Inorganic Chemistry of Life Principles & Properties

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Lecture – 55
Highlights of the course – Part III

Welcome you to the next class on the Inorganic Chemistry of Life Principles and Perspectives. Last 2 classes I have tried to cover some highlights of all the topics that I have discussed and looks like I will have one more class; maybe another class too to cover. Initially I have covered all the highlights of the introductory aspects then I have covered the introductory aspects of the highlights of the alkali alkaline earth and then vanadium, then manganese.

So, let us start with the iron in the bio inorganic chemistry or the biological inorganic chemistry the highlights. The highlights in case of the iron are something arising from 2 categories of enzymes called Heme based and those which are not having heme. And all of these are involved in oxidative reactions, reductive reactions; so therefore oxido reductase reactions.

They are also involved in transport reactions of oxygen, electron and iron. So, therefore, so we have a huge in a plethora huge list of enzymes present under the iron category and that is where you see; if you look at the amount of the element iron present in the body is much higher than any other trace element which is about 3 to 4 to 5 grams per a body weight of 70 kilograms of body this. So; that means, I have huge number of iron enzymes are being involved.

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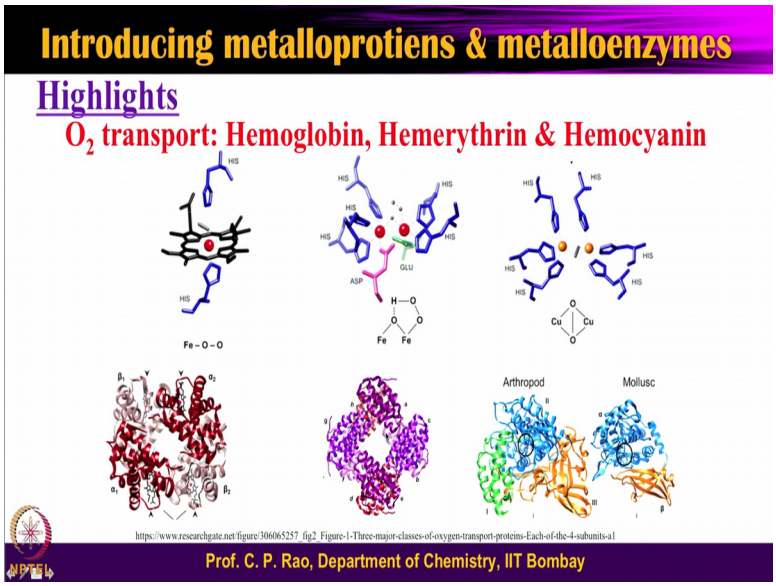

And since it is the highlights I just tell you do some other things; I explained a lot of features dependent on the transport, transport of the oxygen. I have tried to compare transport of the oxygen with respect to that of the stories the oxygen by myoglobin.

And then I compared the Hemoglobin with the Hemerythrin and the Hemocyanin which is in invertebrates and which is in molluscs. So, therefore, you have the hemoglobin, you have the perfirine and these non perfirine with the 2 iron ions and 2 copper ions.

So, the kind of a oxo species is iron OO which is not so much perturb with the oxygen-oxygen bond in case of hemoglobin. And in case of hemerythrin, it is more or less like a HO 2 kind of species; so hydroperoxide kind of a species and when you go to the hemocyanin; it is a basically a peroxo species. In fact, this can be very well established by variety of spectroscopy including vibrational spectroscopy too ok. Aspect of interest in this is that you see that the oxygen nature is different from one to the other to the other; so, when it comes to this; it is a O 2 minus.

So, when it has to act as a O 2 transport; obviously, it has to release not O 2 2 minus; it has to release at the end OH 2. So, therefore, there has to be re oxidation of this and which is taking care in those enzymes whereas, in the enzyme of human this is very slightly spectrum and based on the conformational changes; it can get back to the simple O 2 and the O 2 is liberated.

So, therefore, the protein conformation itself will take care of ensures that the O 2 is released not the O 2 or O 2 minus dot kind of thing.

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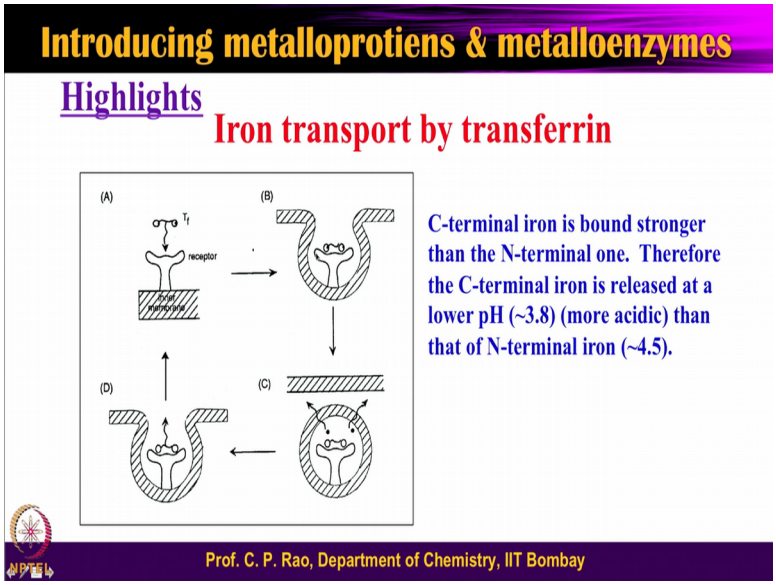

Also I have explained about the iron transport by transferring; transferring has got 2 sites C terminal site, N terminal site; both the sites iron is bound. Important point is in these cases; the iron is bound only when carbonate ion is present and we know that it is allosteric effector because in order to form the metal core you require the carbonate factor that we have seen. And these 2 N terminal and C terminal differ by a very small change in their strength and this is indeed reflected when these are released to ok.

So, the receptor sites and the cell membrane will receive the transferrin which is bound with the iron ions and will basically make recycle and engulf inside. So, once it is engulf inside as the pH changes, the ions are released. Initially the N terminal ion is released at a slightly higher pH such as 4.5 and at 3.8 at a lower pH which is around 3.8 C terminal is released and this how the iron transport in fact, takes place.

