

5.03, Inorganic Chemistry
Prof. Daniel G. Nocera
Lecture 2 Mar 11: Oxygen

General

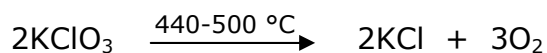
Most abundant element of the earth's surface:

23% atmosphere

46% lithosphere

85% hydrosphere (85.8% oceans, 88.81% pure water)

Prepared on huge scales (100 million tons) by fractional distillation (Air Products, Linde, Praxair, Air Liquide). In the laboratory, usually prepared by decomposition of oxoacids:



3 stable isotopes: ^{16}O (99.762%), ^{17}O (0.038%) and ^{18}O (0.200%). ^{17}O has a nuclear spin ($I = 5/2$), so can be used for NMR studies, as well as double resonance EPR techniques.

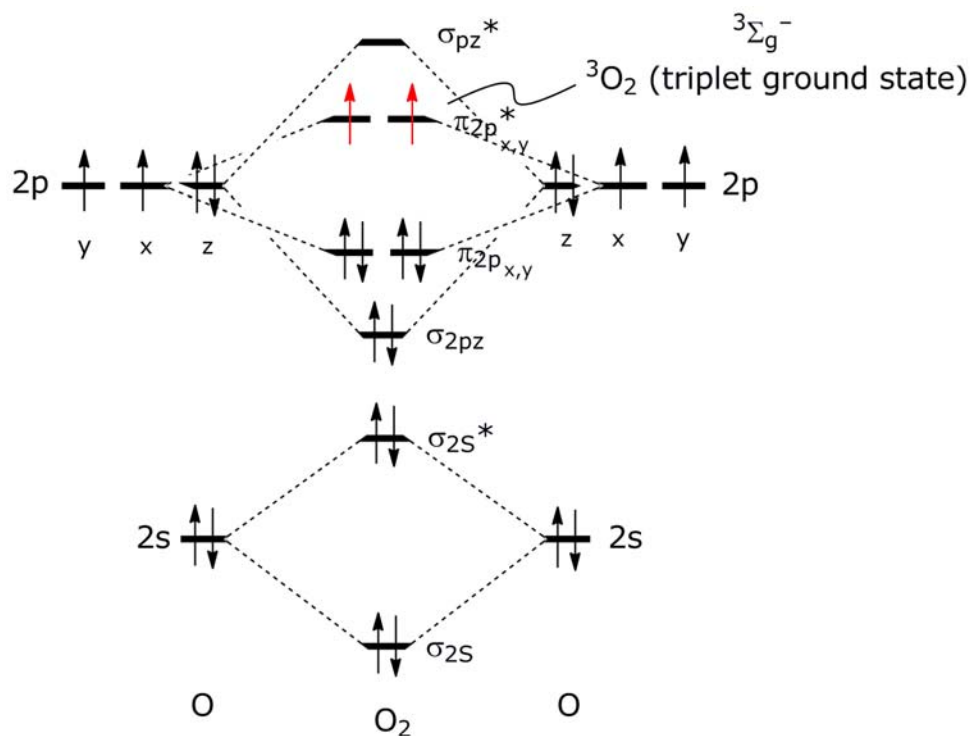
A Brief History

- 15th century Leonardo DaVinci notes air has substance to support combustion
- 1773 Priestley and Scheele discover oxygen, prepared by many different routes
- 1775 Lavoisier recognizes O as an element and in 1777 calls it "oxygen"
- 1781 Cavendish determines water composed of hydrogen and oxygen
- 1800 Nicholson and Carlisle electrolytically produce O_2 from H_2O
- 1818 Thenard discovers hydrogen peroxide, H_2O_2
- 1840 Schönbein discovers ozone, O_3
- 1848 Faraday notes O_2 is paramagnetic, Mulliken determines MO in 1928 to explain paramagnetism (see next page)
- 1877 Oxygen liquefied by Cailletet and Pictet
- 1881 Oxygen produced industrially for the first time (from BaO)
- 1896 von Linde produces liquefied O_2 on industrial scale
- 1903 Harries discovers ozonolysis of alkenes
- 1929 ^{17}O and ^{18}O isotopes discovered by Giauque and Johnston
- 1931 Singlet oxygen discovered by Childe and Mecke
- 1941 ^{18}O tracer studies show that photosynthetic O_2 comes from H_2O and not CO_2
- 1951 ^{17}O detected by NMR by Weaver, Tolbert and LaForce
- 1963 First reversible oxygen binding with an organometallic complex by Vaska
- 1974 Rowland and Molina show that CFCs could catalytically destroy ozone
- 1985 Furman discovers ozone hole over Halley Bay, Antarctica

