Biological Inorganic Chemistry
Professor. Debashis Ray
Department of Chemistry
Indian Institute of Science, Kharagpur
Lecture No. 09
Metal Ion Insertion

Hello good morning students, so we will continue in our courses in module 2 where we are talking about the biological ligands. And now we just today we will just come to a very important part where we will talk about the insertion of the metal ions which is very important. As we know from the history of the coordination chemistry that you need a metalloion and which can be surrounded by many types of ligands starting from your water molecule to ammonia.

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So, in this particular class what we will just try to cover based on the different concepts where we can talk about the Lewis acids. The Lewis acids are nothing but your metal ions and where they are now attaching they are not the typical ligands like water ammonia or ethylene diamine as we know from our school days but they are the corresponding bigger molecules the macromolecules or the protein molecules they are the apo proteins.

Then we will define something which we can consider as Chelatases what are these Chelatases? The Chelatases are nothing but the corresponding crate formation when a bidented ligand comes to bind to a metal ion all we know like the ethylene diamine.

So, ethylenediamine molecule when comes to bind your nickel 2 plus or iron 3 plus centre we all know it forms a 5 membered cyclic ring. Then during this particular metalation reactions what we will try to understand about the different steps that means the multiple steps what are those different steps will be operating there to incorporate the different middle ions.

And most interestingly when we go to our individual chapters when we will be talking about your haemoglobin and microbial molecules there will see that how the very important macrocyclic ligand is there which is your tetrapyrrole, the name itself tells you that it is a macrocyclic ligand where 4 such pyrrole units are in a cyclic form forming a huge macrocyclic ring. So, in that macrocyclic ring how you can incorporate the metal ions that we also see.

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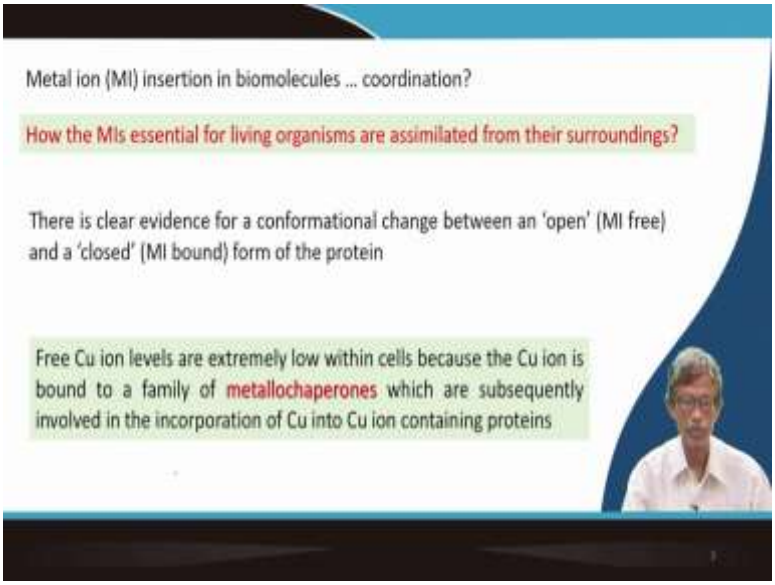

So, first we will see about the metal ion insertion in the different biomolecules not with the attachment to the typical ligands starting from your ammonia to EDTA we all know is hexadentate ligand ethylene diamine tetra acetic acid. So, we will just talk about that does it mean that it again goes for the coordination? Yes, it will also be a type of coordination but the donor atoms or the donor groups available to your this formation of metal of biomolecules are different.

So, how we can go for this particular insertion reaction that we will see which are very much essential for us which are essential for living organisms and how they are getting assimilated from the surroundings. What does it mean then? That if we have a particular type of ligand in hand say your tetrapyrrole molecule or your big apoprotein molecule.

So, when the apoprotein molecule is coming and if the metal ion is available what will happen then is nothing but the typical metal ion and the ligand anion coordination reaction. So, basically the metal ion complexes will be forming over there but now since the origin of your ligand part the origin of your ligand part is a typical biomolecule so that typical biomolecule will now give you the metal of biomolecules.

So, these are very important then so during that coordination what happens so there are evidences definitely there are evidences are there where we can confirm that ok the metal ions are binding to give a typical coordination geometry. And the typical coordination geometry is also important for the change in the conformational structure of the 2 states.