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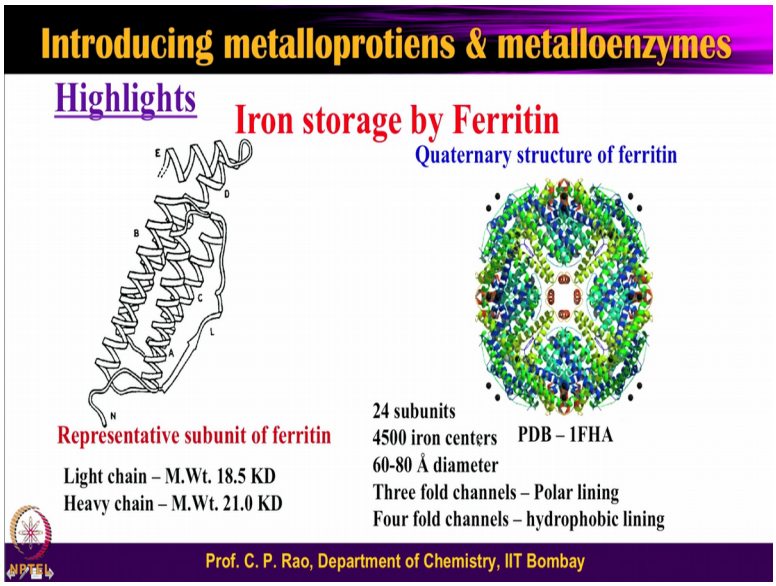

Followed by this, I have talked to you about the iron storage by ferritin; ferritin is a huge protein having 24 subunits, 4500 iron ions, about 7 to 8 nanometers diameter. And there are 2 major features; one is three fold axis of channels and fourfold axis a channel, these are the life lines of the ferritin. So, these will carry ions from output in or from into out; it could be ions, it could be reducing equivalents etcetera all of these things are being.

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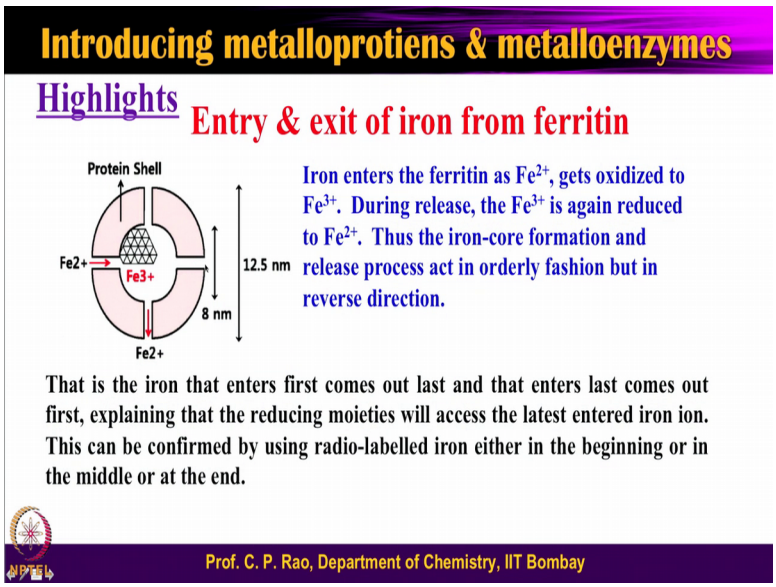

In fact, the way if you see the aligning inside as the iron 2 plus enters in iron 2 plus binds to the carboxyl terminals interior, then oxidized by the oxygen and then further bridges

by the phosphate. So, you get basically some kind of an iron oxo phosphate kind of a bridge kind of a species which will grow from one to the other.

And when you release this by using the reducing equivalents again iron 3 plus is reduced to iron 2 plus and then the iron 2 plus come out; I am sure you know why iron it has to be converted to iron 2 plus. Because iron 2 plus is highly mobile as compared to labile; let us just use the word labile as compared to the iron 3 plus.

So, that is where the things are happening and entire thing is very orderly fashion it happens both the formation of the iron cluster formation inside, as well as the release of this forms very highly. So, therefore, you have the entry and exit the iron from the. So, it enters as iron 2 stays as iron 3, but releases as iron 2 again and this is what we need to remember.

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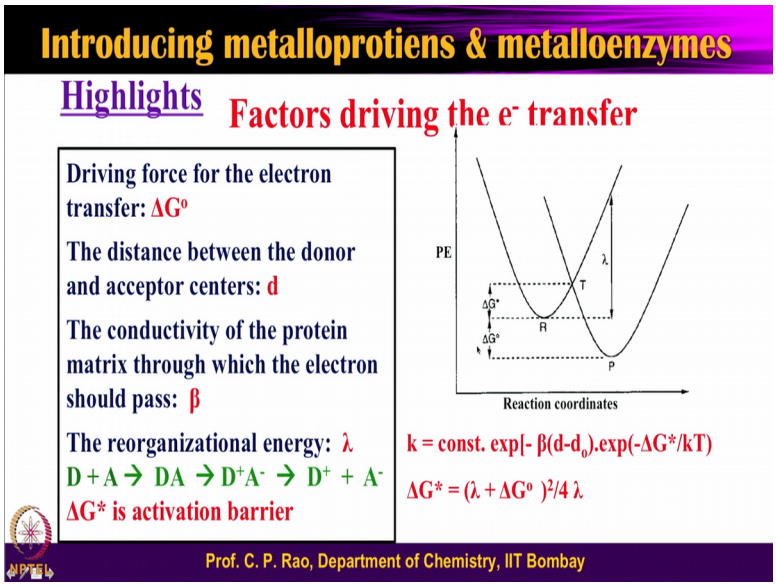

Followed by the all this transport phenomena; I have come to the stage of the electron transfer to introduced, I have introduced electron transfer. Of course, electron transfer depends upon the potential difference between the donor and acceptor in terms of delta G 0. So, as long as the delta G 0 is negative; then this is physical kind of a reaction.

What else does it depend on? It does depend upon the distance between the donor acceptor, it does depend upon the conductivity of the medium between the donor and acceptor ok. And it also depends upon the reorganizational energy; what is the

reorganizational energy? That is you have you see that when the donor, acceptor come close by; you get a donor acceptor complex.

But that donor acceptor complex may not be in a good posture to transfer the electrons. So, it has to change its posture and this portion change is by the conformational change or reorganization. So, this particular energy difference is referred as the reorganizational energy. So, the smaller this value the greater the rate of the reaction is there.

