Biological Inorganic Chemistry
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Lecture No. 10
Organic cofactors and siderophores

Good morning everybody. So, welcome back where we are talking about the coordination of the metal ion into the biological ligands. So, in this lecture number 10 we will consider that the different organic cofactors and another group of molecules will be talking here is the siderophores. So, how organic cofactors can handle the metal ions that means how the metal ions can be incorporated in these organic cofactors and what are the siderophores the bacterial origin of.

So, definitely for our diseased conditions and all these cases we will be considering this siderophores which has also again very good affinity for the metal ions.

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So, in this lecture we will try to consider the different concepts which are during the formation what happens basically formation or generation of Fe-S proteins. So, is the formation of not or formation of Fe-S proteins. Then anion incorporation in iron sulphur clusters. So, we just quickly define there what are these iron sulphur proteins and how these iron sulphur proteins are involved because these are very important and ubiquitous in nature in our system our biological system. Everywhere you have these iron sulphur proteins in our body also.

Then the metal ions for organic cofactors then how the metal ions are getting incorporated in the different siderophores. And finally we will talk about the very important molecules we all know nowadays that the RNAs and the DNAs. For these nucleic acids whether these nucleic acids can function as the ligands. How you can understand this particular point that we all know that the acetic acid the acetic acid itself can be a very good ligand.

Similarly, when we go from acetic acid to another example we just told you in our previous class is your ethylene diamond tetra acetic acid or in its deprotonated form the tetra acetate anions. So, acetate ions are always a very good ligands to the metal ion system. So, if you have a big nucleic acid since you have the acidic functions over there so these acidic functions having charged also can be very much useful whether it can be useful also for trapping or binding or incorporating the metal ions into the system.

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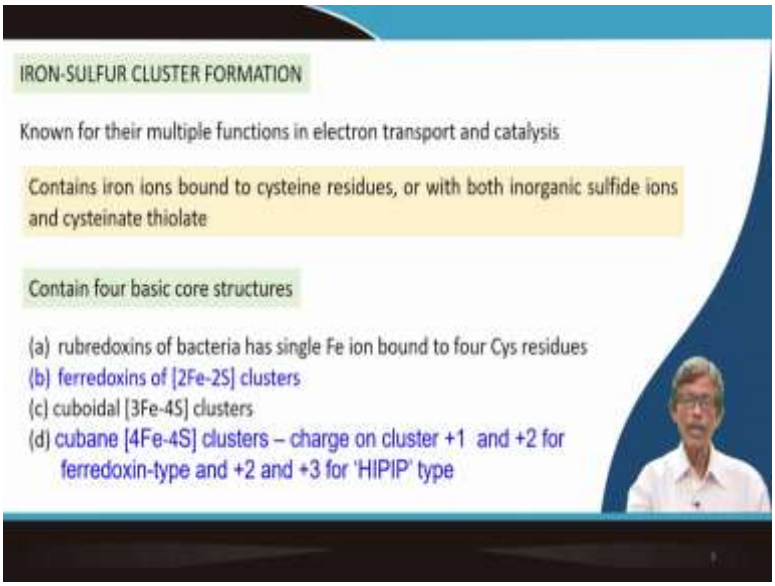

So, how we can define the formation of iron sulphur cluster? So, what this particular sulphur is? Because, in the biological world if we consider the different amino acid residues we all know the cysteine is there the cysteinate is there and methane is there all are having sulphur function sulphur based functions which are your pendant groups. Apart from your backbone having carboxylate acid and the one function and amine function on the right hand side.

So, if those sulphur groups are available it can function in a different way but mostly for the electron transport and catalysis. When you function as electron transport it is not that the isolated metal ions. In our system in our body also it is difficult to see the electron

transport behaviour from the bare Fe 2 plus or Fe 3 plus. The way we know in our laboratory in your test tube or in your conical flask your reaction chamber that Fe as the corresponding ion if it is ferric ion so hexacore ferric ion we know when you go for the analytical chemistry class you go for the titration.

And that titration tells us that this particular iron centre can react with some oxidizing agent or a reducing agent for electron transfer. But, for your biological world it is typically different one or different perspective you have to see that when it is bound to a big protein chain or a big protein molecule whether that iron centre which is bound to that particular protein molecule can again give you electron ejection or electron abstraction.

Similarly, if it is a redox catalysis whether that particular molecule can function in the catalysis also. So, it will have iron ions bound to cysteine residues or cysteinate ions. That means you have S minus you have the backbone made up of your NH2 and COH function but you have the pendant group as S minus from the cysteine residues. And both inorganic sulphide ions and the cysteinate thiolates can bind to the iron.

So, iron will have the iron centre will have a very good affinity for coordination to your thiolate sulphur S minus as well as inorganic sulphide. And in case of inorganic sulphide we all know like your water molecule water molecule we know H2O having a pair of lone pairs of electrons we know through that lone pair of electrons it can form bond to the metal ion centre.