When you have the only tetrapyrrole ring that means the tetradentate macrocyclic ligand in your hand and when the metal ion is not present MI is abbreviated as the metal ions so it can be considered as between an open and a closed form of the protein. So, you have a huge protein structure and during that protein structure if it is the apo protein part the metal ion is not bound to the donor groups available to that particular big molecule. So, that will have a 1 particular conformation.

But, when metal 1 is coming into the picture and binding all the available donor groups will have a different structure. So, the metal of protein or the middle of biomolecule structure will be completely different from the free state that means the open state the middle iron free means is open state. And the closed form is the middle iron bound form. So, if we take a very simple example where we all know the EDTA 4 minus ethylenediamine tetra acetate 4 acetate groups are there.

So, you have these 4 acetate groups which are available for coordination as well as 2 nitrogen. So, these are there so what is the corresponding structure in solution or in the solid state if you crystallize the corresponding salt as a sodium n a 4 EDTA or Na2 H2 EDTA we can find that it is a typically open structure since the metal ion is not there.

But, if you put calcium or magnesium into it we know that it will try to form a octahedral coordination geometry around the calcium or the magnesium ion. So, it will form a typical octahedral structure and the conformational structure of the ligand will be such that it will have a sphere like arrangement around the metal ion.

Since, we know octahedron has a spherical symmetry so in the bound form the small molecule like EDTA 4 minus can try to have a corresponding sphere like structure. Similarly, the protein has a particular structure we call sometimes the globular protein so this globular proteins but there are vacancies when you do not have the metal ion bound to it.

Such as we find that when you have the different ions like copper ions. So, copper in 2 oxidation states the cupric ion and the cuprous ion and it is extremely low within the cells. So, the inside cell concentration and outside cell concentration these also matters are while we are studying this particular type of arrangements.

So, copper and bound when they are bound so metallochaperones so metallochaperones are there when it can be in the free form like your apoprotein but when it is bound form it will have a different structure. So, this particular thing that means the metallochaperones are involved for the incorporation of copper into copper ion containing proteins.

So, there are some other groups of molecules or other groups of biological molecules will be available which can trap the copper centre and carry it to the protein where we will find that we get ultimately the copper containing proteins or copper enzymes.

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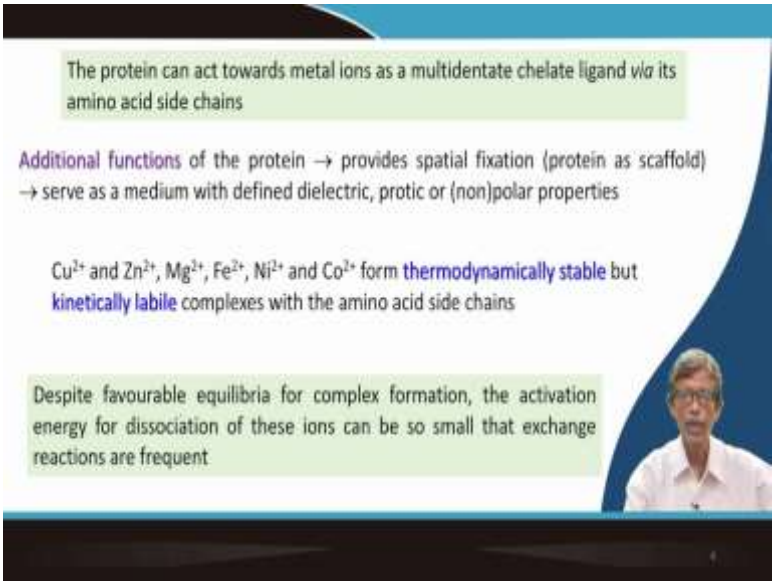

So, the protein can therefore act towards the metal ions is a multidentate chelating ligand via the amino acid side chain. So, why the protein is coming and binding to the metal ion centres this is important. So, definitely like your nitrogen toner or the oxygen toner what

we have for your standard EDTA the typical example I am giving you or a simple amino acid you can see the glycine. What is that?

Glycine is your NH2 CH2 COH and it can function as a bidentate NO donor ligand. So, this particular part is available when you have a polypeptide chain or a simple dipeptide like gly gly or a tripeptide like gly gly gly but these donor groups like the carboxylate function or the amine functions are engaged in amide bond formations. So, they may or may not be available for metal ion coordination.