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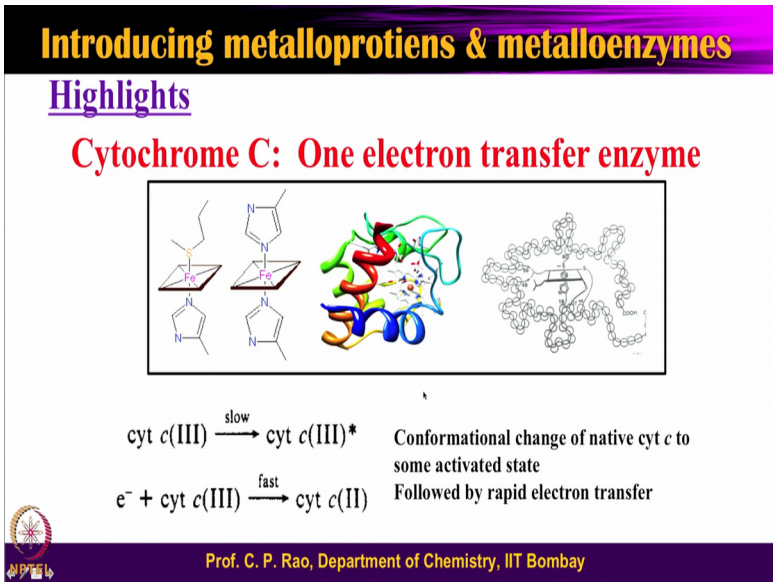

So, these are the factors that are think and the Cytochromes are involved and when the cytochromes both the 5th and 6th coordinations are blocked by histidine or histidine ethylene, then these are not suited for oxygen activation these are suited for only electron transfer.

So, what kind of an electron transfer? Electron transfer from iron 3 to iron 2 ; so, in effect any cytochrome C can only transfer 1 electron not more than that if somewhere 3 or 4 electrons are required; that means, 4 times then it has to work 3 times there has to work etcetera.

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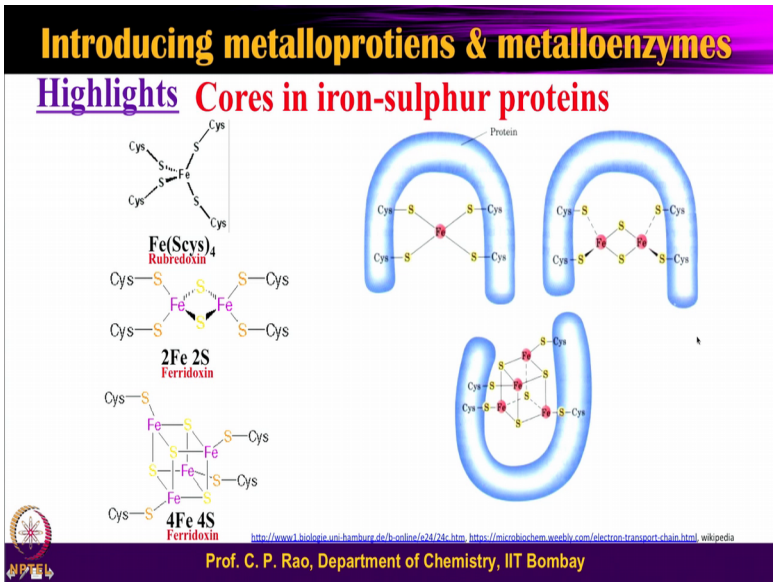

And then after having looked at the heme based electron transfer proteins; I have taken you into the iron sulfur proteins 1 iron 4 cysteine; which is called the Rubredoxin, 2 iron 2 sulfide which is called Ferredoxin, 4 iron 4 sulfur called again Ferredoxins.

These sulphides can be easily understood by adding mineral acid which will give H 2 S and your nose can smell that good enough. And there are systems where protein have got 1 4; Fe 4 S or more than 1 4 Fe 4 S in the same or a combination of these kind of things etcetera. And these differ in their redox potentials of that.

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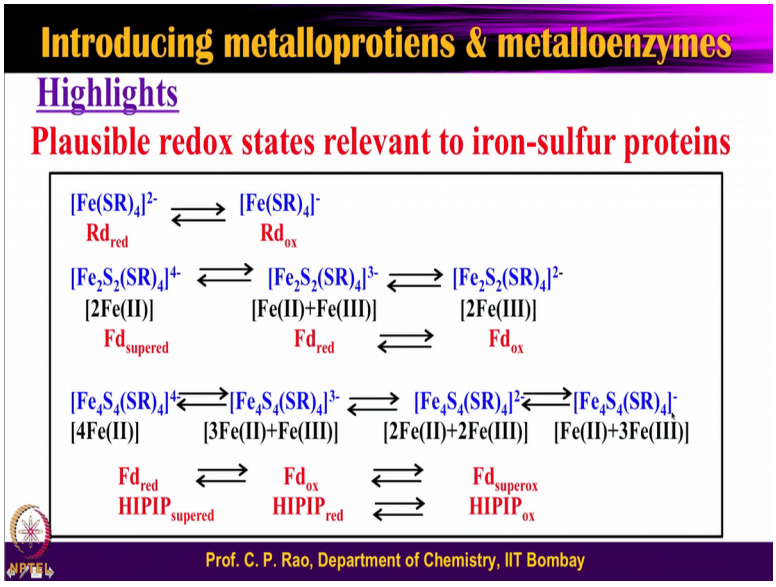

And in some of the cases these iron sulfur proteins clusters are buried inside and stabilized by hydrogen bonds; there the redox potentials are more positive such things are known as a high potential iron sulfur proteins.

And as you can see overall from here whether you have a 1 iron, whether you have a 2 iron, whether you have a 3 4 irons; you always have only 1 facile electron transfer. In 1 iron; obviously, there is one the same reduced in oxidized, when you have 2 iron; there are 3 possibilities, but not all 3 possibilities are formed in enzymes, only these 2 possibilities are formed. So, 1 iron to 1 iron 3 both iron III; not with the both iron II because high reduced enzyme can could be you know dangerous to the system.

Similarly, when you have 4 irons, there are many combinations are there of which the combinations that are possible between this and this ok; Fe reduced, Fe oxidize and if the protein is already in the Fe oxidized, then it can be super oxidized ; this is in the normal ferredoxin. And if you have a high potential iron sulfur protein ferredoxin, it can only go from 3 iron II, 1 iron III to 2 iron II and 2 iron III; never it goes to this at all, never it goes to this at all ok.

So, therefore, several of the oxidation states of these are prevent, are not accessed by the system; because the system will get a too reactive kind of a species and unwanted things can happen. So, that is where the thing.