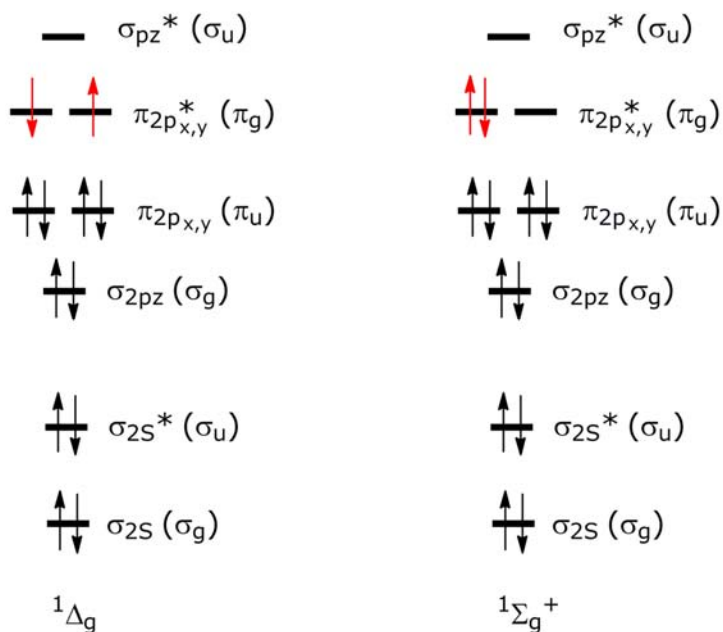
Electronic Structure

Oxygen is extremely electronegative (3.5) only exceeded by F, and possesses a significant ionization energy ($1313.5 \text{ kJ mol}^{-1}$). Atomic O has an electronic configuration $1s^2 2s^2 2p^4$. This gives rise to the diatomic molecular orbital diagram:

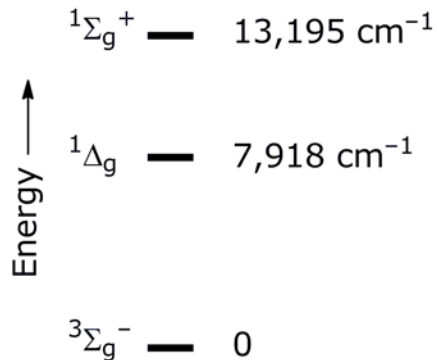
O_2 ground state:



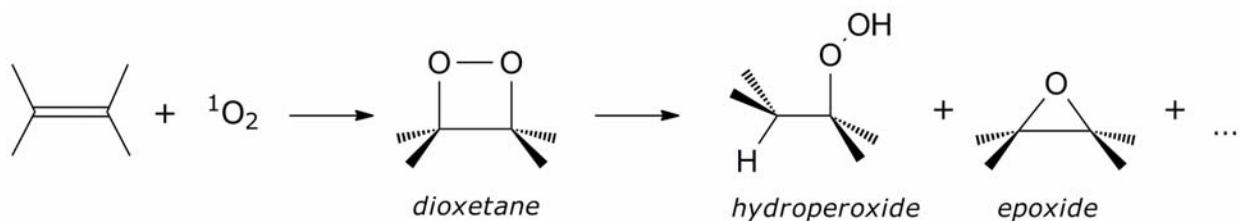
There are two low-lying *singlet excited states*:



The state diagram is:



Singlet oxygen is very reactive. Kautsky in 1931-9 showed the significance of singlet O_2 in organic reactions, but his science was largely discounted. Only again in 1964, did Foote and Corey re-discover the potent oxidizing ability of singlet O_2 , which can readily oxidize hydrocarbons and a host of other organic substrates:



In the body, singlet O_2 damages tissues by:

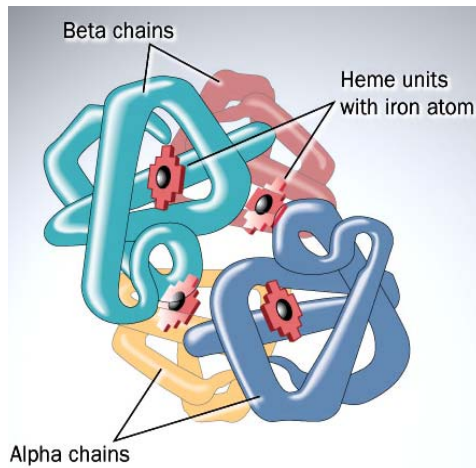
- oxidizing membrane lipids
- oxidizing amino acids in proteins
- crosslinks proteins
- damages DNA

and here is where the story of vampires begins...