But, when these amino acid side chains or the residues are part of the protein chain bigger protein chain that particular amide bond because when we form amide bond we know that the CO NH CO is coming from the carboxyl and of the 1 amino acid and NH is coming from the other part of the amino acid. So, if they are forming a CONH function so neither COH nor NH 2 are free and can be available for the coordination to your metal ion.

So, how it will form a particular bond and what are those groups basically available to us will see. Then the protein can have some other different functions it basically provides a typical special fixation that means the protein scaffold that how it basically folded and then it can serve as a medium that means it can drag the metal ions within that particular scaffold. Scaffold is nothing but a platform.

So, on that platform what we find that if you have a protein platform on that platform you are bringing the metal ions and the metal ions will be positioning at some points depending upon the available donor groups then the corresponding protein can also function as a medium. That means the environment like your organic solvent medium suppose you have DMSO dimethyl sulfoxide and which is there in presence of a round bottom flux or a beaker or a test tube.

Then we will talk about in terms of its property dielectric property the protic environment and the polar properties or the non polar properties. So, protein itself can give you that particular environment. Because, we all know that this is the aqueous environment with our body we do not have the non polar environment but the polar environment always we have.

So, basically what we will consider very quickly there that starting from copper 2 plus cobalt 2. That means if we consider simply about the coordination behaviour of these

metal ions like copper 2 plus zinc 2 plus 2 cobalt 2 plus we know that they can form the complexation. That means we write basically also in that fashion the Cu 2 plus plus 2 L your L can be a neutral ligand like ethylene diamond we abbreviate as En.

So, if it is forming a CuL2 species then we can talk about the corresponding equilibrium and equilibrium constant. When we talk these in terms of the equilibrium constant we know that the thermodynamics is playing some important role and if it is stable that means than the left you have the copper 2 plus plus twice L on the right you go there directly to CuL2.

But, if the k value for this particular process it will have 2 steps in first step it is binding 1 ligand in the second step it is binding the second ligand. So, overall overall formation constant we call that is related to that of the step for k1 for the first step and k2 for the second step. So, if you have a stable product thermo dynamically stable product is present in the solution not that you are isolating from the solution medium but it will have a particular formation constant value and which is little bit higher in magnitude.

So, we can consider that these are thermodynamically stable but what about the kinetics how fast and how quickly it is forming and whether they are labile or not that is also important. So, these 2 properties related to the coordination chemistry also the basic coordination chemistry what you have studied from your school days. You can apply that you know the thermodynamic stability and the kinetic stability of the metal ion complexes.

Now, thing is that you have a very robust or rigid structure of the amino acid side chains which are coming from the protein chain. So, you have a favourable equilibria for the complex formation thats why I am telling that you can have the different k values and related to that the activation energy for the dissociation of the ions these ions is so small that exchange reactions are frequent. That means it will not be exchanged with the other ligands then water is present over there.

So, when the ligand is bound the ethylene diamine is bound to the copper to centre the ligand exchange reaction or sometime the metal ion exchange reaction may not take place. Because, it is not energetically favourable as well as it will not be thermodynamically favourable.

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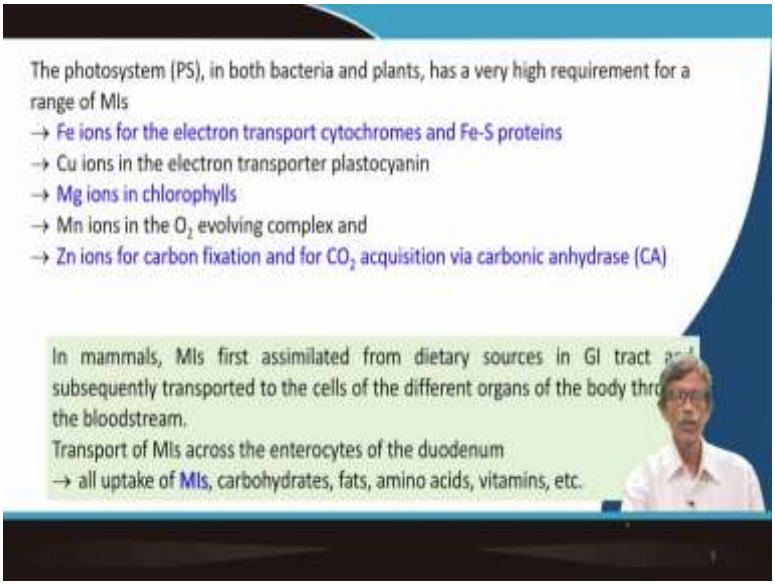

So, we will have quickly will see that what are the examples we can have in our hand so we know from again from the lower level of school also so that we know the photosynthesis. So, the photosystem we know that the photons we are using such that we can synthesize something which will be useful and energetically rich also.