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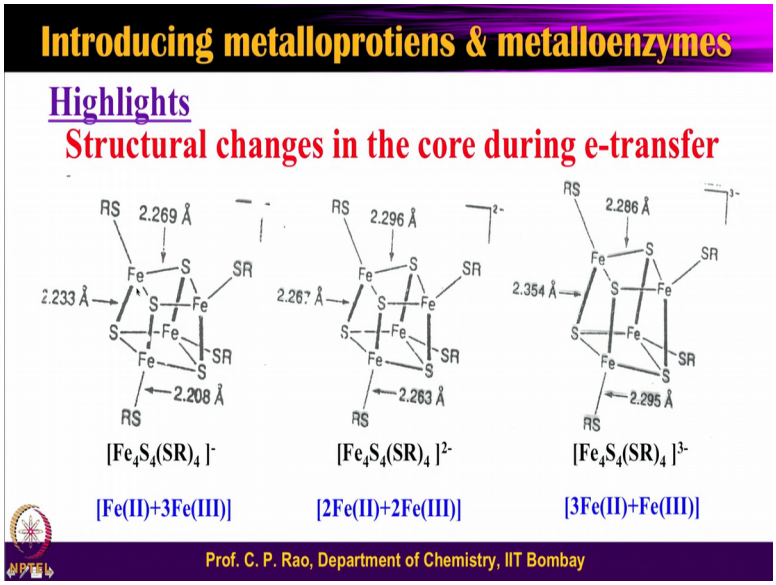

In fact what happens in that; you if you see that as you go from this cluster to this cluster to this cluster; you have 1 minus, you have 2 minus, you have 3 minus, so your the number of a reduced in this, this is the 3 iron 3 is to iron 3 is and 1 iron 3 and that is how it is.

As you reduce; that means, you add electron this particular bound you see that is increasing, this particular bound is also increasing. And so, therefore the core is expanding and if you go in the reverse direction, the core is reducing. So, the core expands and core reduce reduces expansion and contraction; not reduce, contraction. So, expansion contraction in this will take the electron transfer to a kind of a useful thing.

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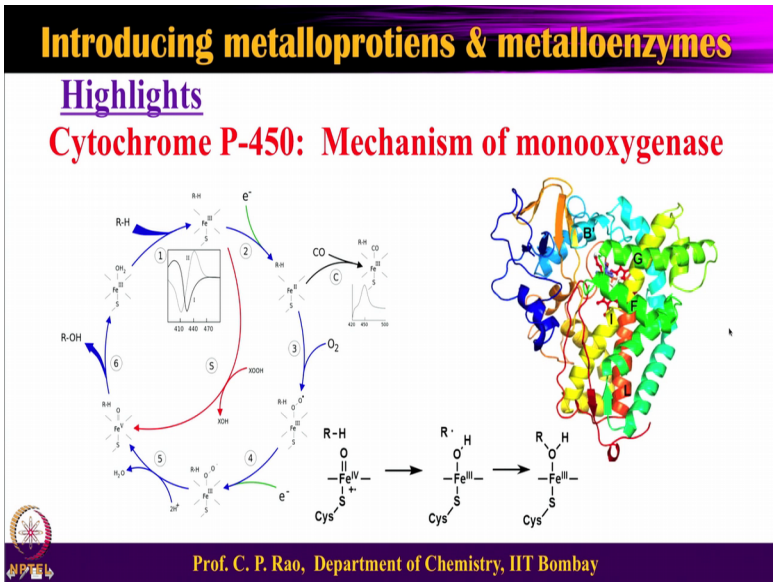

So, during the electron transfer the core of the irons iron sulfur cluster expands and contracts. And that reflects in the conformational state of the whole protein that is being surrounded that.

Having explained the electron transfer, then I have smoothly taken a transition into this the oxygenease enzymes. We have the monoxygenase, dioxygenases both oxygen is based on the heme; not based on the heme, all of these are there in the iron. And I tried to look at explain you at one example at least of each of these things.

And example here given you set up from P-450 and nomenclature etcetera, I am not spending time here; as you know this is from the absorption wavelength etcetera ok.

Some important features in this monooxygenase; monooxygenase means only one O atom of the O 2 is added to the substrate; the other O atom of the O 2 goes as water. In case of dioxygenase both the O's or the O 2 are used for the substrate oxidation and that is what the thing is.

So, the iron enzyme in the iron III form is this is a resting state, when the substrate are enters into the close proximity of the of the iron center; that is a conformational change and this triggers the electron transfer ; that means, enzyme is activated. So; that means, after the substrate comes in only the electron transfer takes place.

Because after the electron transfer takes place; the electron that is being the added to the iron III, becoming iron II is very active species. Therefore, that will is ready to give away the electron therefore O 2 has to be ready in that. So, then O 2 one electron, then second electron etcetera and then goes through the via ferriloxo and then it will add hydroxylation to the substrate and the water will go; so, this is interesting.

Suppose one more to say that here the question is; if the substrate does not come into come close to the enzyme and if enzyme receives the electron is there is any great danger? There is a great danger because the substrate is not there electron comes in the contact, if the oxygen is present there; then oxygen will get activated and you will get oxo radicals.

Therefore, those superoxide radicals are dangerous to the system; the system can get hydroxylated, it can be the same protein can get. So, therefore, the nature has chosen the mechanism in such a way that the first the entry of the substrate and then followed by these things.

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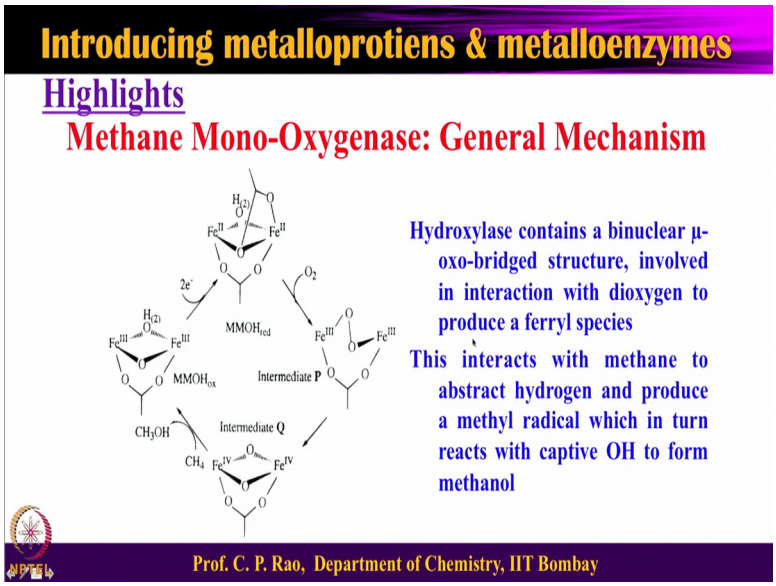

Let us look at an example for the another example this example cytochrome P-450 is used for camphor many other things. But one specific one which is converts the methon; methane to methanol is called the methane monooxygenase.

And methane monooxygenase is unlike the cytochrome P-450 is not a heme kind of a protein, it is a non enzyme. As you can see, in its resting state; in its resting state it is in the di-iron center and this di-iron center is; obviously, activated in presence of the; of course, substrate which is not shown here, but I tell you, it is there in the schemes that I given you.