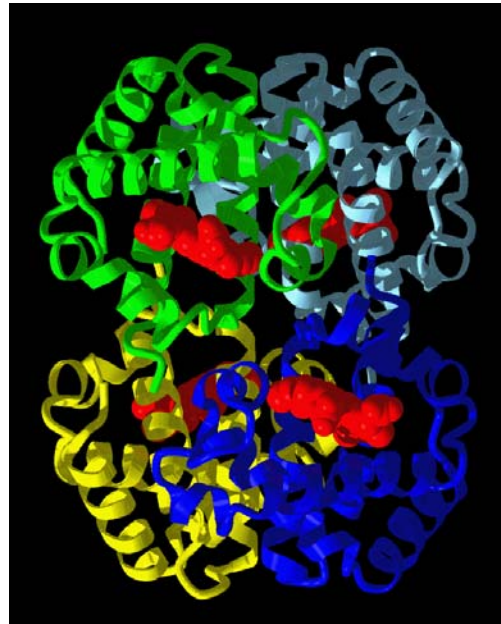


Uncle Fester

In your body, O₂ is transported and delivered by hemoglobin:



- A tetramer
- MW = 64,500
- hemes 25 and 40 Å apart
- binds O₂

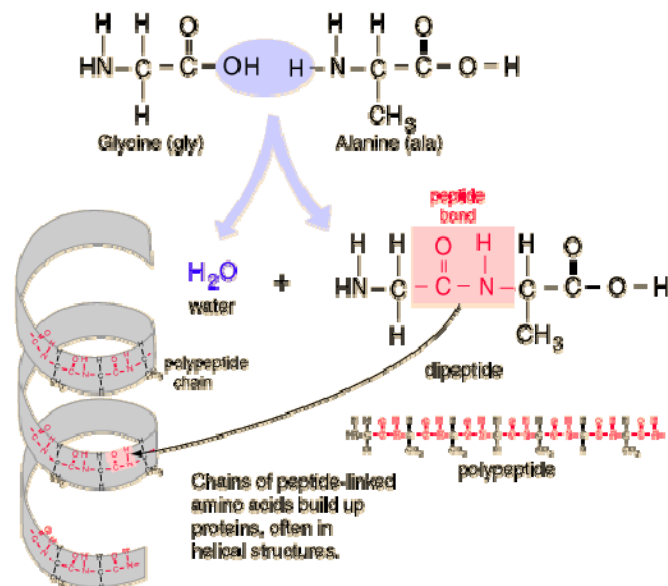


The protein is made up of two major structural components:

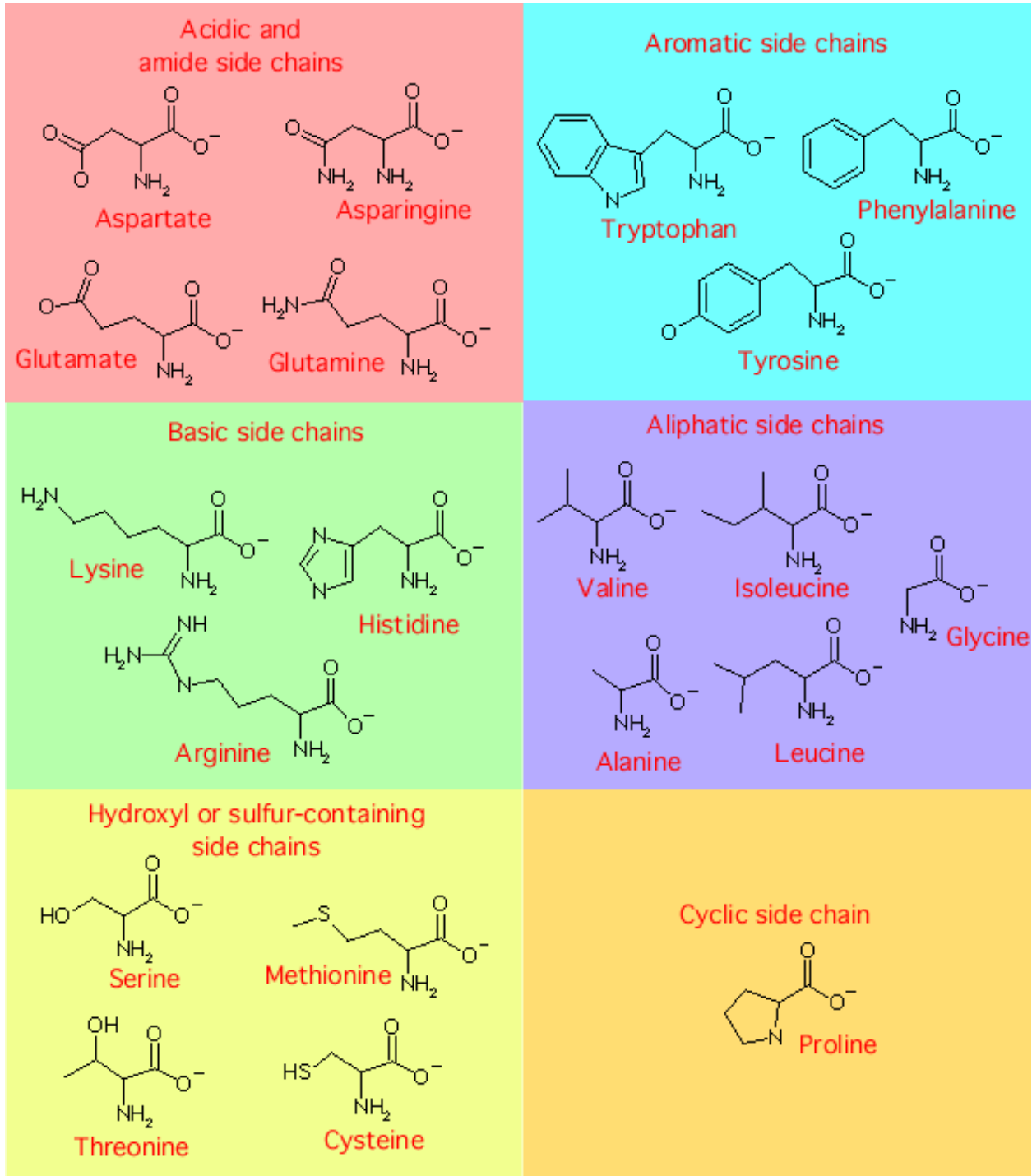
- ❖ Amino acid biopolymer, i.e. peptide
- ❖ Heme cofactor (active site where O₂ binds)

Peptide Backbone

Composed of 20 natural amino acids, which polymerize via the following condensation reaction:

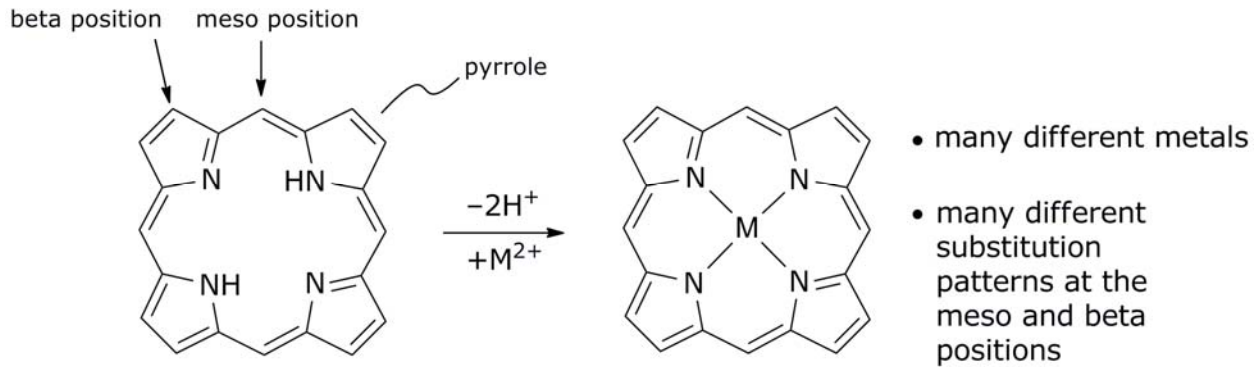


The 20 Naturally Occurring Amino Acids



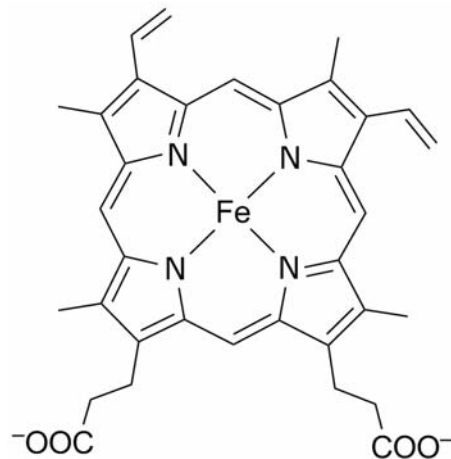
Heme Cofactor

The heme cofactor is a porphyrin. A porphyrin is an aromatic macrocycle that can bind metals in its tetragonal pocket,

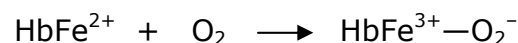


When $M = \text{Fe}$, then the porphyrin is called a heme. There are several important biofunctions of hemes, including: O_2 transport (hemoglobin), mitochondrial cellular energy generation (cytochrome c oxidase), electron transport (cytochrome c), detoxification reactions (cytochrome P450), peroxidase mediated reactions (peroxidases), biosynthesis of steroids, protein synthesis...to name a few.