Similarly, H2S is also a congener of H2O it will have all again the lone pair of electrons on the sulphur centre so it can again go for the deprotonation. So, it can form hydro sulphide anion HS minus or it can form typical sulphide anion that means S2 minus. So, for the point at this star point we just if we consider that we will have the S2 minus only the sulphide anion is available.

So, that sulphide anion if it is there with you how it is binding to your iron we all know that in your analytical chemistry classes you have learned that Fe the ferrous ion or the ferric iron when it is binding to your sulphur it is giving you the ferrous or the ferric sulphide we all know it is the process of mineralization also. Iron can also be available in the earth crust on the earth crust in that particular form the sulphide will be insoluble one.

But, when it is binding to your protein part or the big protein molecule it will not be isolated or separated as your iron sulphide. So, definitely the protein environment will restrict will inhibit the corresponding separation or precipitation of iron as iron sulphide or ferrous sulphide. It will be in the solubilized form but still we have a cluster like arrangement where many number of these sulphide as well as the thiolate sulphurs are available.

What are those? So, there are 4 basic code structures you can have the first one is the simple rubredoxins type and these are mainly originating from bacteria. So, the bacterial rubredoxins are having a single iron centre. So, it is a mononuclear iron centre and when you have a mononuclear iron centre if it is in the safe era state so you have Fe2 plus. So, if the ferrous iron is there and it can have 4 cysteine residues.

That means the cysteine sulphur residues so this cysteine sulphur residues what you can have so you can have these the cysteine sulphur residues S minus. So, you have the cysteine sulphur as the Cys S minus when 2 of them are coming from one side through this my finger tip is these are sulphur ends and another 2 will be coming like this. So, what you get this at the centre?

You will be getting a tetrahedral arrangement with a coordination number of 4 around this iron. So, this particular system is very happy after getting one iron centre only so you are not bringing any inorganic sulphide over there. So, it is the most simplest example of iron sulphur protein where you have 1 iron centre and 4 cysteine sulphur residues are binding to that particular iron.

But, if you go up one step we find that you bring the inorganic sulphide and those are known as ferredoxin molecules. So, the second category of these molecules are your ferredoxin molecules where you have 2Fe 2S clusters what are these 2S, 2S are inorganic sulphurs. That means if you write typically the formula what we are talking about that if you have the ferrous iron S minus is binding so it will have 2 units of ferrous sulphide.

But, it is not that it will not be able to separate it as ferrous sulphide the inorganic ferrous sulphide as this material the mineral like material. But, it will remain as in a solubilized form having a different structure because these 4 cysteine residues what were available for your rubredoxin are still there. So, the protein environment having 2 cysteine sulphur and here again 2 cysteine sulphurs are there.

Now, instead of a mononuclear iron centre you have now a binuclear iron centre FeS FeS so is a diamond core you have. So, these 4 cysteine residues will come basically and these cysteine residues will come and bind or trap the binuclear unit what is that binocular unit this binuclear unit is a 2Fe 2S part. So, your 4 system residues will come like a rubredoxin molecule but not getting the central iron mononuclear unit part but a binuclear part.

So, you get a 2 iron ferredoxin centre then cuboidal not cube cuboidal that means cube like 3 iron 4 S clusters also you can have. That means if you can have a cube we all know it has 8 corners so all the 8 corners are not occupied if one of the corner is vacant you get a 3 Fe 4 sulphur cluster. And finally, the full form or the most simplest one is your 4 iron 4 sulphur cluster which is a cube.

So, alternate corners are occupied by iron centres and other alternate coordinates are occupied by the inorganic sulphide ions. But, the whole charge on the cluster can be plus 1 or plus 2 for a pyridoxine type of molecule which are low potential but if it goes to the higher oxidation state that means the charge on the cluster itself not the individual charge on the iron side can settle between plus 2 and plus 3. So, these are known as HIPIP type what is that is protein of higher potential so higher potential protein is known as HIPIP there.

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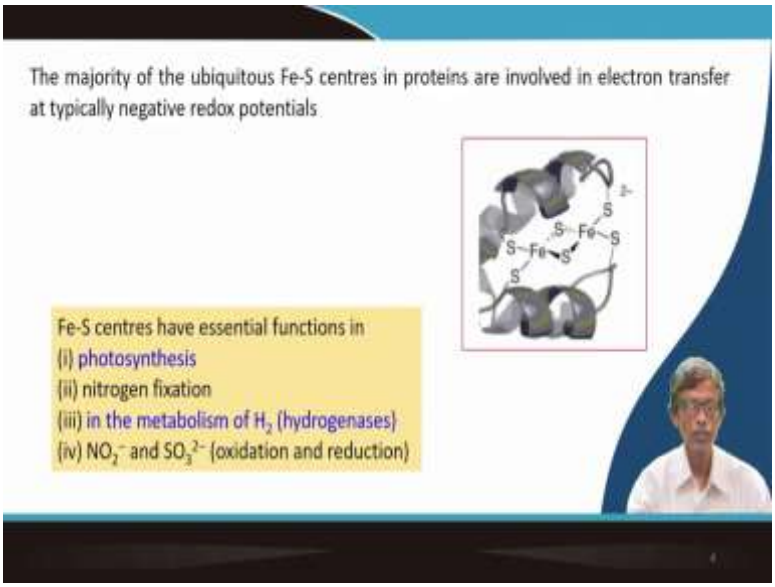