And then takes up 2 electrons and the 2 ions 2, 3s will go to 2 iron II and now it is very well poist for O 2 to be oxidized, O 2 to be reduced. So, the O 2 can bridge between the 2 iron IIIs and then receive 2 electrons; so therefore, you get some kind of a peroxo kind of a spieces. And this will convert to the ferreil kind of a Fe 4 kind of species with the oxygen bridging.

So, you are going from iron III to iron II, iron II to iron III again iron IV. So, II to III to IV and then this will take your methane to methanol and the one of the other oxygen goes as the water and that can circulate. So, some similarities you can find between both of them, but in case of methon monooxygenase; it is not one iron it is the 2 iron centers ok.

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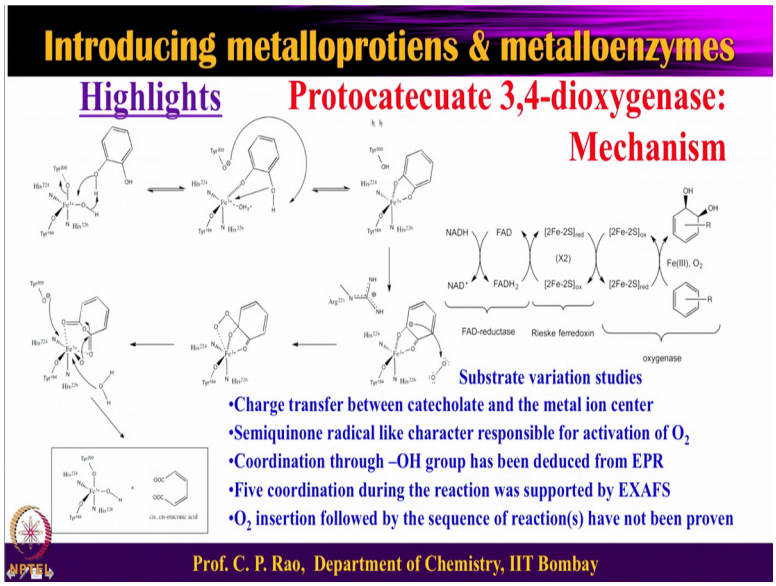

Also explain an example for the dioxygenase; an example of taken was a protocatecuate 3, 4 dioxygenase. And this is again a non heme enzyme; this is again a mono iron center enzyme. And this enzyme has got a 5 coordination with some kind of a tyrosines and histidine bound and where in one of the coordination can be sort of expanded for the binding of the catechol into this.

And if the property the catechols is that you have a phenolic moiety, they can undergo e phenol keto or enol keto kind of tetrometism ; which will go through the radical neutral kind of a species; ionic species. So, binding through mono then become its bidentate and now this can deactivated by this particular electron then electron is introduced into the O 2 at this stage, the O 2 is reduced between the ion; ion in this substrate and then substrate finally, gets cleaved by taking both the oxygen's into it ok.

So, in all these the redox chemistry occurs by NADH; then FAD, then 2 iron, 2 sulfur; another 2 iron 2 sulfur in the active center too. So, we have looked at reduct you know there is other dioxygenase is in there I am not shown in the highlights; was the tryptophan, oxidase kind of a one. So, therefore, in that case it is a heme based enzyme and that also I have given in the class.

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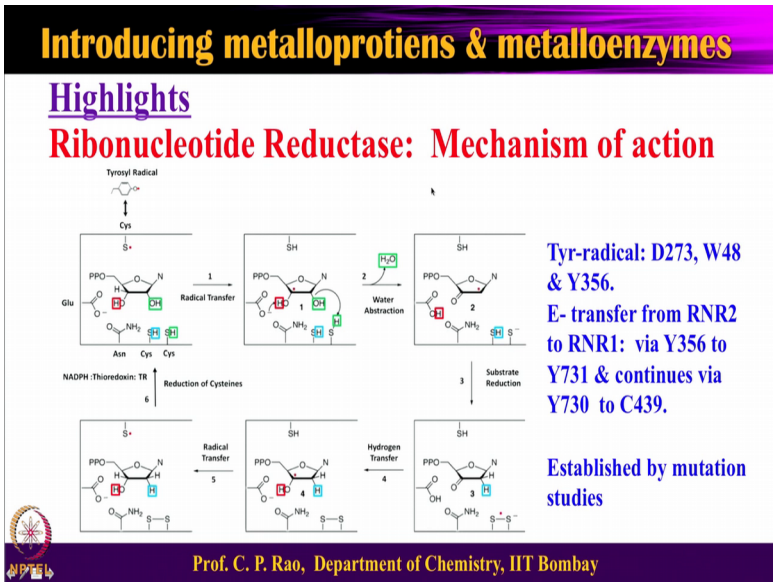

It is so far we have looked at the oxygenaes; then I think we need to look at some of the reduction chemistry. So, Ribonucleaotide Reductase has got a dinuclear iron center, the role of this is stabilizing a radical from the tyrosine which is very close by within 5 Angstroms from this one. And it is this which is involved in the activity, this will generate radical at the cysteinlie center which is in a neighbor subunit. And this radical is transformed to this particular center and from this center it is transformed to this center and then you have a d oxygenation and then goes to this.

So, the role in this particular enzyme is not a direct catalytic; it is an indirect, but it stabilizes the tyrosine radical and rest as things goes like the consequential steps as shown over there.

So, radical-radical formation etcetera and this radical is transferred to this particular position and this is again racemized into that and then oxidation etcetera and then this will lose the oxygen and then hydrogen comes into the reduction. So, you have the dithiol and going into the disulfide and then again back to the dithiol. So, this is one thing and this is the radical and radical is transformed.

So, this whole thing happens in one subunit of the protein, this whole thing happens in the sub another subunit. This is a binding subunit plus the radical which is being transferred subunit; so this can recognize the different nucleotides coming into the

protein. So, therefore you can identify the deoxy ribonucleic acids that are coming into the system too ok.

