Bioinorganic Chemistry
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Lecture - 10
Life with Oxygen: General Introduction

Hi everybody and welcome back to this short course of “Bioinorganic Chemistry”. We have discussed so far the importance of inorganic elements in biology and also have showcased how our life affected directly out of such elements. I also have highlighted in my last four lectures the beautiful design principles adopted by nature in controlling some of the key chemical processes that are extremely important for our life.

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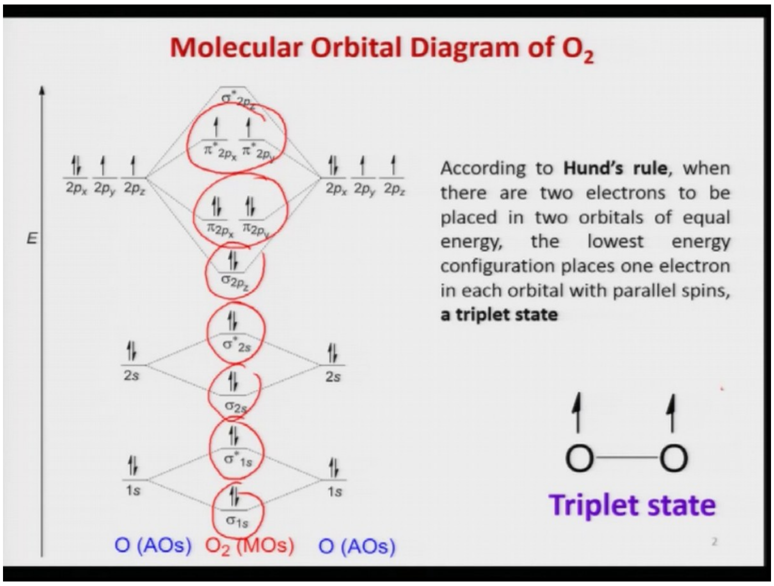

Molecular Orbital Diagram of O_2

According to **Hund’s rule**, when there are two electrons to be placed in two orbitals of equal energy, the lowest energy configuration places one electron in each orbital with parallel spins, **a triplet state**

Triplet state

Now, we will talk about Life with Oxygen. Let us go back to see that molecular orbital diagram of dioxygen. You are all familiar with that. So, this is σ_{1s} then σ_{1s}^*, σ_{2s}, and σ_{2s}^* and then $\sigma_{2px}^2$and π_{2px}^2,π_{2py}^2 and the antibonding orbitals is having two unpaired electron in the π_{2px}^*, π_{2py}^* so, two unpaired electrons so, we call it as a triplet state. So, molecular dioxygen is in triplet state. As you can see that antibonding orbital two unpaired electron and that is why we call it as triplet state.

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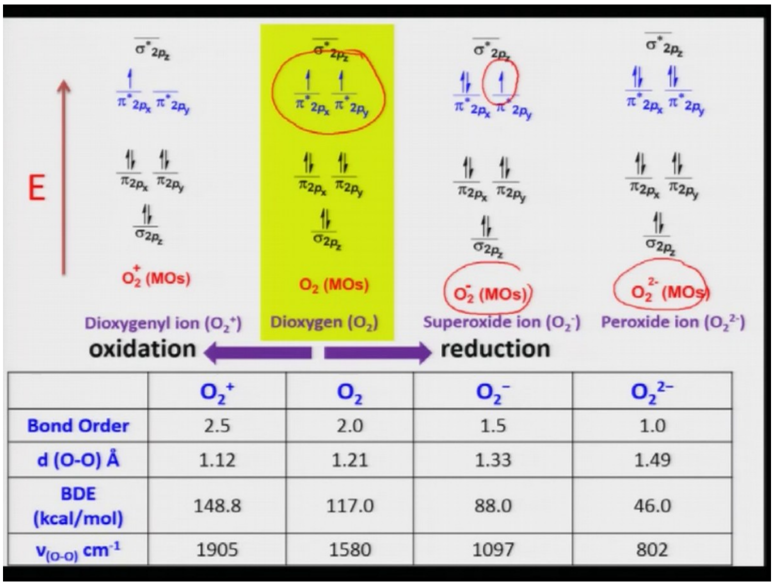

Dioxygenyl ion (O_2^+) Dioxygen (O_2) Superoxide ion (O_2^-) Peroxide ion (O_2^{2-})

oxidation ⟵ ⟶ **reduction**

	O_2^+	O_2	O_2^-	O_2^{2-}
Bond Order	2.5	2.0	1.5	1.0
d (O-O) Å	1.12	1.21	1.33	1.49
BDE (kcal/mol)	148.8	117.0	88.0	46.0
$\nu_{(O-O)}$ cm^{-1}	1905	1580	1097	802

Now, what would happen if you oxidize by one electron then the electron which would be removed is from antibonding then it will form Dioxygenyl ion O_2^+. And if we reduce it by one electron then two electron it will generate O_2^- which is called Superoxide ion. In the Superoxide ion as you can see that there is only one unpaired electron now and after two electron reduction it is O_2^{2-}, it is called Peroxide ion. In the Peroxide ion as you can see that $2p_x^2$, $2p_y^2$ both the π^* antibonding orbitals are filled and this is what I compare between O_2^+ Dioxygenyl, O_2^-superoxide and peroxide.

If you look at this bond order; bond order in O_2^+ as you can see it is 2.5, O_2 it is 2.0, O_2^- it is 1.5 and O_2^{2-} it is 1.0. So, bond order is decreasing from left to right and what happens to the distance, O-O bond distance is gradually increasing from Dioxygenyl ion O_2^+ to O_2, then O_2^- then O_2^{2-}. Bond association energy as you can see if O_2^+ certainly the bond association energy would be very large 148.8 kcal/mol and then O_2 117.0, O_2^- 88.0 and O_2^{2-} it is remarkably less, it is just 46.0. So, you see that peroxides having a very small bond association energy and stretching frequency will decreases from O_2^+ to O_2, $O_2^-$and O_2^{2-}.