So, you see the majority of these iron sulphur centres in proteins are involved in electron transfer and typically negative redox potential. That means they are strong reducing agents because we all know that the ferrous ferric potential in aqueous medium with

respect to that of our normal hydrogen electrode we all know is close to 0.774. So, that potential is quite positive 1. But, when the environment you are changing you are getting a negative potential due to the presence of cysteine sulphur.

So, it will try to stabilize basically the lower oxidation state in that particular fashion. So, ultimately what we are getting over here is that is that your system so what we are talking about the binding of this particular 4 sulphur group. So, these are your original 1 so you have this 2 sulphur and these 2 sulphur on the right and these 2 sulphur and these 2 sulphur on the left.

So, these 4 cysteine sulphur residues are available to you and that 4 sulphur residues that means the originally it can be with that of your rubredoxin type but it is now elongated one. Because, you have to accommodate now 2 iron centres so the FeS FeS the diamond core this FeS FeS diamond core what you can get is being trapped by 4 system residues and in this particular form before electron transfer reaction the overall charge is 2 minus.

So, by looking at the corresponding charges on the anions that means the donor group the cysteine sulphur will have 1 minus charge 1 negative charge. But, the sulphide sulphur inorganic sulphur at the centre have 2 negative charges you can have some good idea about the oxidation states of these irons. So, where we get these iron sulphur systems or iron sulphur centres so they are basically important once I discussed you that it is available there for your photosynthesis.

So, in the photosynthesis we require large number of electron transfer reactions. Where from you will be getting the electrons you will not be able to use some reducing agent or oxidizing agent the way we do the chemical reactions in the laboratory. So, the biochemical reactions are very complex and all these biochemical reactions even for supply of the very useful reagent electron is always very much important.

So, for these photosynthesis if you require the transfer of the electrons many number of electron transfer if it can take place there we see that these iron sulphur proteins the Fes proteins are useful. Because, they can settle between the one is the lower oxidation state potential values and another group is the high potential iron proteins HIPIP high potential iron proteins.

So, either these high potential iron proteins are involved or the low potential iron proteins are involved these are of 2 categories depending upon the requirement of an

electron at a particular potential. So, for photosynthesis also the system is dependent on your iron sulphur protein. So, photosynthesis is nothing but a process which is iron sulphur protein dependent process.

Similarly, if you have the nitrogen fixation we all know the reduction of dinitrogen molecule to the formation of ammonia there also you have the transfer of 6 electrons as well as 6 protons. Because you have 2 nitrogen N2 the dinitrogen molecule which is getting reduced to your 2 molecules of ammonia so all together you will be supplying 6 electrons and 6 protons. So, is a multi-electron multi proton transfer reaction then it is again dependent on this iron sulphur protein. Because, iron sulphur proteins are in your hand which can supply the corresponding electrons at a designated potential value.

Similarly, during the metabolism hydrogen that means for the hydrogen production also or hydrogen consumption also in hydrogenases. These hydrogenases are metal ion dependent or metalloproteins are there for the hydrogenase function that we will also see. But, for the reduction of the protons also when you have the proton supply when you have the electron transfer at some point the side reaction can be the production of hydrogen.

Instead of reducing the nitrogen N2 you can have the side reaction that okay the electrons are available protons are very also greedy for electron so protons will be reduced to give you the hydrogen, not that your nitrogen will be reduced to ammonia. Then that nitrite and the sulphide groups are there and they can also be involved for their nitride reduction or the sulphide reduction or the sulphide oxidase or the nitrite oxidase reactions or the reductases. So, reduction reactions or the oxidation reactions can have.