Both bacteria plants basically can use this photo system and this particular photo system basically can have some good requirement for a different type of a different range of metal ions. So, if we consider that iron ions that means the ferrous or the ferric ions are involved there how they are involved.

So, when we talk that it is Fe ions having 2 oxidation states that Fe 2 plus and Fe 3 plus we can immediately consider it as maybe you can have the corresponding change in the oxidation states that mean it can settle between these 2 oxidation states. If it is there in the reduced form that means the ferrous ion it can go to the ferric form and give you 1 electron to the system.

So, it can vary would function as a electron transport chains within the electron transport chains there are several cytochromes and sometime we will find also the iron sulphur proteins also. Then copper also we all know they are redox active so the electron transporter in plastocyanin type of copper proteins then magnesium ions.

So, when you read it basically try to understand and try to focus your attention that if you I am telling you magnesium but whether your magnesium is redox active or not. But, in chlorophylls there must be some electron transfer reaction so that will discuss when

we individually discuss all these things will find out where from you get the corresponding electron transfer.

So, the presence of magnesium so when you have the chlorophyll you should be able to match it that magnesium is present. Similarly, for the magnetic ion for the O2 evolving complex in photo system also PS2 we call the oxygen evolving centre is there. And water is getting oxidized producing O2. So, manganese ions are involved over there.

Then for the hydration of carbon dioxide to give you the carbonic acid that H2 CO3 we require a corresponding enzyme which is zinc based enzyme which is nothing but your carbonic anhydrase. So, these are the different metal ions. So, these metal ions are first assimilated when we take our food from the dietary sources it takes this and these 2 things you can be able to remember MIs are the metal ions and the GIs is the gastrointestinal tract.

So, within the GI tract it can absorb first and then can be transported to the cells and the different organs of the body and finally to the bloodstream. So, the transport of these metal ions is therefore is important and across the enterocytes and duodenum so these are basically considered as are the biological terms you should all know what are the meaning of these endocytosis will be trolling sometime. So, enterocytes also and the duodenum we know the intestine we have the duodenum.

Then all are involved in the uptake of your metal ions. So, uptake of these metal ions is not only taking place in your GI tract but also other ingredients in your food material or the dietary sources are also available to you. So, in that particular case you have the carbohydrates you have the fats and you have the vitamins also. So, these are basically absorbed over there along with the metal ions.

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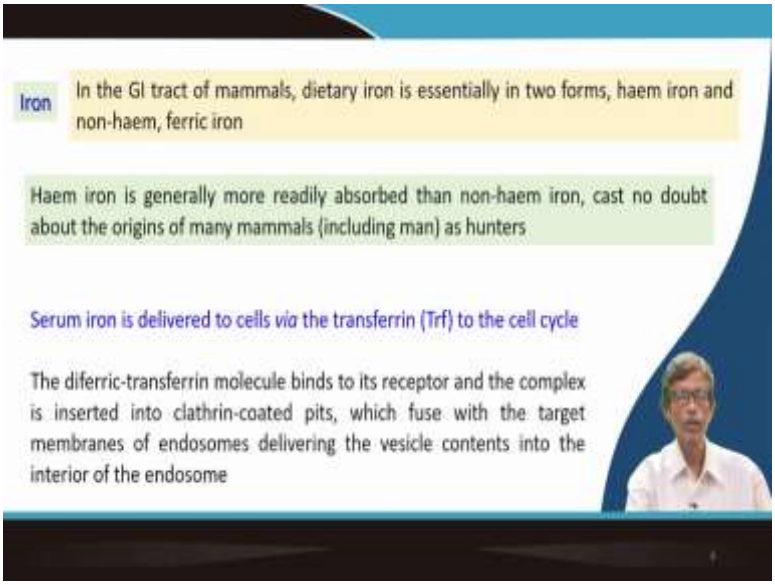

So, during this absorption how these metal ions can play some important role for the absorption for assimilation and finally incorporation in the protein or in the tetra flow ring. So, if we simply the see the iron what about iron we should know so the GI tract of mammals GI tract for animals and the dietary iron now so that diets we are taking the food materials we are taking.