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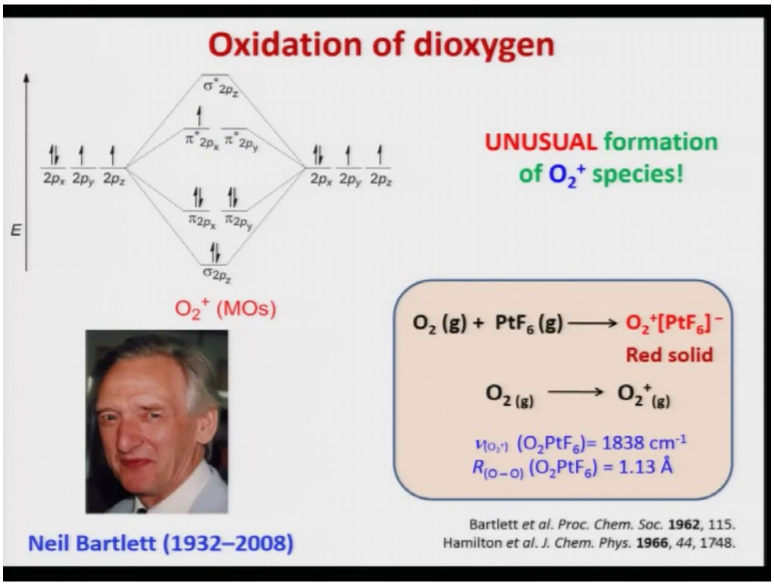

Oxidation of dioxygen

O_2^+ (MOs)

UNUSUAL formation of O_2^+ species!

$O_2\,(g) + PtF_6\,(g) \longrightarrow O_2^+[PtF_6]^-$

Red solid

$O_{2\,(g)} \longrightarrow O^+_{2\,(g)}$

$\nu_{(O_2^+)}\,(O_2PtF_6) = 1838\ cm^{-1}$
$R_{(O-O)}\,(O_2PtF_6) = 1.13$ Å

Neil Bartlett (1932–2008)

Bartlett *et al.* *Proc. Chem. Soc.* **1962**, 115.
Hamilton *et al.* *J. Chem. Phys.* **1966**, *44*, 1748.

We all talk about reduction, but this oxidation of dioxygen as you can see has been achieved by Neil Bartlett long back and what he did he took this O_2 gaseous oxygen PtF_6 also another gas and once they combine it forms red solid O_2PtF_6 and where actually O_2 convert to O_2^+. Bond oredr increases it is dioxygen oxidation and this has been very clear presence of O_2^+ with H_2O stretching frequency is 1838 cm^{-1} which confirms that it is O_2^+. That distance is 1.13 Å. So, all this characteristic features confirms the presence of O_2^+ in this molecule.

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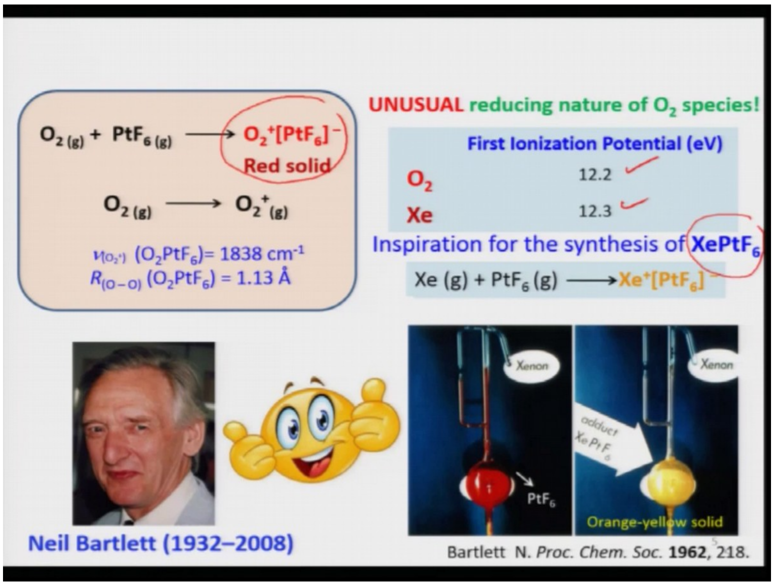

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$\nu_{(O_2^+)}\,(O_2PtF_6) = 1838\ cm^{-1}$
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UNUSUAL reducing nature of O_2 species!

	First Ionization Potential (eV)
O_2	12.2 ✓
Xe	12.3 ✓

Inspiration for the synthesis of $XePtF_6$

$Xe\,(g) + PtF_6\,(g) \longrightarrow Xe^+[PtF_6]^-$

Neil Bartlett (1932–2008)

Bartlett N. *Proc. Chem. Soc.* **1962**, 218.

Once this professor Bartlett looked at this molecule and he saw the first ionization potential between oxygen and xenon. In oxygen it is 12.2 eV and in Xenon it is 12.3. Then he was surprised that Oxygen and Xenon, as you all know Xenon is a inert gas and inert gas will not react at all and that is the reason why it has been kept separately in the periodic table.

Having seen this first ionization potential he could make this O_2PtF_6 successfully isolated as a red solid. It inspire him to look for the synthesis of very similar molecule $XePtF_6$ which he has achieved and as you can see that the Xenon gas and PtF_6 gas forms a beautiful orange yellow solid and this was first noble gas molecule has been synthesised in the laboratory.

So, this tells very clearly that noble gas which supposed to be highly inert can also be reactive and this is the beginning of a new era where the noble gas molecule started synthesising in the laboratory across the globe. In the textbook you will find so many noble gas compound, however, this is the first molecule which was synthesised in the laboratory by Neil Bartlett. So, it is a remarkable achievement.