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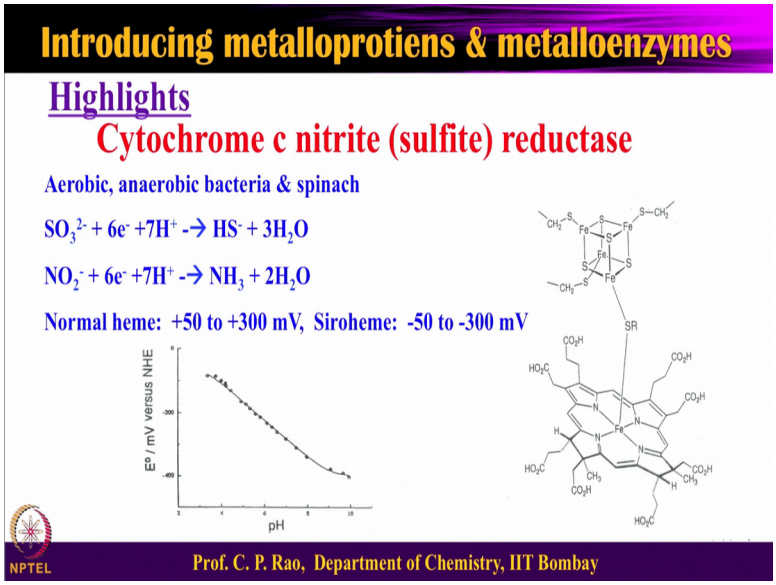

Some additional highlights on the iron enzymes start taking their shape from let us say other kinds of reductases. See here example cytochrome c nitrite sulfite reductase.

So, sulfite S O 3 minus HS minus this is a 6 electron, 7 proton reaction ; nitrite to ammonia, this is a 6 electron plus 7 protons, this is the ammonia and 2 H 2 O. And this kind of things you know you require a lot of number of electrons; therefore, simple heme are not sufficient enough.

Therefore, these hemes are connected with the iron sulfur cluster and such a situation is called siroheme. So, sirohemes are important essential for doing such a huge level of the huge level of the reduction. You see 6 electrons; 6 electron there is a proton; so, how do you find out electron proton combination in a redox process is just by looking at the redox potentials as a function of pH ; these are called poor box plots from this the slope you can identify the number of electrons versus the number of proton ratio as well. It is a very powerful which I explained in the beginning.

So, we have cases where the iron sulfur clusters are there; the we have cases where the iron hemes are there, we have a case where both of these are present simultaneously together in the nitride sulfite oxidase too.

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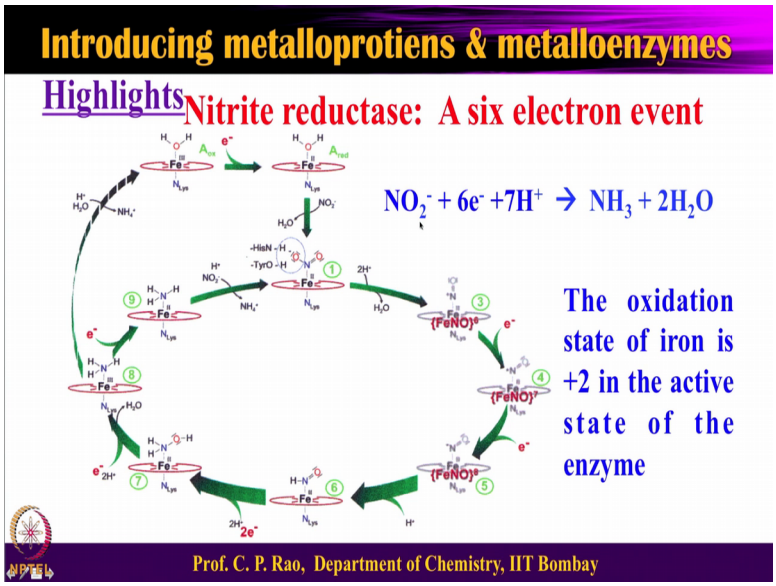

Another bit more the complicated one; which I talked to you was in the previous slide was the nitrate reductase and this is N O 2 minus 6 electron, 7 protons give N H 3 into H 2. So, the resting enzyme in iron III with water and in presence of the electron; first electron it gets activated.

Once it is activated; the first electron it is ready for binding to the nitro group and this nitro group will displace the water that is present at the iron center. Now it is ready on the platform; now it has come into the basically a Kabaddi court. So, it is basically like a this is a court is getting ready, the player is entering here and then ready with the playing for the Kabaddi kind of a play and then it goes with the proton, electron; proton, electron kind of a sequences.

Here N O 2 binding reduction, another reduction and then makes this one into the gen O. And then H 2 N OH like somewhat like hydroxyl amine species and then where you lose your water and then the ammonia etcetera.

So, that is how it is basically you to lose the ammonia and water, one water is going in the first step and the second water goes at this particular thing. So, that is where you have; this is the O 2 water and then you know these steps where the electron. So, you have totally the 6 electrons and 7 proton kind of a situation that you have. So, therefore, in the active site is plus 2 and resting state is plus 3 for the iron in all these cases.

So, essentially what we have looked at in the iron enzymes huge number, we have looked at the transport of oxygen and stories of oxygen, transport of iron, storage of iron; all of these transport of electron, transport of by cytochromes, transport of electron by iron sulfur proteins how the ion sulfur clusters expand and contract during the electron transfer the ions 4 iron, 4 sulfur clusters ferredoxin clusters ok.

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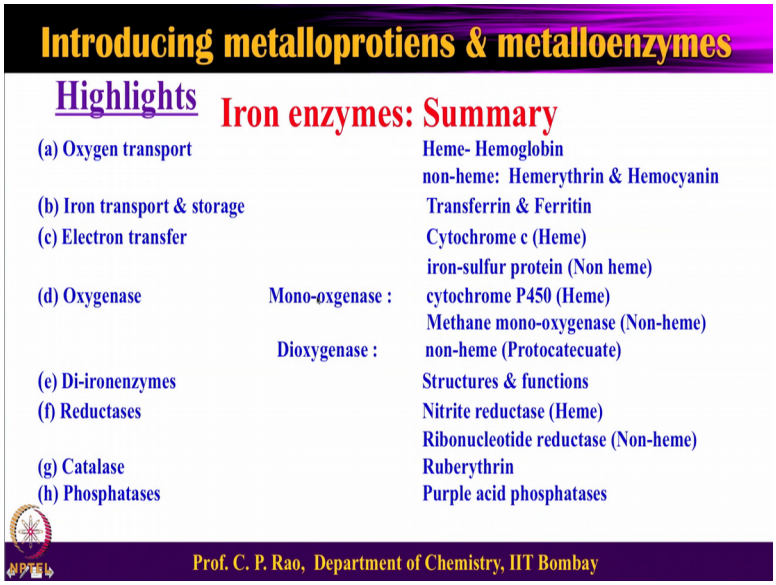

So, oxygenase then I took the cases of oxygenase; monooxygenase and dioxygenase. Monoxygense both the the heme and the non heme is methane to methanol, dioxygenase is that where the protocatecuate case. And I have not in the highlights explained, but I explained in the regular class the the tryptophan oxidase all those things; so, absolutely which is a heme based one.

Then I took over a lot of the iron diiron enzymes, explained the reductases rabunucleated reductase very well. Then I have also explained the nitrite, sulphate reductases all these where multiple electrons are required; where siroheme is involved.