Hemoglobin has the substitution pattern as follows:



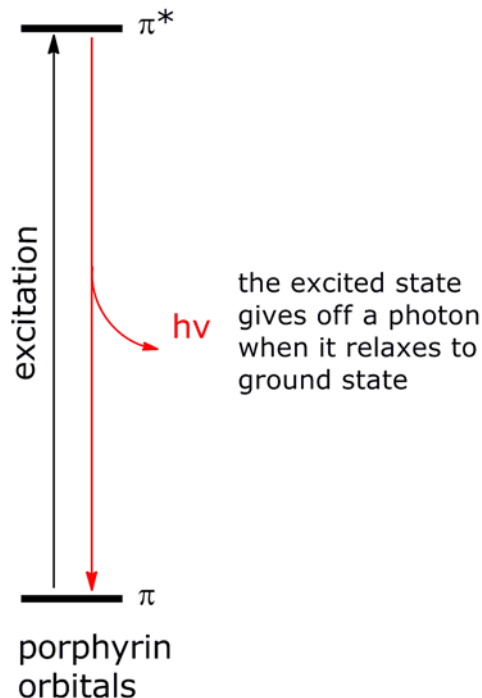
Hemoglobin is good at binding but also good at releasing O_2 to the cell, i.e., the on/off rates are fast. Everybody knows that carbon monoxide is poisonous—it competes for the O_2 binding site at heme. Interestingly, O_2 is 20x faster at binding hemoglobin than CO , *but* CO doesn't come off easily once bound, hence it is a toxin. Oxygen binds the Fe^{2+} state of heme and the binding is assisted by an internal electron transfer to temporarily produce Fe^{3+} -superoxide. Superoxide, O_2^- is the one-electron reduced form of O_2 :



Electronic Structure of Porphyrins and Hemes

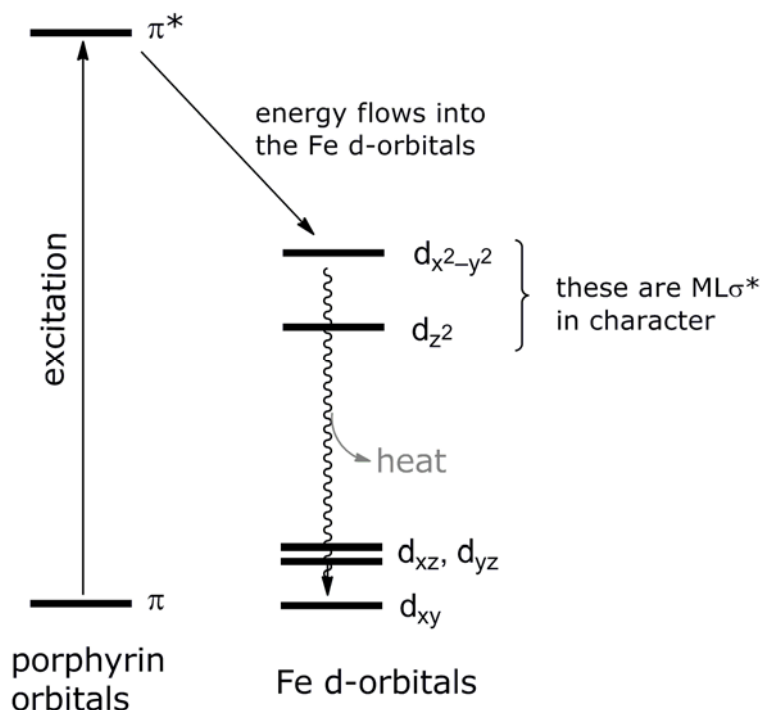
Porphyrin Excited States

Porphyrins are aromatic π -systems. Just like any aromatic (i.e., benzene), the HOMO is of π -symmetry formed from the bonding linear combination of p-orbitals and the LUMO is π^* symmetry formed from the bonding linear combination of p-orbitals. The $p\pi^*$ orbital is relatively rigid, and thus the excited state energy cannot dissipate readily. Thus, the $p\pi^*$ excited states of aromatics are long-lived (nanoseconds to milliseconds) and highly emissive (they give off a photon).