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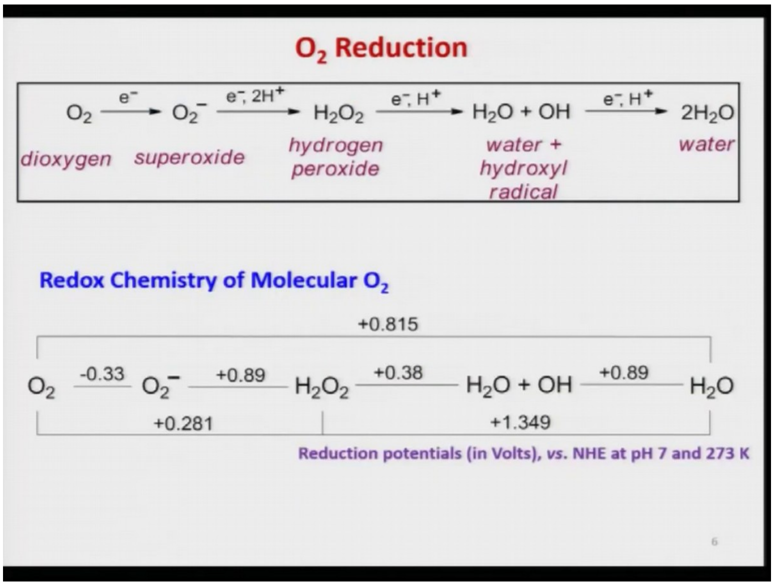

O_2 Reduction

$$O_2 \xrightarrow{e^-} O_2^- \xrightarrow{e^-,\ 2H^+} H_2O_2 \xrightarrow{e^-,\ H^+} H_2O + OH \xrightarrow{e^-,\ H^+} 2H_2O$$

dioxygen superoxide hydrogen peroxide water + hydroxyl radical water

Redox Chemistry of Molecular O_2

$$O_2 \xrightarrow{-0.33} O_2^- \xrightarrow{+0.89} H_2O_2 \xrightarrow{+0.38} H_2O + OH \xrightarrow{+0.89} H_2O$$

Reduction potentials (in Volts), *vs.* NHE at pH 7 and 273 K

Let us look at the dioxygen reduction which is very popular. So, dioxygen O_2 after one electron reduction it will form O_2^- as we have just seen, it is called Superoxides. Further reduction is gives rise to O_2^{2-} minus with a proton it forms hydrogen peroxide which a very popular chemicals in the laboratory. If you reduce one more electron in presence of proton you get water and $^{\bullet}OH$ and $^{\bullet}OH$ if you reduce one electron and have one proton together it also forms water molecule.

So, this is the dioxygen reduction. And we will now look at very carefully their redox chemistry. This dioxygen as you can see O_2 to O_2^- the potential is -0.33 Vand then O_2^- to H_2O_2 +0.89, to H_2O and $^{\bullet}OH$ is +0.38 and then +0.89 toH_2O. However, if O_2 convert to water directly the potential that is required is +0.815 V.

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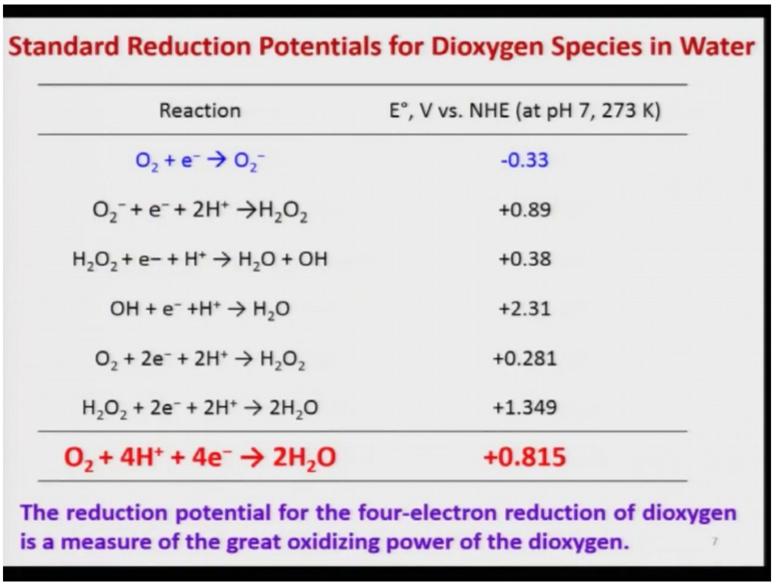

Standard Reduction Potentials for Dioxygen Species in Water

Reaction	E°, V vs. NHE (at pH 7, 273 K)
$O_2 + e^- \rightarrow O_2^-$	-0.33
$O_2^- + e^- + 2H^+ \rightarrow H_2O_2$	+0.89
$H_2O_2 + e- + H^+ \rightarrow H_2O + OH$	+0.38
$OH + e^- + H^+ \rightarrow H_2O$	+2.31
$O_2 + 2e^- + 2H^+ \rightarrow H_2O_2$	+0.281
$H_2O_2 + 2e^- + 2H^+ \rightarrow 2H_2O$	+1.349
$O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$	**+0.815**

The reduction potential for the four-electron reduction of dioxygen is a measure of the great oxidizing power of the dioxygen.

This has been tabulated over here this is the first reaction one electron reduction $O_2$to O_2^- which produce a negative potential of -0.33 and indeed all other potentials are very positive. The most important reaction that $O_2 + 4H^+ + 4e$ gives rise to two water molecules and the potential is 0.815. The reduction potential for the four electron reduction of dioxygen actually shows the great oxidizing power of dioxygen. This reaction indeed represents the major source of energy in aerobic organisms when coupled with oxidation of electron rich food such as glucose.

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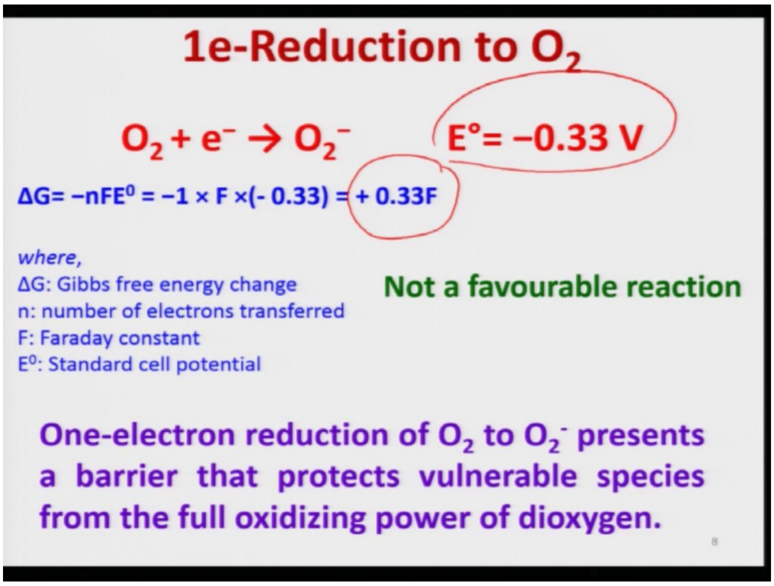

1e-Reduction to O_2

$O_2 + e^- \rightarrow O_2^-$ $E° = -0.33$ V

$\Delta G = -nFE^0 = -1 \times F \times (-0.33) = +0.33F$

where,
ΔG: Gibbs free energy change
n: number of electrons transferred
F: Faraday constant
E^0: Standard cell potential

Not a favourable reaction

One-electron reduction of O_2 to O_2^- presents a barrier that protects vulnerable species from the full oxidizing power of dioxygen.