And then I also explained in the regular class ruberethren and I have also talk to you about the hydrolase kind of thing; which is purple acid phosphatase and the switch in the highlights I am not cover, but I have covered in that kind of a situation ok.

So, iron is a huge story of all these kind of things. So, we have a very nice highlights of this and please be advised in the highlights I may not be covering all the enzymes. So, I am just trying to take some features to bring to your notice.

So, following this huge you know play with the iron for over 7, 8, 9 classes or so. Then I entered into the cobalamin story; where the cobalt ion is involved. Cobalt ion is involved in the entire bio inorganic chemistry in only one aspect; that is in vitamin B 12; vitamin B 12 is a coenzyme, it is not an enzyme.

But this coenzyme is associated with a huge number of enzymes in bringing 1 2 hydride shift kind of a reactions.

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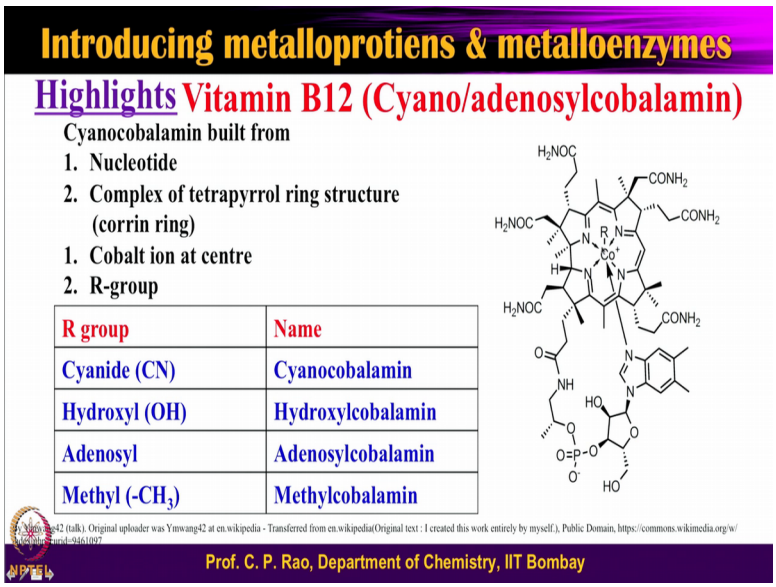

So, this is a adenosylcobalamin is the natural one and as you can see here, this is the coring part and this is the benzimidazole part which is bound. And this is the group which is the one which will play a role and therefore, this bond CO 2 R bond can break homolytically with dot dot cobalt 2 N R dot, can break heterolytically; cobalt 3 R minus, a cobalt 1 R plus and both of these are possible all these 3.

These 3 situations are possible based on the binding strength and the protein that is there; how it is influencing the strength of these ones. And this all we have studied in the class explained how the 1 2 hydrate shift lead to the product formation. In some cases, there is a water elimination and other kinds of reactions happening in that too.

So, adenosylcobalamin is also involved in reductase activity like ribonucleotide reductase activity; which is very similar analogous to that found with the with iron enzyme. So with the iron reductase; so therefore, I have not taken too much of importance to introduce that in this highlights methol.

And so, following this I have talked to you on nickel enzymes; I must have spent about 3 4 classes on this.

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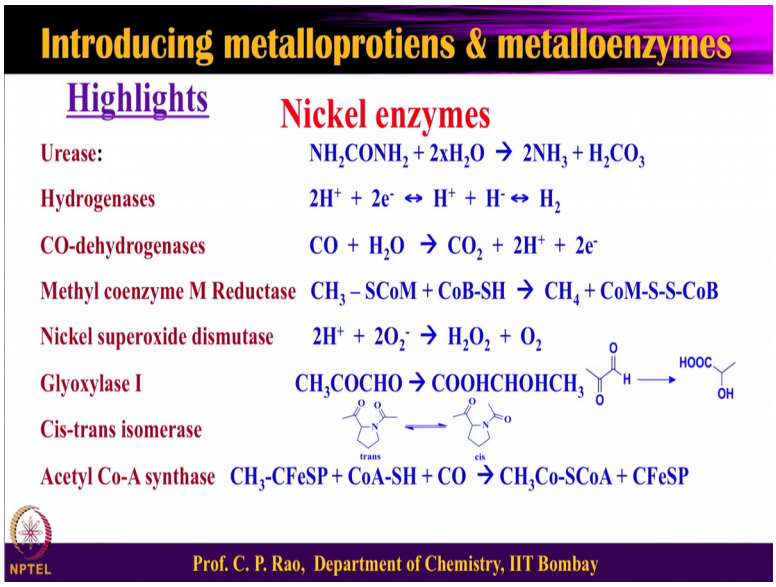

We have a hydrologist kind of enzymes like Urease, Hydrogenases reaction, dehydrogenase reactions, Methyl coenzyme M Reductase, superoxide dismutase, Glyoxalase, Cis-trans isomerase and Acetyl Coenzyme-A synthase.

So, many different kinds of enzymes have been covered under the nickel and nickel is also very important enzyme. Urease, it hydrolyzes urea to ammonia and H 2 CO 3; hydrogenous is the proton to hydrogen using the electrons and it is a reversible kind of an enzyme.

And CO-dehydrogenases is carbon monoxide dehydrogenase going to the carbon dioxide kind of thing. Methyl coenzyme M reductase would reduce the a co enzyme methyl group to methane moiety and that methane is further used by the methanogenic methane used using bacteria or even methenogenic one; where the methane is converted to the methanol methane oxygen is etcetera etcetera.

So, nickel also involved in superoxide dismutase and you know very well superoxide dismutase; in the first step O 2 minus dot will lose the electron and go to O 2. In the second step, it will take another electron and O 2 O 2 minus. So, that will be effect you will get 1 H 2 O 2 1 O 2 and H 2 O 2 is taken care by the catalase afterwards. So, there is a Glyoxylase enzymes, Cis-trans isomerase and Acetyl coenzyme A synthase of it.