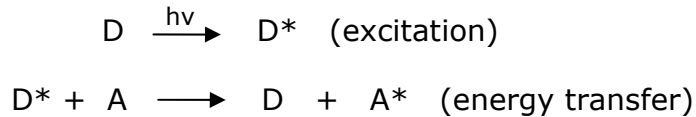
Heme Excited States

Hemes have the $p\pi$ HOMO and $p\pi^*$ LUMO electronic structure too. But they differ in one significant way. The Fe center brings in low-lying dd states. The lowest energy transition in the heme is therefore NOT the emissive and long-lived $p\pi^*$ excited state but rather is a M—L σ^* excited state. Because these states are antibonding along the s axis, the excited state energy is dissipated efficiently by molecular vibrations (this is called non-radiative decay) and the excited state energy is given off as heat. The excited states of hemes are extremely short-lived, on the order of a picosecond.



Energy Transfer

The consequence of the short-lived excited state of heme, and the long-lived-excited state of porphyrin is manifested in energy transfer. Energy transfer is the process where energy from one excited state molecule (donor, D) is transferred to another molecule (acceptor, A) to produce the excited state of that molecule. The energy transfer process in solution is a bimolecular reaction,

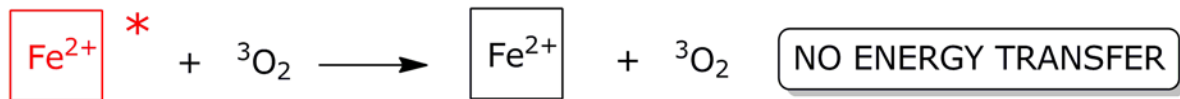


where $d[A^*]/dt = -d[D^*]/dt = k[D^*][A]$.

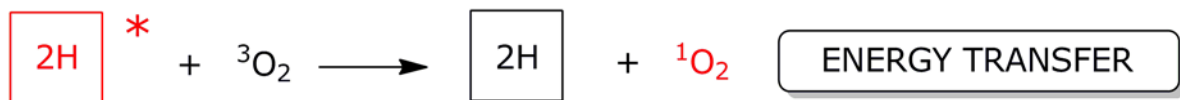
Note that the D^* has to be long enough lived to diffuse to A. Thus the excited state must live at least tens of nanoseconds. This is the case for free base porphyrins (i.e., the porphyrin with no metal, just the two protons). However, the hemes are too short-lived (remember, their excited states are picoseconds) to participate in a diffusional process. The excited state energy in a heme is dissipated as heat before it can transfer it to another molecule.

With regard to A, 3O_2 can accept energy in an energy transfer process to produce its singlet excited state, 1O_2

For the case of hemoglobin, however, energy transfer is circumvented owing to the short excited state lifetime (owing to the presence of the low-lying dd states of the Fe center)



whereas for free base porphyrin (i.e., hemoglobin with no Fe^{2+} center, only two protons), energy transfer to produce 1O_2 is energetically a favorable process,



Thus sunlight shining on hemoglobin (i.e. your blood), does not produce the potent oxidizing agent, 1O_2 . However, if your blood had hemoglobin with missing Fe^{2+} centers, then 1O_2 would be produced.

Clinical Genealogy of a Disease Called "Porphyria"

1898 Reports two brothers have solar sensitivity and free base porphyrin in urine

McCall-Anderson, *Br. J. Dermatol.* **1898**, 10, 1

1911 Classifies a disease associated with skin sensitivity to light and names it porphyria

Günther, *Dtsch. Arch. Klin. Med.* **1911**, 105, 89

1913 First to synthesize free base porphyrin, and then after making it, injects into himself 200 mg of free base porphyrin. Wraps partly of himself in tape and leaves part of his skin exposed. Notes that skin exposed to light is damaged, and connects the disease of porphyria to free base porphyrin

Meyer-Betz, *Dtsch. Arch. Klin. Med.* **1913**, 112, 476

Friedrich Meyer-Betz, a German physician, injected himself with porphyrin in 1912 to test whether it made humans sensitive to light. The first photograph shows him four days later, after he took a walk on a sunny day. Most of the swelling subsided by the sixth day, second photograph, but he remained light-sensitive for several months.

