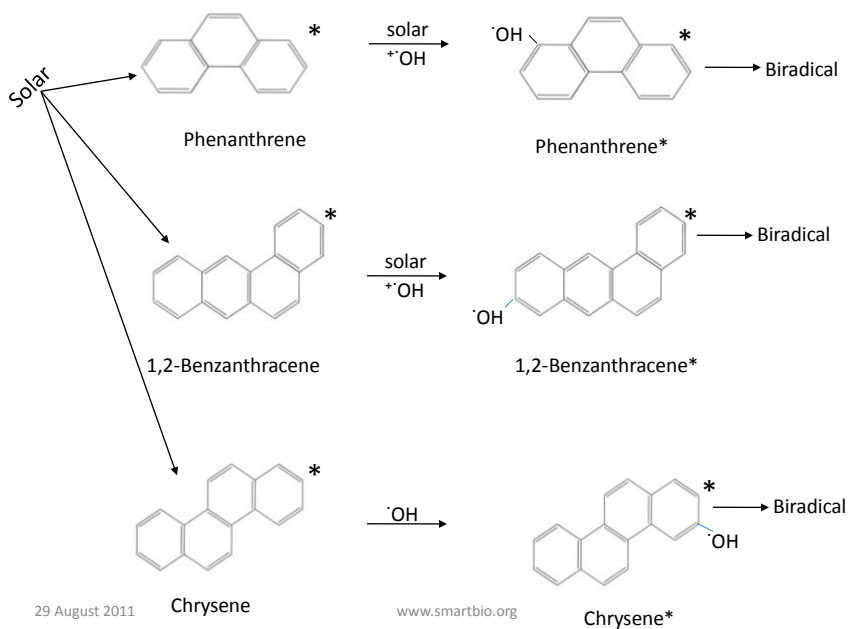
The polymers have high density of electron, enabled it to deliver electron (within mV) to other molecular blocks generating flow of energy in the living system



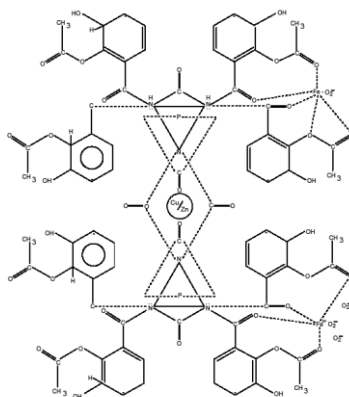
The FRET (Fluorescence Resonance Energy Transfer) showing the resonance (energy induction) when the excited molecules donating electron to the surrounding molecules



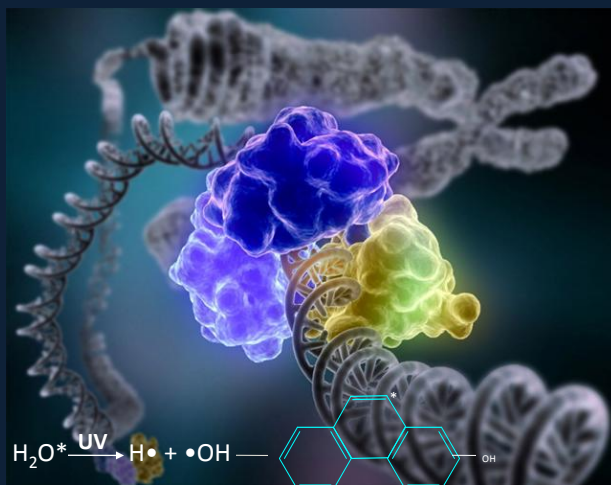
Tar's cluster acting as Mobile Electron



Other possible nanosized molecular block



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Thank You