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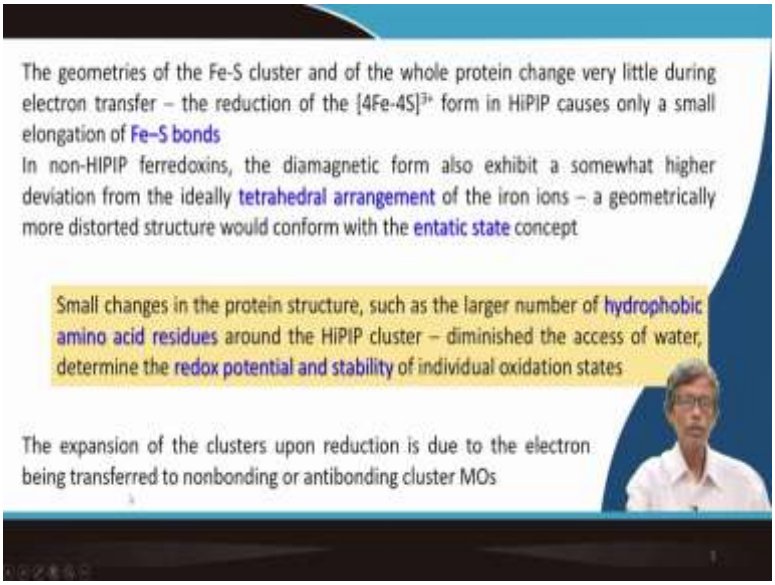

Then already I discussed you so these particular languages are useful for you if you forget or if you are not able to write in your copies. So, talk about the geometries I already told you that how these geometries are useful to you. And these geometries for these clusters are not very much different so the geometries around this iron environment that means the iron that means the tetrahedral geometry whether it is present as a mononuclear rubredoxin or a tetra nuclear ferredoxin.

But, during that electron transfer reaction also very little change in the protein structure takes place. So, the reduction during that particular reduction of 4Fe 4S system from the high potential iron protein it causes only a very slight change in iron sulphur bonds. That is why these electron transfer are very much facile as well as very much fast also unlike other iron compounds iron complexes or bare iron as hexacore species.

So, in non-high potential iron proteins or basically the low potential iron proteins type of ferredoxins the diamagnetic form 1 form is diamagnetic not even paramagnetic. So, they are so localized the magnetic interaction is such that the antiferromagnetic interaction can take place overall it is giving a diamagnetic product. So, ideally the tetrahedral arrangement of the iron ions a geometrically more distorted structure would conform to the entatic state.

That means the excited state little bit of excited state from the ground state but which is catalytically much more active and catalytically much more useful. So, if we have a small change in the protein structure such as the larger number of hydrophobic groups of the amino acid residues around these clusters which can also restrict because you have

the more hydrophobic groups that means the protein backbone not the corresponding anionic functions or the ionic donor groups.

So, the protein backbone if it is the hydrophobic one, it will try to repel the water molecules. So, it will also decrease the entry of the water molecules there and since that particular availability of water is there so it will also consider or control the corresponding redox potential and the stability of the individual oxidation states of these proteins.

So, basically the protonation as well as deprotonation, access of the water all will basically change the corresponding e0 values of these proteins molecules. And sometimes if you put the electron inside the cluster always you expect that you can have some expansion. So, the expansion of the clusters upon reduction that means you transfer electron to the system and during that particular transfer where the electron is going.

We all know that when a molecule the molecular orbital picture tells us that you have the bonding levels in the lower then you have the non bonding level then you have the anti bonding levels. So, when you put the electro if the electron has no space or no access for the bonding levels it will either move to the non bonding level or will move to the anti bonding level of the molecular orbitals.

So, that will also change or will contribute to the corresponding metal ion donor group bond distances as well as the structure finally.

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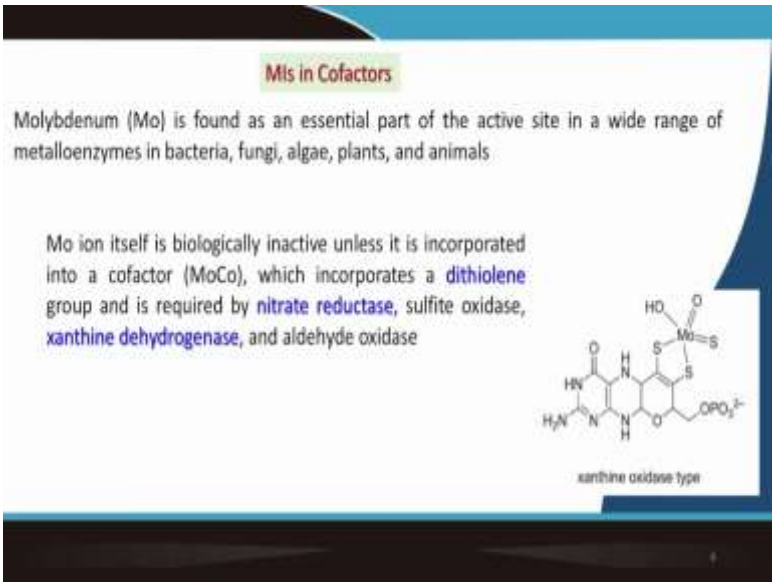

When we see that how the MIs are there in the cofactors what is that cofactors because it is basically assisting factor, co is basically assisting some business. If we find that molybdenum itself with some cofactor then in bound form of this is there in different metalloenzymes not metalloproteins sometimes we have to consider the metalloenzymes also of bacterial origin, fungal origin, algal origin, plant origin as well as the animal origin.