But, when we are taking iron along with that food material will be calling it as a dietary iron. And these are of 2 forms, one will be calling as the haem iron another is the non-haem iron or some simple ferric iron. Haem iron what is that haem iron and that will also see. So, which basically nothing but when it is bound to the tetrapyrrole ring just now we are discussing about the tetrapyrrole ring so the ligand is your tetrapyrrole ring which is bound to your iron and form a species which is more readily absorbed than non-haem iron.

And therefore, it discloses the fact about the origin of us the origin of many mammals including man as the hunters. So, that is why we try to have the meat try to have the flesh animal flesh such that you can readily get the haem iron very quickly because you have the absorption. Then that particular iron if it is available in your bloodstream so you have the serum iron and that serum iron is basically delivered to cells by it another important molecule the transferrin molecule.

And the transparent molecule is involved in the cell cycle that means it is carrying iron then it is liberating as the free state that means only the ligand part or the apoprotein

part. So, 2 centres are there so we will discuss all in detail but right now in terms of your simple definition and understanding what does it mean about the transferring.

So, you have 2 centres which are ferric centres within the transferrin molecule and they can function as a receptor and the complex is inserted into some pit. So, you have the cell and above the cell you have short certain pits and the pits are clathrin coated. So, these are again some organic molecule big protein type of molecule and those are involved for engulfing that means to drag the iron centres.

And you have the target membranes of endosomes delivering the vesicles content in the interior of the endosome. So, when you have the cell so on the surface of the cell you have the clathrin and the clathrin coated pits are there which will take up those irons and it can go inside the cell. So, we discuss all these things do not worry for all these we will discuss in detail afterwards when we talk about the transferrin the iron transferring molecules.

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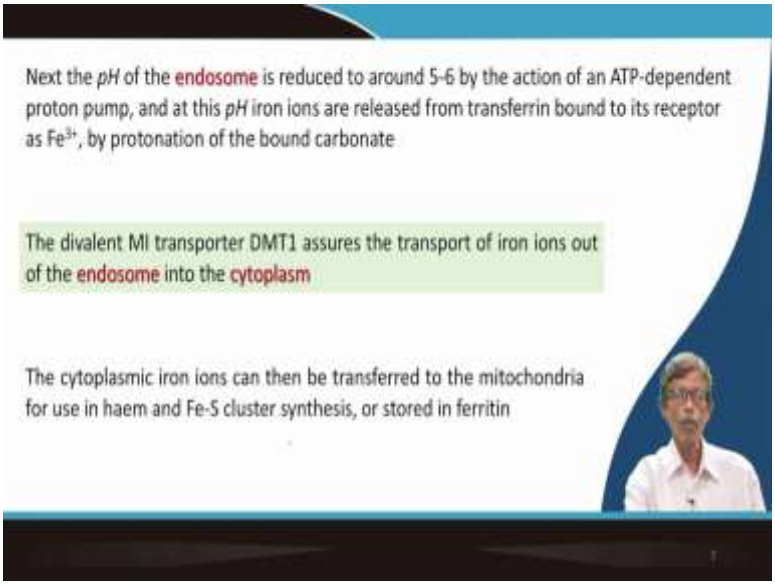

So, then we have to see the function of the pH. So, when you have the endosome so within the endosome the pH is basically balanced at 5 to 6. And a proton pump which is dependent on ATP molecule so ATP dependent proton pump is there which can not only like that offer electron transfer but it can also transfer protons such that it can modulate the pH values in that particular environment.

So, if the release of protons are very high the more number of protons are being released your pH of that particular environment can be reduced. So, in transferrin molecule will

see that not only that is the binding of the iron to the protein molecule but another carbonate is there the synergistic carbonate when we take up oxygen we produce carbon dioxide and when that carbon dioxide is getting hydrated forming the carbonic acid the H2CO3 and that H2CO3 when it is getting deprotonated it will form HCO3 minus or CO3 2 minus.

So, that carbonate is basically endogenously produced that means the system is producing the your body is producing a beautiful ligand which is binding to your iron centre in a bidentate fashion. So, when you protonate that carbonate, carbonate will be released and that also facilitate the release of your iron from that particular site. So, what we will have during this transport will get DMT1.