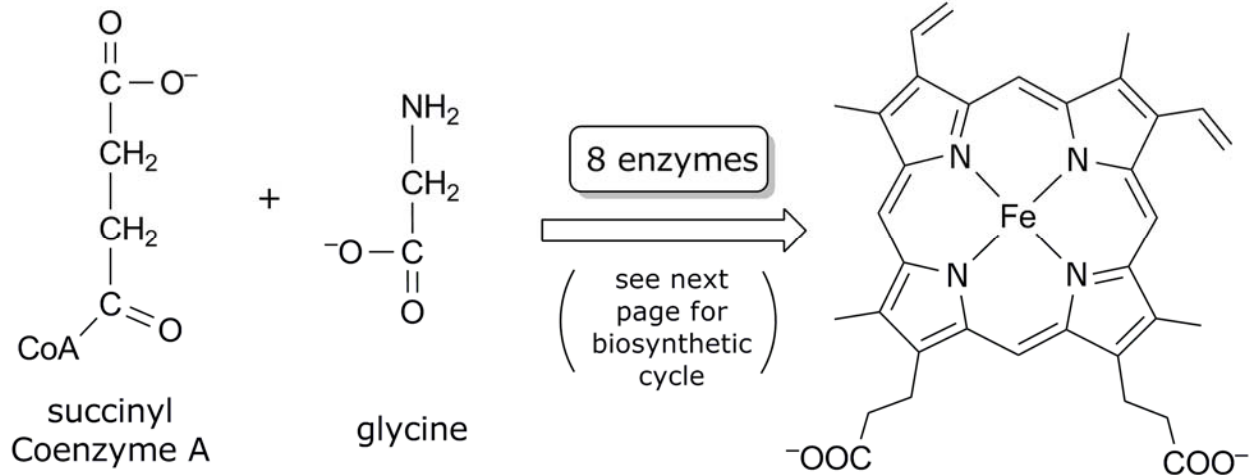


courtesy A. M. McDonagh, UCSF (2)