Let us look that one electron reduce species O_2^-as I have shown that the potential E^0 is negative -0.33. Now, if you convert to Gibbs free energy ΔG you will see a positive values that means, this reaction is not a favourable reaction. However, if you look at all other reactions E^0 is all high positive highly favourable; that means, the oxidising power of dioxygen which is clearly reflected at the end like $O_2 + 4H^+ + 4e^-$ gives rise to water with a potential of 0.815.

This is highly favourable, but this one electron reduction is a unfavourable reactions. So, one electron reduction of oxygen to O_2^- presents a barrier that protects vulnerable species from the full oxidizing power of dioxygen. However, to get the full oxidizing power this $4H^+$ and $4e^-$ have to be given in a concerted way so that they produce water and this oxidizing power of dioxygen can be utilized.

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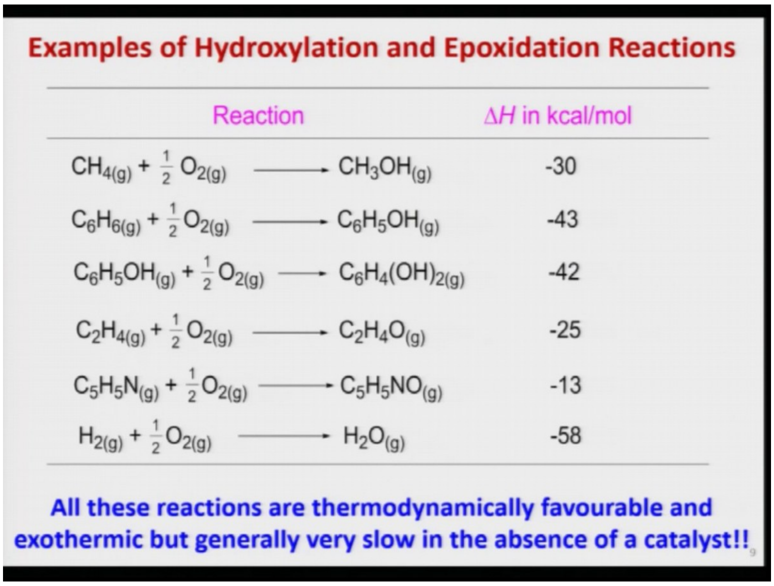

Examples of Hydroxylation and Epoxidation Reactions

Reaction	ΔH in kcal/mol
$CH_{4(g)} + \frac{1}{2}O_{2(g)} \longrightarrow CH_3OH_{(g)}$	-30
$C_6H_{6(g)} + \frac{1}{2}O_{2(g)} \longrightarrow C_6H_5OH_{(g)}$	-43
$C_6H_5OH_{(g)} + \frac{1}{2}O_{2(g)} \longrightarrow C_6H_4(OH)_{2(g)}$	-42
$C_2H_{4(g)} + \frac{1}{2}O_{2(g)} \longrightarrow C_2H_4O_{(g)}$	-25
$C_5H_5N_{(g)} + \frac{1}{2}O_{2(g)} \longrightarrow C_5H_5NO_{(g)}$	-13
$H_{2(g)} + \frac{1}{2}O_{2(g)} \longrightarrow H_2O_{(g)}$	-58

All these reactions are thermodynamically favourable and exothermic but generally very slow in the absence of a catalyst!!

If you look at the hydroxylation and epoxidation reaction, some of these reaction I am showing. Like $CH_4(g) + O_2$ which are all in gaseous phase it forms methanol and ΔH is -30 kcal/mol. It is actually an exothermic reactions. Benzene converted to phenol all this reaction of dioxygens are indeed thermodynamically favourable and highly exothermic, but generally very very slow in absence of a catalyst.

So, although it is a favourable reaction, it never happens just by adding this, you need a catalyst to get that product. Say for example hydrogen and oxygen is giving rise to water it is a highly favourable reactions. But it never happens in environment otherwise we cannot survive because all hydrogen and oxygen which are present in environment will combine and gives rise to water and then this universe will not survive but it never happens.

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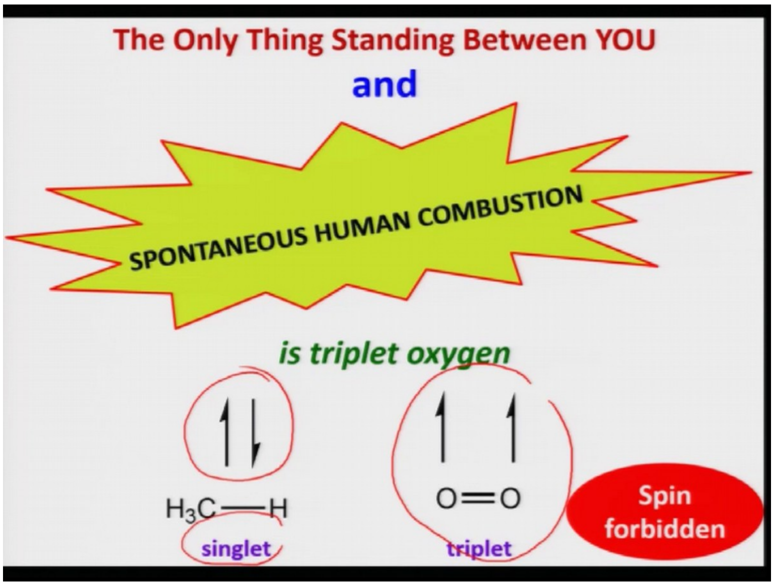

The Only Thing Standing Between YOU

and

SPONTANEOUS HUMAN COMBUSTION

is triplet oxygen

What is the problem? The only thing standing between you and spontaneous human combustion is the triplet nature of dioxygen. Say organic molecules are all spin paired and thus it is called singlet. However, a dioxygen which I have shown you there is two unpaired electrons and in the ground state of course and this is triplet. Thus the singlet and triplet they are actually spin forbidden. They generally do not react and the reaction will be very very slow. So, this is what is the problem ok.