So, DMT1 again the MI transporters that means the metal ion transporters and the transport irons of the endosomes into the cytoplasm. So, these are red marked or species that means that basically your keywords. So, you should little bit you read the biology books also what are these endosomes and what are these cytoplasms. So, then we will think about the we are bringing metal ions there and to talk about in terms of how it is happening in the endosome and how it is going to the cytoplasm.

So, the iron available in that particular environment that means the cytoplasmic iron ions can then be transferred to the mitochondria by use of your haem iron that means the iron perforin unit or in some cases your iron sulphur clusters. So, this particular thing can be utilized for your haem iron synthesis and the iron sulphur cluster synthesis. And sometime if excess iron is transferred it will be stored in our ferritin molecules.

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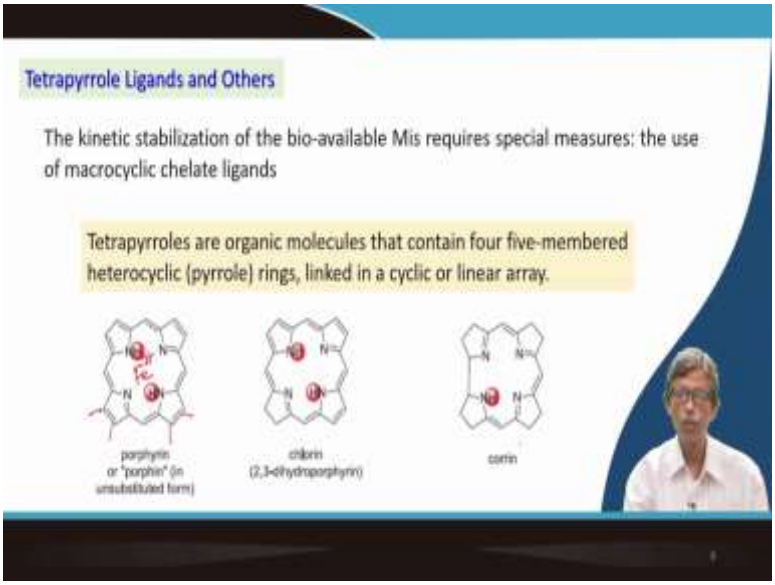

So, ferritins are nothing but your iron store house. So, how we get this tetrapyrrole ligands you have now a kinetic stabilization of the biologically available metal ions and then we use the macrocyclic cluttering and when it is binding to that particular tetra pyrroles the organic molecule contain 4 five-membered heterocyclic pyrrole rings and in is linked in a cyclic or a linear array.

But, when it is a cyclic 1 you get the porphyrin ring. So, you see that is very important that you can have this particular case that means you get these as your iron centre over here so you will be able to insert iron over here. So, it will be iron 2 plus or iron 3 plus. Similarly, this is also a macrocyclic ring and this can also be a very good macrocyclic ligand to trap the iron centre.

So, one is your porphyrin or porphin when you do not have any substitutions because we all know that you can have the substitutions from here and here, here and here all these places are the positions where you can have the substitutions. Then the chlorine ring which is nothing but your 2 3 dihydro porphyrin. Then another one is basically when you have a reduced ring so these rings are reduced you see these are not typical pyrrole rings these are reduced and instead of this methylene bridge you have the direct connection on the left hand side you get a corrin ring. So, this corrin is also utilized for binding cobalt centre or some other metal line centres that will see.

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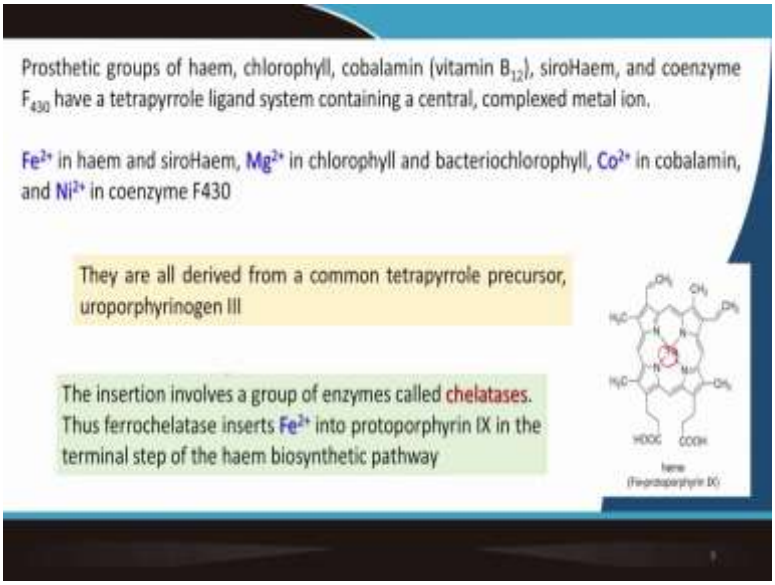