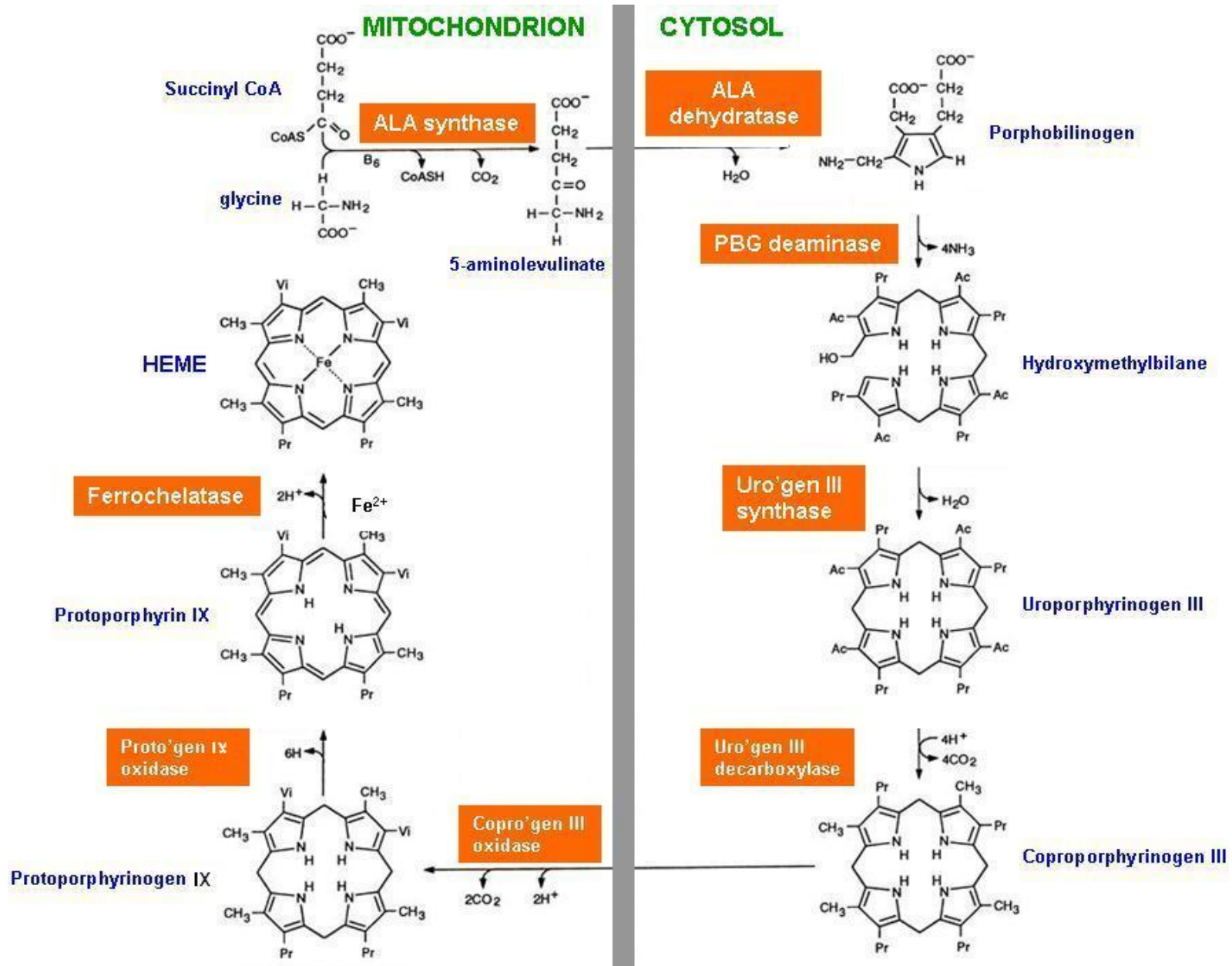
SCIENCE 82

Heme Biosynthesis

Heme is synthesized in all cells, but most prevalent in liver and bone marrow. The synthesis of heme relies on *eight* enzymes. The next shows the complete biosynthetic pathway.



8 different "porphyrias" associated with missing one of the 8 enzymes. Most typical porphyria is the one arising from the lack of ferrochelatase—the enzyme that places Fe^{2+} into the porphyrin ring (the last step of the biosynthetic pathway).



The Eight Porphyrrias

| Enzyme | Location of enzyme | Associated porphyria | Type of porphyria |
|---|--------------------|---|-------------------|
| δ -aminolevulinate (ALA) synthase | mitochondrion | X-linked sideroblastic anemia (XLSA) | erythropoietic |
| δ -aminolevulinate (ALA) dehydratase | cytosol | Doss porphyria/ALA dehydratase deficiency | hepatic |
| hydroxymethylbilane (HMB) synthase (or PBG deaminase) | cytosol | acute intermittent porphyria (AIP) | hepatic |
| uroporphyrinogen (URO) synthase | cytosol | congenital erythropoietic porphyria (CEP) | erythropoietic |
| uroporphyrinogen (URO) decarboxylase | cytosol | porphyria cutanea tarda (PCT) | hepatic |
| coproporphyrinogen (COPRO) oxidase | mitochondrion | hereditary coproporphyria (HCP) | hepatic |
| protoporphyrinogen (PROTO) oxidase | mitochondrion | variegate porphyria (VP) | mixed |
| ferrochelatase | mitochondrion | erythropoietic protoporphyria (EPP) | erythropoietic |

So now let's reconsider the **MYTH** ... in light of the science of O₂ and porphyrins:

INSANITY and AGGRESIVENESS

Hepatic porphyrias affect nervous system, resulting in mental illness. First diagnosis of porphyria often by a psychiatrist.

TRANSYLVANIA

> 200 genetic variants traced back to Finland, Estonia, Hungary, Bulgaria and you guessed it, *Romania*.

GARLIC

If you have an asthmatic attack, your body goes into overdrive to produce heme. But if you have porphyria, then you make a lot of free base heme, and exacerbate the disease. This attacks triggered by drugs, chemicals, and certain foods. Genetic studies of one of the first lineages goes back to a family line in Romania – brothers. Genetic markers show that they were allergic to garlic.

NIGHT CREATURES

Necrosis of the skin in light. Sunlight penetrates millimeters into the skin. If you have porphyria, then you need to stay out of bright sunlight

DRINKS BLOOD

Hematin and heme arginate are the drugs of choice in acute porphyria...you literally eat iron pill supplements to swamp your system with Fe²⁺ so that it can be delivered into the free base porphyrin. In 17th and 18th century – it was noticed that people got better when they drank cows blood (to get iron).

DO NOT LIKE TO LOOK IN MIRRORS

Necrosis can cause scarring and horrible disfiguration

HAIRY

Increased hair growth on areas such as the forehead – hypertrichosis

RED MOUTHS

Heme precursors may accumulate in the teeth and fingernails, giving them a reddish appearance

FANGS

Lips and gums become so taut that the teeth project. "Canine" teeth (known as the cuspid) become very pronounced.

WHITISH SKIN

Teeth and skin can become fluorescent owing to accumulation of free base porphyrin. The fluorescence from free base porphyrin is a light yellow green color. So your skin looks to take on a whitish tint.

NEVER DIE

Genetically carried disease especially among males – passed from father to sons. Note, people do not go out a lot. So a son grows to look like a father, and so on.