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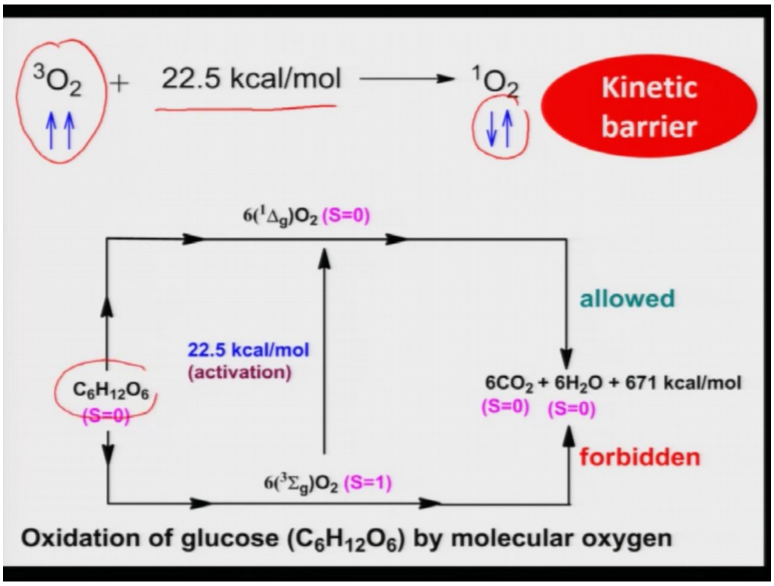

$^3O_2$ + 22.5 kcal/mol $\longrightarrow$ $^1O_2$

Kinetic barrier

Oxidation of glucose ($C_6H_{12}O_6$) by molecular oxygen

So, this is a kinetic barrier that the triplet oxygen if you give 22.5 kcal/mol energy then triplet convert to singlet and then there is no problem. The singlet oxygen can react any organic molecule and it is a spin allowed. However, there is a barrier we call it as a kinetic barrier. They have to overcome this energy to reach to the singlet and then this oxygen is highly reactive. You can see yourself in the respiration what is happening the glucose which is as you all know organic molecule, the singlet and the normal atmospheric oxygen which is a triplet oxygen will not produce $6CO_2 + 6H_2O$ + 671 kcal/ mol.

So, this pathway is a forbidden pathway, the reason is that it is spin forbidden. So, one is singlet dioxygen is triplet so, it will not happen. When it happen when this dioxygen is activated by giving an energy of 22.5 kcal/mol, then this triplet dioxygen convert to singlet dioxygen which immediately reacts with the glucose gives rise to carbon dioxide, water and huge amount of energy. This is what is happening in respiration. So, dioxygen need to be activated in order to react with the glucose which gives rise to lots of energy, which is the source of most of the energy we have in our day to day activity.

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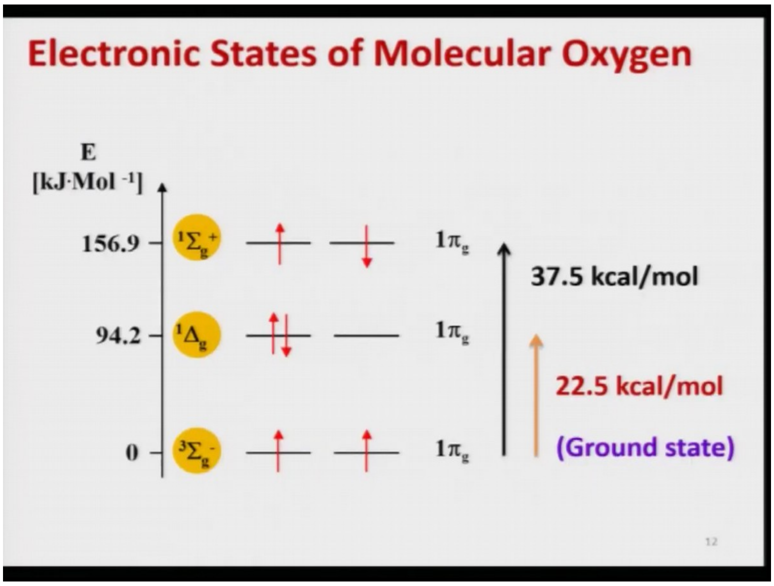

Electronic States of Molecular Oxygen

Let us look at this electronic states of molecular, oxygen as this is the ground state which is Σ, is a triplet state, this is $1\pi_g$ and the first excited state is a Δ state, it is singlet $^1\Delta_g$ and the energy which is required to convert from a triplet to singlet $^1\Delta_g$ is 22.5 kcal/mol. And if you add like 37.5 kcal/mol energy then it will leads to another singlet state the next excited state. You see that this is also a singlet but one is up spin one is down spin.

So, eventually it leads to a singlet state and $^1\Delta_g$ you see that both the spins are paired and leading to a singlet stateof course, you need to provide a energy of 22.5 kcal/mol to reach to that state. Then the dioxygen which is otherwise not a reactive species becomes highly reactive. It reacts immediately with organic substrate. We will see some of these reactions for example, it is a highly reactive singlet oxygen.