So, if it is there for this biological inactive this molybdenum is so you need some help from the cofactor. So, if it is bound to that particular molybdenum then the whole assembly or entatic can be effective as a cofactor. And which is basically incorporating a diethylene type of group that means sulphur, sulphur adjacent by dented group. And is required for many enzymes starting from your nitrite reductase to aldehyde oxidase.

So, these are the oxidoreductase group of molecules so these oxidoreductase family of molecules are dependent on this change in the corresponding oxidation states of the molybdenum and molybdenum we all know which is down to chromium in the periodic table. And it can go from a lower oxidation state of plus 2 plus 3 to up to a oxidation state of plus 6 which is also available for your chromium.

Where we get chromium in the hexavalent state? It is in the chromate it is in the dichromate also. So, this particular case also where we find that how it is binding so this is the diethylene part the SS part. So, this SS part if it is there molybdenum is coming and molybdenum we all know it has a very affinity molybdenum vanadium all will have a very good affinity for the oxo species formation.

So, not only oxo species but also it can form the thio species. So, when the function of xanthine dehydrogenase or xanthine oxidase can come into the picture we know that you have a bidentate ligand support as your cofactor and the molybdenum bound that diethylene molecule is your cofactor and which is be responsible for your electron transfer reactions for your some reaction which you have the substrate is getting converted to your product.

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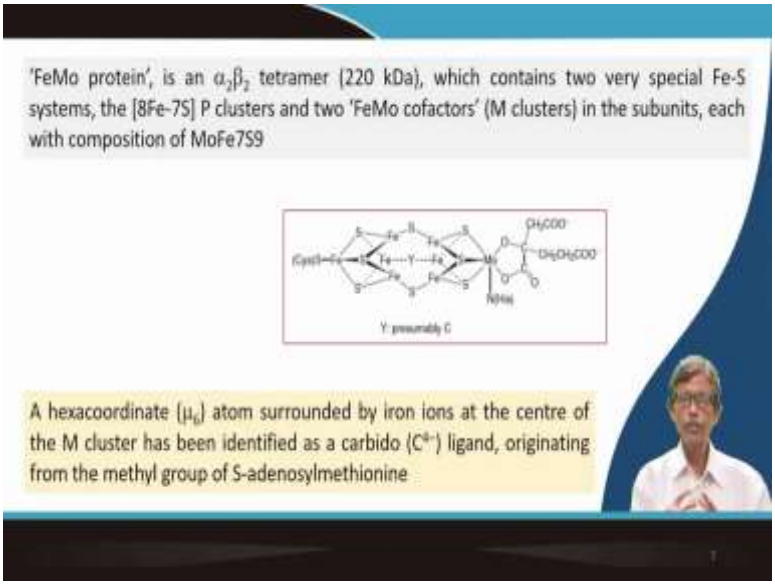

Then we find that the corresponding molybdenum iron protein which is nothing but a alpha 2 beta 2 tetramer and which contains 2 special iron sulphur types of clusters. And if you just double it it will be 4 Fe 4 sulphur system but 1 sulphur less which is known as P cluster and then iron molybdenum cofactor.

Now, your life is getting little bit complicated but do not worry much about this point but you now just know only what are the possibilities of studying all these things what is M cluster and what are the metal ions basically because all the time we are not deviating from anywhere we are not studying anything which is hardcore biology but we are focus our attention on the metal ions only.

The property of the metal ions will be exploited in understanding all these things. So, we will talk about the structures all the time we talk about the functions and we will talk about the activity in terms of its catalytic activity or something like that. So, if you have a huge structure of this type so it is in the nitrogenases then you can have also not only iron but also molybdenum but many sulphur.

So, again like your ferredoxin and rubredoxin molecule what we bring we are bringing nothing but the organic sulphur as cystine ion and the inorganic sulphide ion S2 minus. But interestingly, we find at some vacancy over there which is your Y and that Y vacancy can sometime be only a carbon charged carbon. Which we all know that carbon can have a charge which can be even C4 minus.

That CH4 we know methane if we take out all the hydrogen as protons that means H plus if methane is losing 4 such as your protons you will remain with C4 minus. So, that is the methide or the carbide system present within this particular cavity. And when it is coordinating basically not only it is showing this dotted line but it can also have some dotted lines with the other 4 iron centres.

So, you can have a corresponding mu 6 environment and which is identified can be identified as the corresponding carbido species or the carbido ligand originating from the methyl group of S adenosine methionine. What is methionine? We all know probably methionine is the amino acid where your sulphur is methylated that means S methyl function is there.