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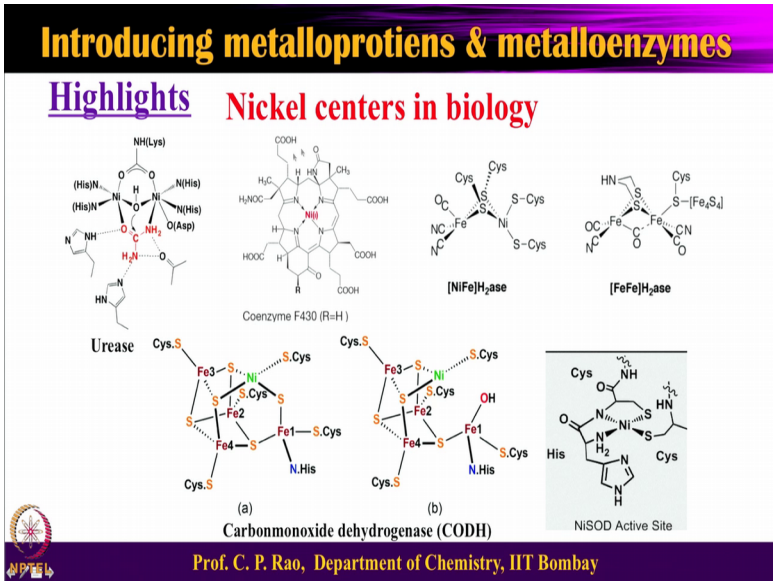

Kind of a cores you see that a dinuclear nickel with a bridge; the carboxyl, hydroxy this is used in the urease and this is nickel in centers factor F-430 which is involved in hydrogenase kind of enzymes etcetera.

And again these things are there nickel iron centers and these are in the hydrogenase. Carbon monoxide dehydrogenase which is having different kinds of a centers as you can see and these are involved in the reactivity and this is the superoxide dismutase.

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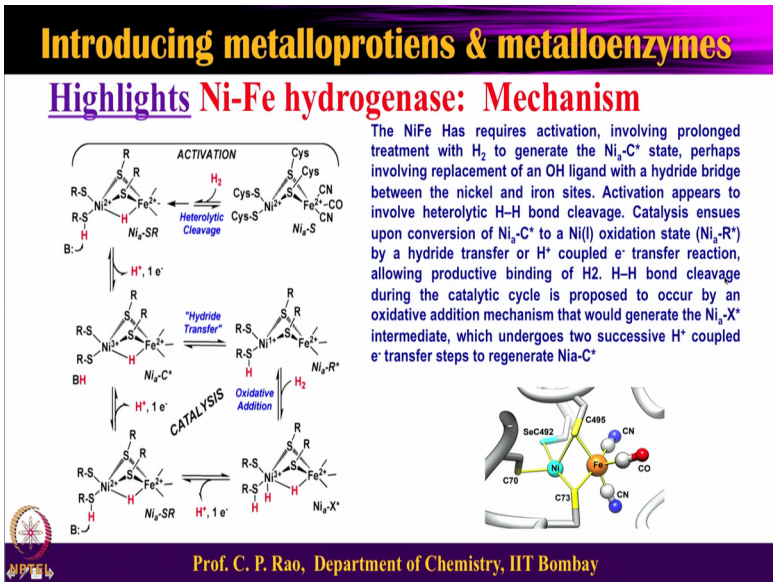

So, if we look at the nickel hydrogenase enzyme; there is a activation cycle, there is a catalysis cycle. So, activation cycle; catalysis cycle if you follow it is very interesting, it is very simple and easy that you can understand.

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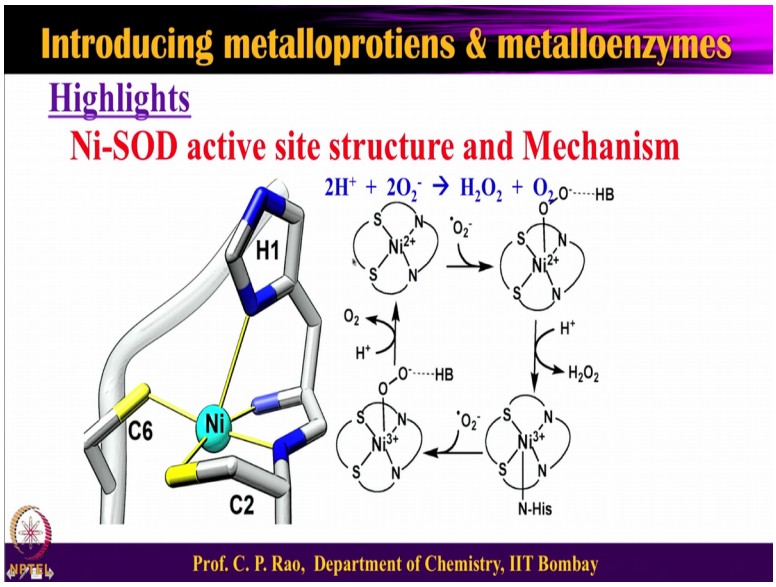

I have already explained to you SOD; if nickel 3 plus then O 2 minus. So, O 2 will bind and take out this one go as O 2 gets oxi O 2 minus get oxidized and Ni 2 plus 3 plus gets reduced; Ni 2 plus this will take another mole of O 2 minus and that will reduce further. So, therefore, nickel gets oxidized and then goes as H 2 O 2.

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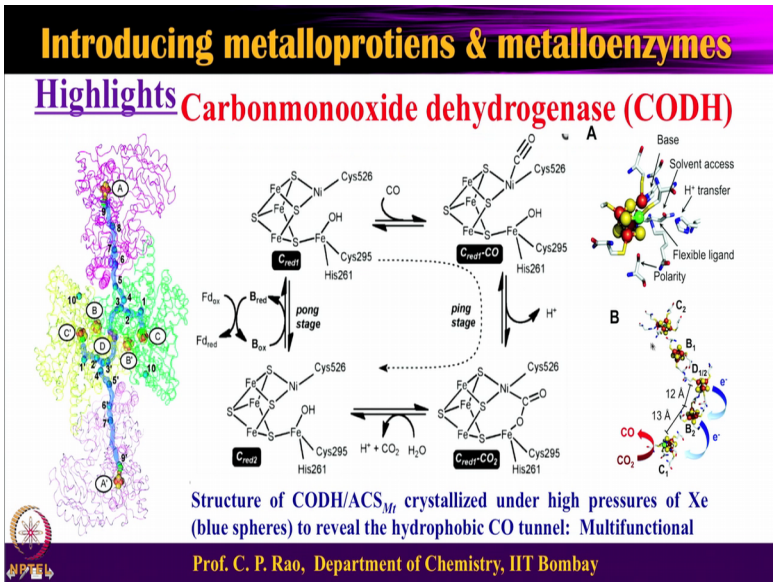

So, as I have mentioned all this. So, what are the important enzymes which is a very complicated kind of an enzyme is that the carbon monoxide dehydrogenase; where you can see it stores from this cluster and the electron flows go through this and then finally, CO and CO 2 and this is shown for the rivers and a Fe system.

So, huge clusters of iron sulfur clusters are there in this. So, I have a few more highlights to cover; then I will start with the tutorials in the next class, I will complete the remaining highlights and then get to the tutorial.

Thank you very much.