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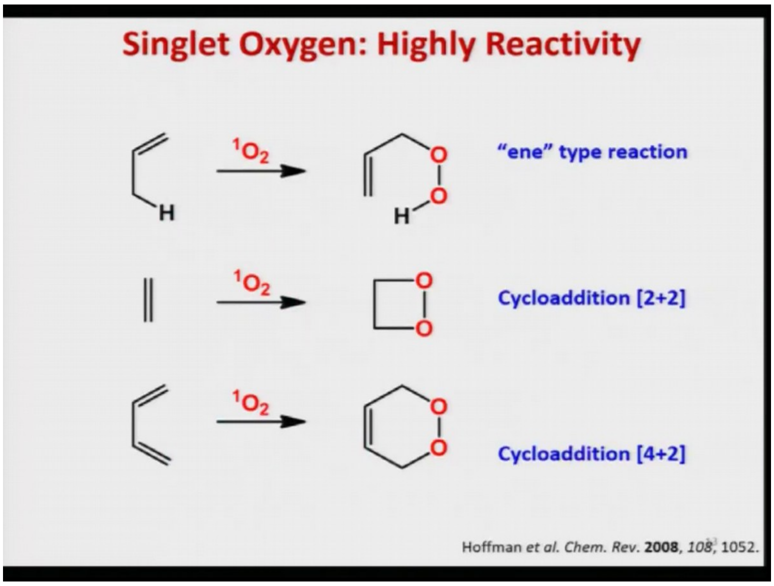

Singlet Oxygen: Highly Reactivity

"ene" type reaction

Cycloaddition [2+2]

Cycloaddition [4+2]

Hoffman *et al. Chem. Rev.* **2008**, *108*, 1052.

Once we produce this singlet oxygen, it immediately react with the organic substrates and there is a large number of substrates which is there any text book you can find it. I am showing just three examples to let you know that how reactive it is? like this singlet oxygen it produce like O-O (Refer Time: 18:22) as you can see over here this is ene type reactions. And if you have a double bond with the singlet oxygen it can forms a cycloaddition [2+2] and if you have something like this with the singlet oxygen it produce a cycloaddition [4+2]. There are many many examples known now where the singlet oxygen shows remarkable reactivity.

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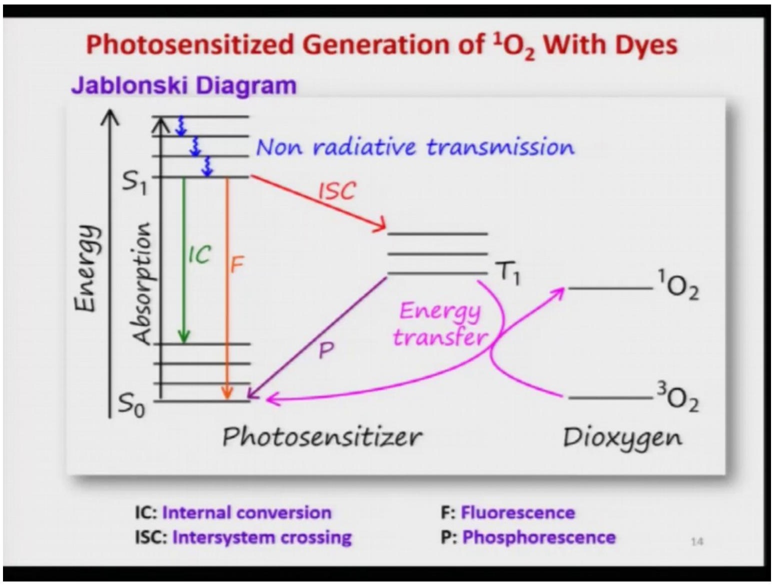

Photosensitized Generation of $^1O_2$ With Dyes

Jablonski Diagram

IC: Internal conversion
ISC: Intersystem crossing
F: Fluorescence
P: Phosphorescence

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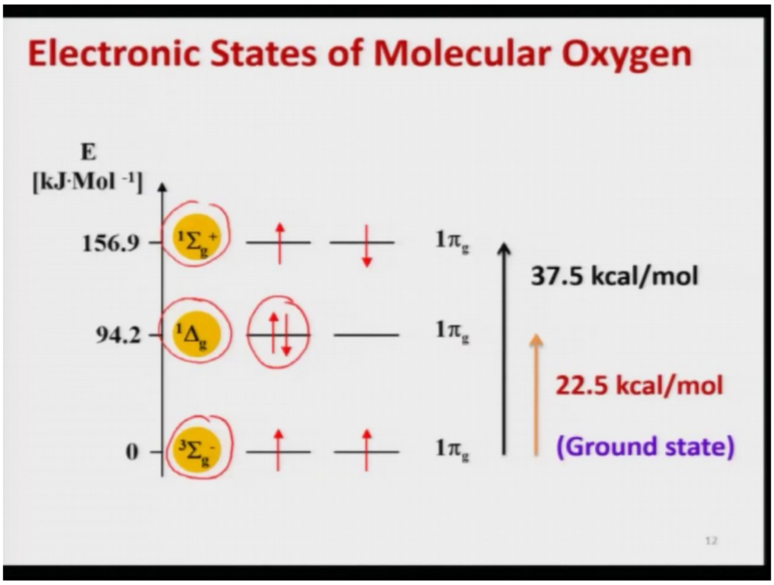

Electronic States of Molecular Oxygen

This singlet oxygen as I have already said that you require something 22.5 kcal/mol which is a huge amount of energy. You all know the Jablonski diagram very well. What is exactly happening if you have a photosensitizer see it has a ground state as zero and you shine light and then what would happen? The photosensitizer will be in excited state of course, this is also a singlet state and there are many excited state like S_1, S_2, S_3, S_4 and after non radiative transmission it can comes to this S_1 state and this can go back via the internal conversion to the ground state again.

And if it goes back to the S_0 state this will produce it is called fluorescence. However, via intersystem crossing it can go to the triplet state and then from triplet it goes back to the singlet state the ground state. And you see that this is not a favourable transformation triplet to singlet and this would be a slow and this is phosphorescence.

This triplet state is a high energy state as you can see this can transfer energy and dioxygen which is the triplet state can take that energy and convert to the singlet oxygen. So, coupling of these two leads to the formation of the singlet oxygen and this singlet oxygen can be utilized for a various chemical transformations. I will show you some very interesting applications which all of you are aware of.