So, if you are able to get that methyl group for the transfer you get the methyl function first that means CH3 minus, then further deprotonation from there it can ultimately produce the C4 minus. So, that 4 minus is therefore finally being trapped and the strapping is very important and very useful for the sustainment or that means you sustain the structure otherwise the structure will be collapsed.

So, the formation or generation of that particular C4 minus species from S adenosine methionine is important and trapping of this C4 minus is also important within this particular cluster. So, the cluster life basically is important on the availability of this C4 minus and its binding.

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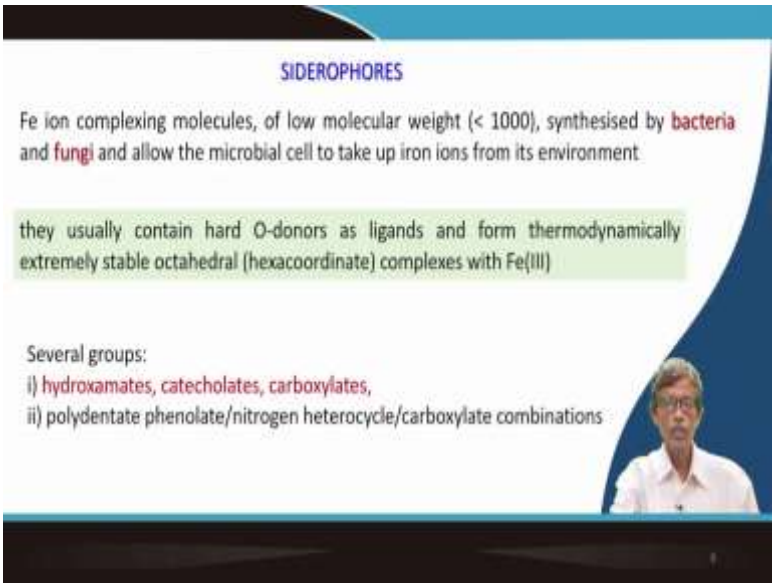

Then quickly we will see the siderophores that siderophore like chromo 4 chromophore is nothing but for the colour absorbing species or the photon absorbing species. Similarly, the siderophore are there to trap the iron centres. Because, it is a fungal origin so microbes are there we all know the microbes are there which can take up iron and they also need iron like us.

We are we need iron for the production of many important bio molecules starting from your blood. Similarly, these are available but it is now a different type of chelating groups which can cover the iron centre in a hexa coordinate fashion. And this hexa coordination is important to give you the corresponding tonal groove that means 6 donor groups or donor atoms around this iron centre from these.

So, the nature will be discussing in terms of some groups like your carboxylate functions the EDTA function similarly you should also know what are hydroxamates what is that is the hydroxamic acid. So, hydroxamic acid functions are there you go and take the name of this what is that hydroxamic acid. Then hydroxamic acid can be deprotonated and that can be a very good ligand.

Then catechol so OHOH on the phenol the phenol with adjacent OH and the carboxylates already we are discussing. Then the combination of phenolate nitrogen heterocyclic and the carboxylate combination can be useful for your this particular type of binding by the siderophore molecules.

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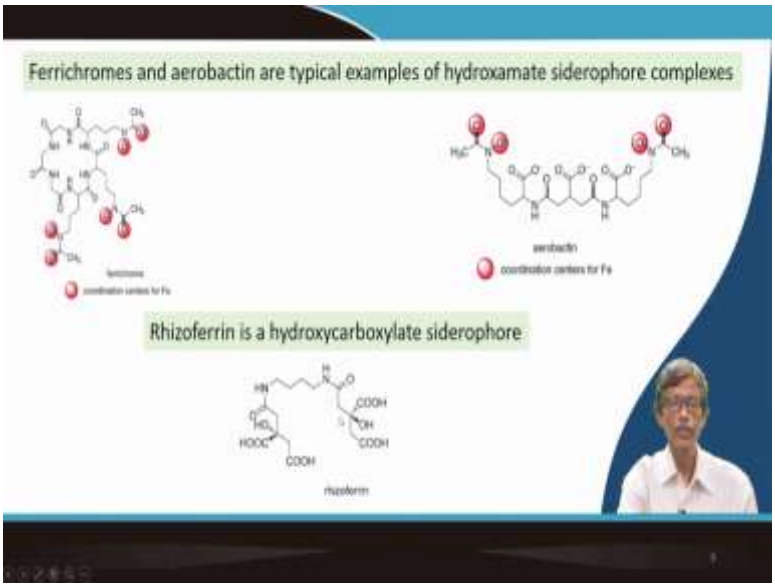

So, one such example is your ferric chrome and ferric chrome and aerobactin are typical example of hydroximate siderophore. So, if you have the only the hydroxamate group and that can function like this is a very huge molecule very interesting and a fascinating molecule in your hand.