So, the prosthetic groups of heam that means the bound form of the macrocyclic ring in the chlorophyll where magnesium is present in cobalamin where cobalt is present and many other examples are there like sirohaem and one such the latest discovery around last 20 years we get is the coenzyme F430. Where the nickel centre is bound to it.

So, on all these cases your tetra pyrrole ring is there and which is bound to the metal ion centre and metal ion is sitting inside the cavity of that particular tetrapyrrole ring. So, iron is there in haem and sirohaem the name will immediately tell you and as discussed just now that magnesium will be there in the chlorophyll and the cobalt is there in the cobalamin and nickel 2 plus is there in the coenzyme F430.

So, they are basically derived from a common tetrapyrrole precursor which is uroporphyrinogen 3. And how it binds now? You see that this is the part where you can have this particular 1 that iron is bound and this particular iron is bound over there and this particular case you see just now I told you that you have the iron and this iron basically giving you this particular coordination over there.

So, we get a particular result as your haem function and that haem iron that is why we get for your understanding. So, insertion that how it is getting inserted so that some other enzymes are there which are nothing but your chelatases and in case of iron the iron is stacked with the ferro thing that is ferro chelatases is available to incorporate the iron in the terminal step of the haem biosynthetic pathway.

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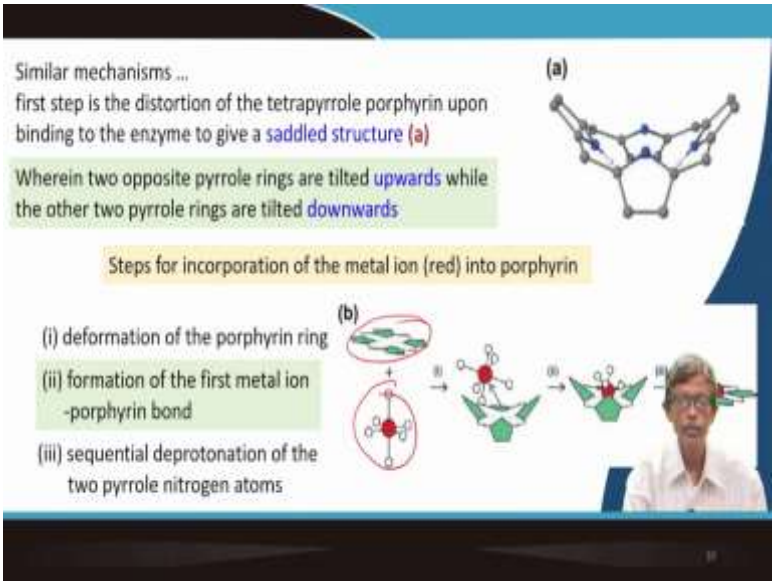

So, there are several similar mechanisms are operating and the first step is nothing but the distortion of the tetrapyrrole ring. So, it is not a flat molecule it will have some saddle structure. So, the tetrapyrrole ring will have a saddle structure and that saddle structure is important where two opposite pyrrole rings are tilted upwards while the two others are tilted downwards.

So, these two you see these two are tilted downwards and these two are up and that particular system is available for binding your metal ion. So, the steps for incorporation of the metal ion to this for porphyrin ring is therefore that you have the porphyrin ring so this is your porphyrin ring. So, this is your perforin ring which is taking your octahedral hexagon iron centre and that hexagon they are forming 1 after another bond.

So, 4 bonds will be forming over there and then finally your iron is sitting comfortably within the pocket. So, remember that at this point that you are going for the formation of 4 such bonds. So, how these 4 bonds are forming which one is forming first which one is the next and then ultimately third and the fourth bond is forming to giving you the haem iron.

So, first you have the deformation then the first middle iron to the porphyrin bond form and then sequential deprotonation because you have 2 NH groups or 10 NH functions are there and those NH functions are getting deported during the trapping of your iron centre.