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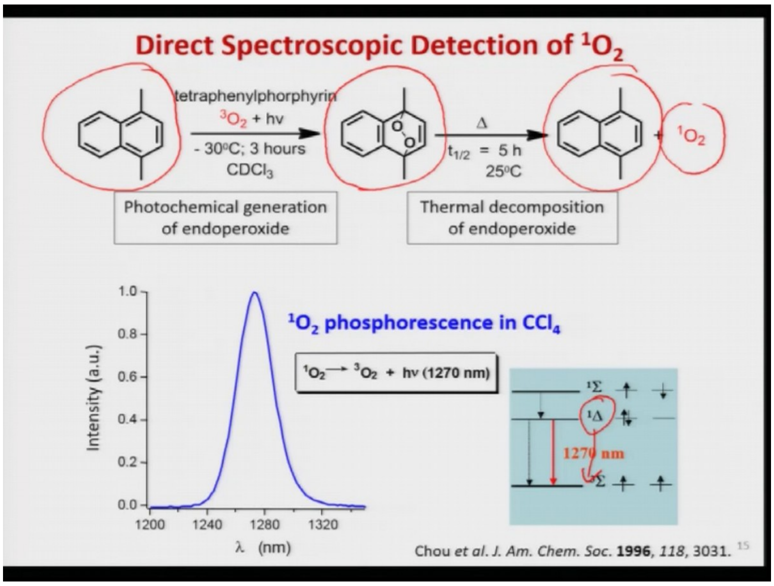

Direct Spectroscopic Detection of $^1O_2$

Photochemical generation of endoperoxide

Thermal decomposition of endoperoxide

$^1O_2$ phosphorescence in CCl_4

$^1O_2 \rightarrow {}^3O_2 + h\nu$ (1270 nm)

Chou *et al.* *J. Am. Chem. Soc.* **1996**, *118*, 3031.

Now, this singlet oxygen also detects its spectroscopy. You see that tetrapphenylphorphyrin just like I have shown that if we irradiate triplet oxygen with light in the presence of tetrapphenylphorphyrin at -30°C for 3 hours, then it will give the singlet oxygen which will react with 1,4-dimethylnaphthanlene and produce this types of endoperoxide intermediate with $t_{1/2}$ around 5 hours at 25°C converts back to the parent molecule and releases very reactive singlet oxygen which as I have shown it can be detected in phosphorescence.

This peaks comes at 1270 nm, when it is coming back from the Δ to the Σ to the ground state the triplet state, it produces phosphorescence band at 1270 nm which confirms the formation of singlet oxygen during this process. The singlet oxygen is highly reactive, and it can be utilised by it for various chemical transformations, various important applications. So, one of this very important applications is the PDT drug, photodynamic therapy drug.

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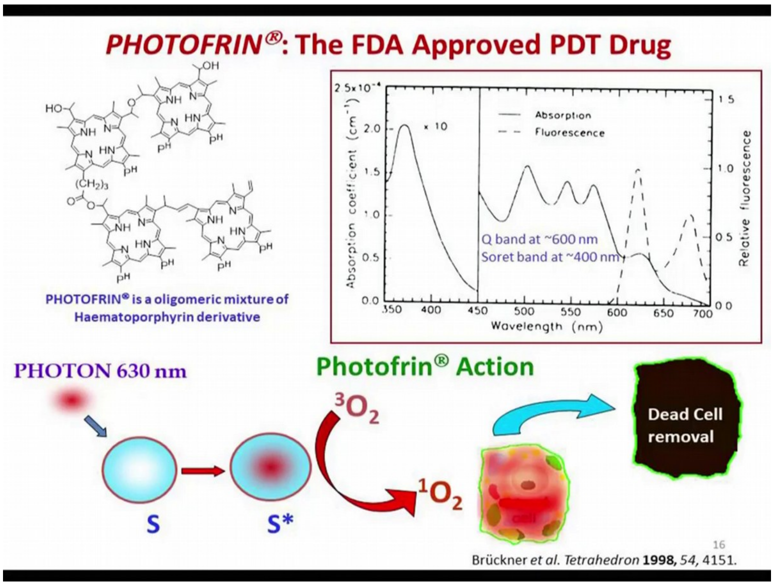

PHOTOFRIN®: The FDA Approved PDT Drug

PHOTOFRIN® is a oligomeric mixture of Haematoporphyrin derivative

Brückner *et al.* *Tetrahedron* **1998**, *54*, 4151.

For example, what is happening that the substrate if you keep photon the light, what will happen? The photosensitizer will go to the excited state S^* and as I have shown earlier so, this state can transfer the energy to convert the triplet dioxygen to a singlet dioxygen. It is a coupled process and once this you form a singlet oxygen the singlet oxygen as I have said that highly reactive indeed the cancer cell if you give the singlet oxygen. singlet oxygen will burn this cancer cell and the cancer cell becomes dead cell.

This is one of the very popular technique that are being used as a photodynamic therapy and photofrin which is actually a oligomeric mixture of this multiporphyrin molecule and this is a photosensitizer that is what is being approved so far and popularly utilised. Now, there are many many PDT drug know today which are showing better activity and this is very promising field of research. You see that what you are using? you are using light and dioxygen, both are very friendly and as a result of that and of course, you are using a photosensitizer here it is photofrin, but you generate a singlet oxygen which is highly reactive which are used to kill the cancer cell ok.

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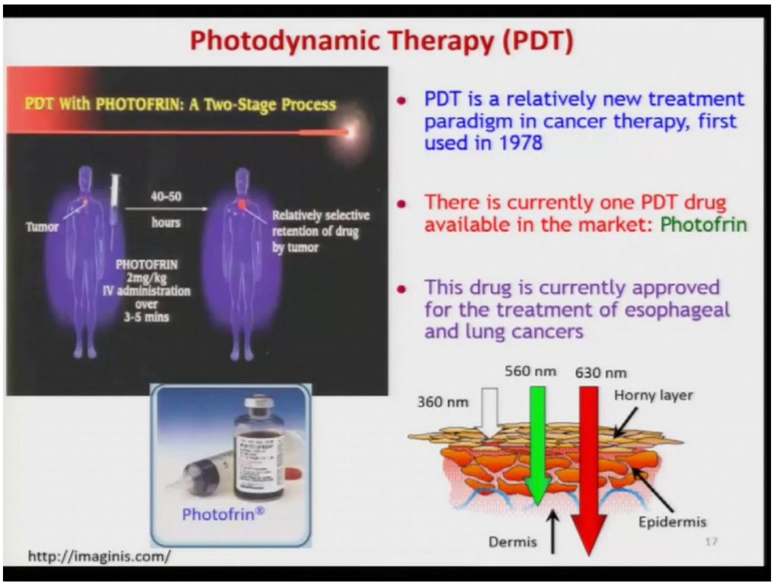

Photodynamic Therapy (PDT)

- PDT is a relatively new treatment paradigm in cancer therapy, first used in 1978
- There is currently one PDT drug available in the market: Photofrin
- This drug is currently approved for the treatment of esophageal and lung cancers

http://imaginis.com/

This techniques here I will give little bit more information about this photodynamic therapy. Photodynamic therapy is relatively new treatment in cancer therapy, first used in 1978. There is currently one PDT drug photofrin. This drug is currently approved for the treatment of cancer. So, what is actually happening in this PDT photodynamic therapy? If you shine light so, most useful light is around 630 nm which is called a red light. Why red light? Because red light penetrates the cell more than the other light.