And we all know there is a ferric chrome and the coordination centres for iron. So, if this is the hydroxamic function hydroxamic acid group. So, you know that CH3COOH is your corresponding carboxylate function and if you carboxylate as in the OH can be replaced by NHOH from hydroxylamine that is your hydroxamic acid. And if that is attached to some long chain to a some macrocyclic ring.

So, you see that this macrocyclic ring is the amide 1 2 3 4 5 so 1 2 3 4 5 so immediately you count the 5 carboxylate function from the COCONH functions. So, how many CONH functions are there so 1 2 3 4 5 6 so is basically a cyclic hexapeptide. So, like your tetra pyrrole, the cyclic hexapeptide is there but that cyclic hexapeptide is not available for coordination of your iron centres.

But, the other dangling part or the pendant part this NOCO function NOCO functions so all these NOCO functions which are the typical bident part so those typical bidentate parts are there and those bidentate parts will be available for iron coordination.

So, that means some reorientation can take place very interesting coordination chemistry can take place over there and you will be amazed to see the structure what we are getting afterward. Because, you have the iron centre and this big molecule will come from the top and this is the hexapeptide part from the top and one bidentate part will come another bidentate curve will come and another bidentate part will come to trap the iron centre.

Similarly, one is the linear one, the aerobactin. So, this bidentate part and another bidentate part this these are the centres basically available for coordination of the iron side. So, you will have a big molecule and having some pendant or dangling donor points or the bidentate parts which are available for coordination.

Then rhizoferrin, rhizoferrin also will have the corresponding OH and COH like your lactic acid the hydroxy carboxylic function. So, hydroxy carboxylate side door force are there which are available for binding or trapping your metal ions.

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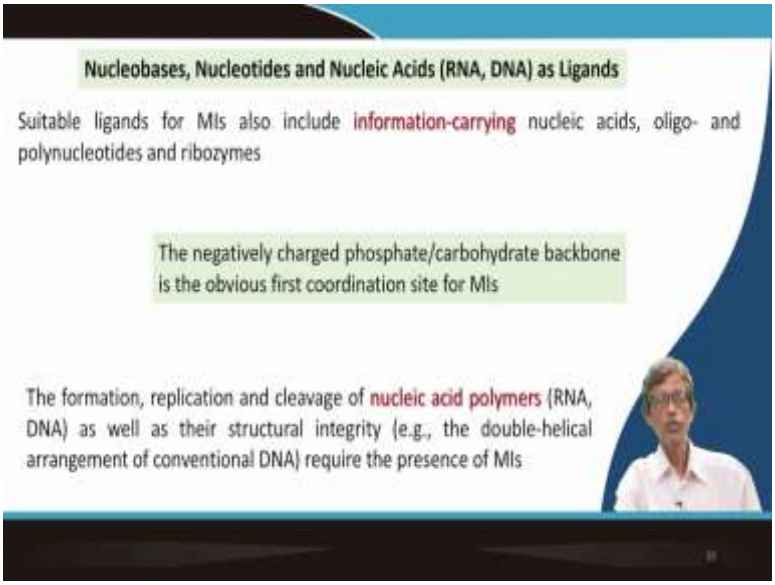

So lastly, we will see the different nucleobases the nucleotides and nucleic acids. We all know the DNAs and RNAs are information carrying molecules and the different polynucleotides and ribozymes you can have the dependence on the metal ions. So, they are function they are binding and all these things are dependent on the metal ions. So, the phosphate backbone or the carbo carbohydrate backbone if they are charged in nature so those charge groups can be available to bind the metal ions through its first coordination pair.

So, directly those groups basically will come and bind to your metal ion centres. So, during the formation your replication and cleavage of the nucleic acid polymers like DNA and RNAs and their structural integrity that means the double helical arrangement of conventional DNA. Sometimes, these functions basically require the presence of many numbers of metal ions.

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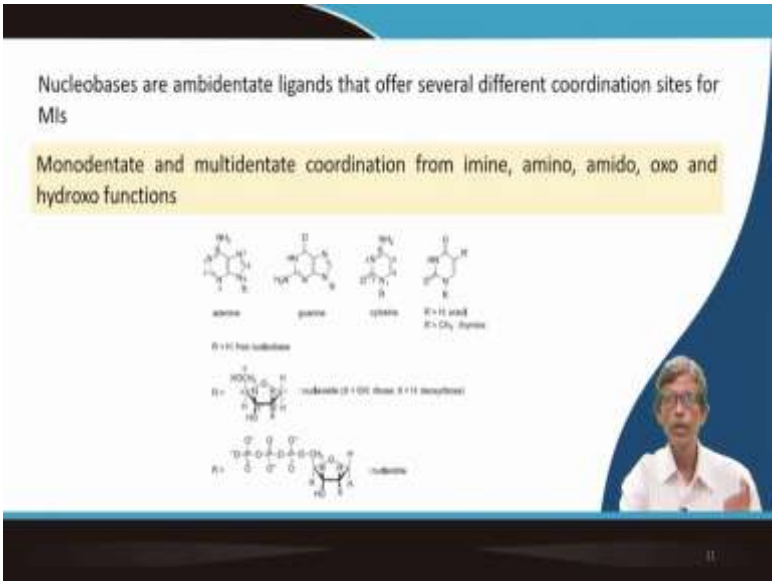