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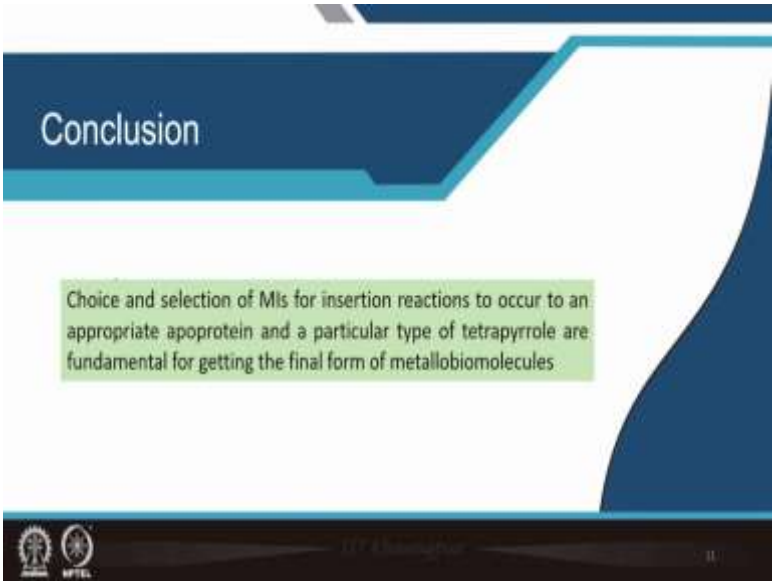

So, we have come to the end basically and what we have learned and what we have seen in this particular point we will see that slowly we will see that the choice and selection of the metal ions. So, what metal ion you are choosing whether you are choosing magnesium 2 plus or you are choosing iron 2 plus or 3 plus. So, choice of this metal ion is important and how it can be incorporated within the protein part if you have a huge protein part that will see also when we talk about the myoglobin and the haemoglobin.

The corresponding formation of the porphyrin bound to the iron centre is there but you have to bring the globin the globin chain the protein chain you have to bring which is again coordinating to your iron centre in a monodentate fashion. So, this metal ion for insertion reaction to occur to an appropriate apoprotein and a particular type of tetrapyrrole are fundamental for getting the final form of metal of biomolecules.

So, what we are talking here is nothing but how the metal of biomolecules are forming and how you bring the metal ion and how you will be able to insert that metal ion within the cavity of the apoprotein or the porphyrin chain.

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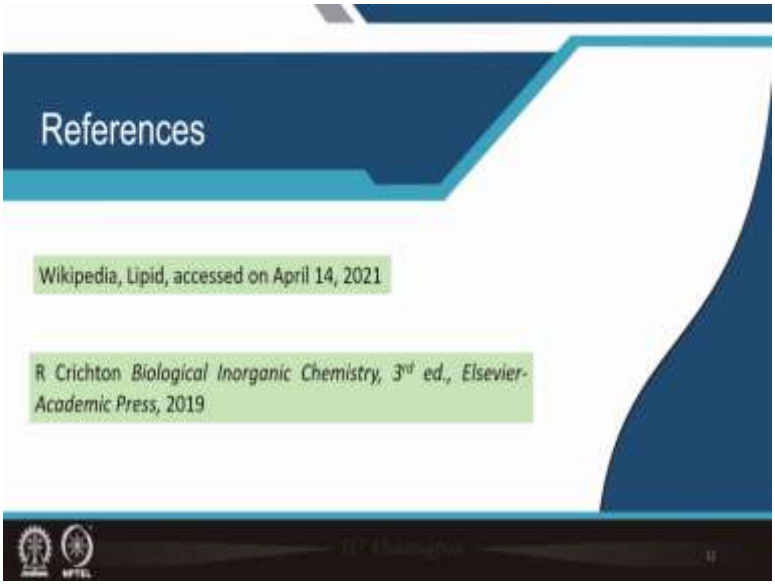

So, the references what we can have every day I am seeing that you just see the Wikipedia pages for all these then the lipids also you can access as in our last class we have considered you can also consider the corresponding one as the metalloions in biological systems. And the book what we are considering every day and every time because mostly I am focusing on attention on this particular book biological inorganic chemistry book there will get everything in detail but if you need only then you just go for the reading this book, otherwise any bioorganic chemistry book will be helpful for you for your understanding for at this particular point. Thank you all.