So, that is why red light is so important. So, red light actually penetrates the tissue and it reaches the point. So, how it is happening? For example, here this is a diagram is showing like PDT with photofrin like the patient having tumour cell say for example, here it is tumour is there is shown over here it is a tumour. So, 40 to 50 hours before you are injected the photofrin the photosynthesizer is basically 2 mg/kg and slowly slowly you are added this photofrin and then this photofrin will selectively of course, it goes in other parts of your body as well but it also concentrated to this tumorous cell.

And then if you shine a red light and produce singlet oxygen then cancel cell will be burnt out of those singlet oxygen, then your cancer would be cure. So, this is such a simple technique cost is much less and you are only using dioxygen and light for this process and produce singlet oxygen. So, this has various applications that one can utilize this singlet oxygen.

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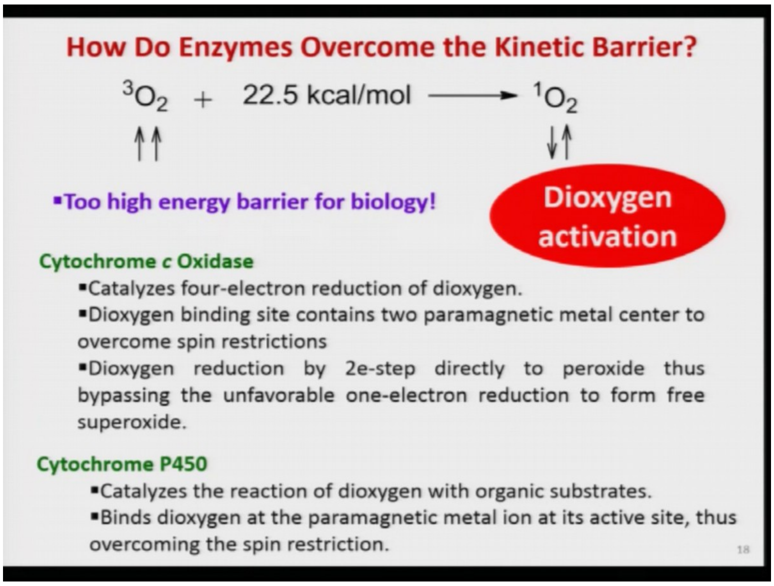

How Do Enzymes Overcome the Kinetic Barrier?

$$\underset{\uparrow\uparrow}{^3O_2} + 22.5\ \text{kcal/mol} \longrightarrow \underset{\downarrow\uparrow}{^1O_2}$$

- **Too high energy barrier for biology!**

Dioxygen activation

Cytochrome *c* Oxidase

- Catalyzes four-electron reduction of dioxygen.
- Dioxygen binding site contains two paramagnetic metal center to overcome spin restrictions
- Dioxygen reduction by 2e-step directly to peroxide thus bypassing the unfavorable one-electron reduction to form free superoxide.

Cytochrome P450

- Catalyzes the reaction of dioxygen with organic substrates.
- Binds dioxygen at the paramagnetic metal ion at its active site, thus overcoming the spin restriction.

Now, coming back to this triplet oxygen and singlet oxygen. So, there is as I have said that triplet oxygen if you give energy of like 22.5 kcal/mol you produce singlet oxygen. So, there is a kinetic barrier one has to cross so, that the singlet oxygen can then be highly reactive and you can do that in the laboratory this 22.5 kcal/mol energy is too much for a biological system. Now, how do enzyme overcome this kinetic barrier? Now, this is what is called dioxygen activation.

Indeed the dioxygen need to be activated. This amount is too much for the biology. One need to reduce this energy in order to make use of this singlet oxygen, otherwise it is impossible to do that ok. So, dioxygen activation we these days we are hearing this; this is basically how biology can reduce this energy so that it can be affordable then ok. Say I will give just two example so, you just tell you that how biology actually bypass or overcome this kinetic barrier. Now I will be discussing in details indeed the Cytochrome *c* oxidase which actually produce energy where as dioxygen gives rise to water and release huge amount of energy.

So, what is happening that if you add four protons and four electrons in a concentrated way, this is thermodynamically favourable, then you do not go through that one electron reduce species. So, dioxygen binding side contains two paramagnetic metals centres, one is iron one is copper where dioxygen binds and it actually formsO_2^{2-}. Dioxygen is in triplet state, is a paramagnetic. So, the paramagnetic to paramagnetic metals centre binds the dioxygen and then it reduce by two electrons produce peroxides and thereby bypassing these unfavourable one electron reduction process to form superoxides.

Now, I will give another example which we will discuss it in details in subsequent lectures, is that Cytochrome P450, another very popular enzyme. This enzyme catalyses the reaction of dioxygen with organic substrates. Here also the dioxygen binds at the paramagnetic metal ion and thus overcome the spin restrictions. So, your dioxygen is triplet paramagnetic, your metal is also paramagnetic so, no problem. So, it overcomes this kinetic barrier and reaction is possible and nature utilize this path to overcome this kinetic barrier.

There are many such examples not all enzymes go through the same way where some enzymes activation is required. I am not going to discuss today in details. In summary I have discussed today how we are protected from the great oxidising power of dioxygen. We talk about thermodynamic and kinetic barriers for the reactions with dioxygen and also how one can overcome that. In my next lecture I will talk about how dioxygen is utilized in respiration to produce huge amount of energy that we use every day.

Thank you.