So, metal ion dependence is always very important and these metal ion dependencies always we see for their function. And they satisfy the different coordination sites for these metal ions. So, monodentate and multi-dentate ligands basically are there so from the binding from the amine amino acids and the oxo and hydroxy functions of adenine, guanine and cytosine.

So, this adenine, guanine and cytosine when the R is H or R is the corresponding sugar unit or R is the phosphate bound sugar units we get the nucleotides and the nucleotide. So, there are many number of these PO bonds and this negatively charged O minus can be useful like that of your binding of your magnesium centre.

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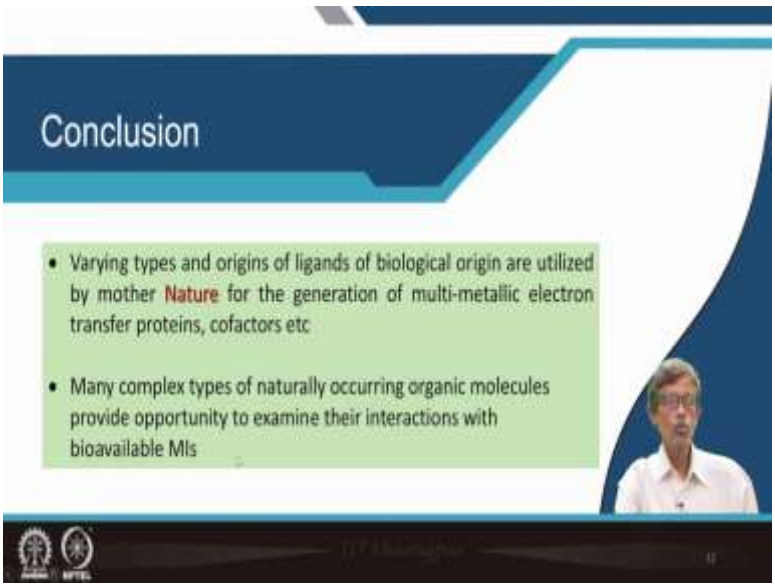

So, like your EDTA basically it can bind your magnesium centre and thus we have seen here in this particular case that the different types and origins of the ligands of biological origin definitely can be utilized by mother nature. Mother nature is producing all these ligands for us even when bacteria is producing siderophore it is also some fact is attached to that that it will be required for binding your iron centre.

So, you get the multi metallic electron transfer proteins sometimes you get the cofactors and all these many complex types are basically naturally occurring organic molecules and it basically require us that particular opportunity where we can find the interaction that means the formation of the coordination. That is why we another definition of this particular type of classes are calling as the coordination or bio coordination.

So, bio coordination chemistry can be available to us through studying this particular coordination of these metal ions.

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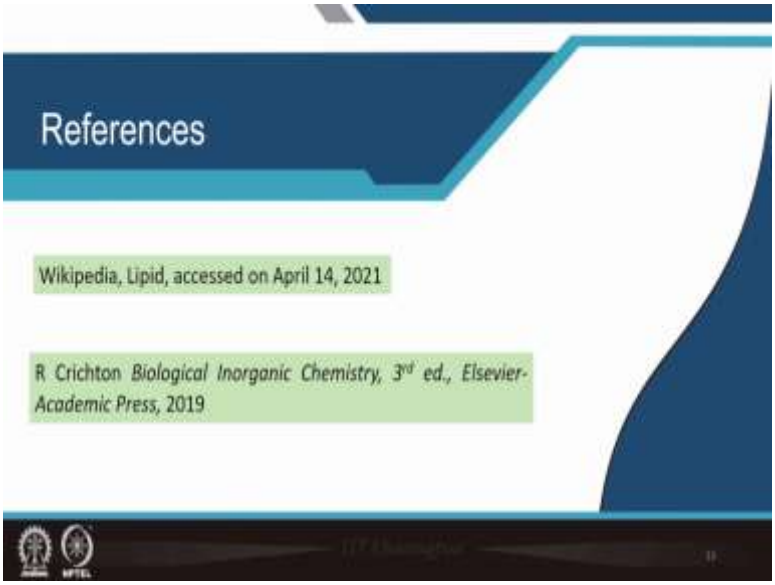

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