Bioinorganic Chemistry
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Lecture - 05
Metals in Biology: Nature's Selection
[Part-4 of 4]

Hi. So, we have discussed so far, the importance of inorganic elements in biological system and also how those elements are being selected out of so many elements present in the periodic table. Although, the metal ions are present in extremely small quantities and surrounded by a huge protein chains, the biological activity are performed only at the metal centers which clearly justify the crucial roles played by the metal ions.

Cobalt is an essential trace element in both prokaryotes and eukaryotes. Nevertheless it occurs less frequently in metal proteins than other transition metals. This low occurrence appears to be due to the metals low abundance in natures.

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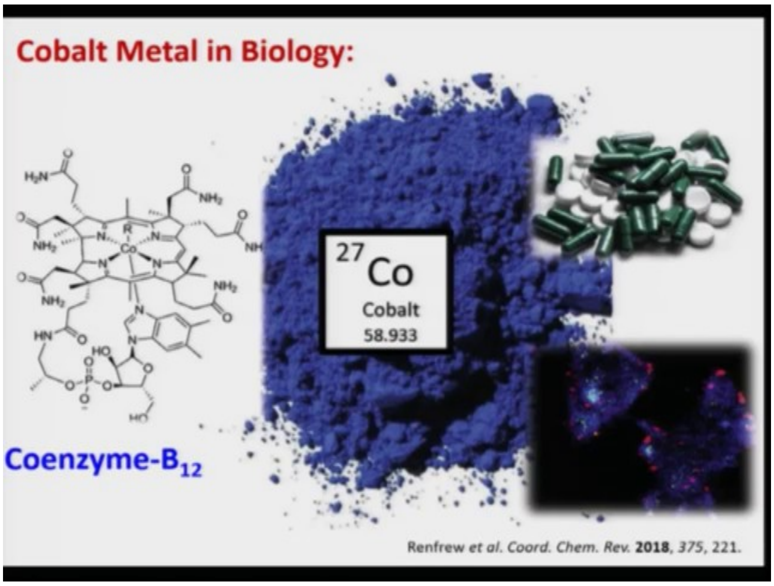

Today, we will be talking about cobalt metal in biology. You can see that coenzyme B_{12} is an enzyme containing cobalt. Enzymes are biological catalysts that speed up chemical reaction by lowering the activation energy of the reaction.

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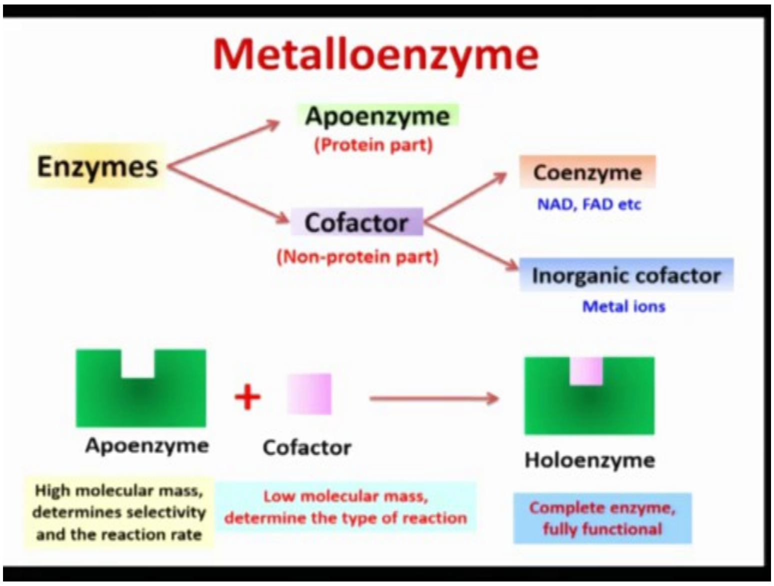

Enzymes are generally made up of protein and non-protein parts as shown over here. Protein part is called apoenzyme and non-protein part is called cofactor. Non-protein part can be divided into two types again based on their chemical nature. Organic cofactor like NAD, FAD, etc. are called coenzymes. Cofactor can also be metal ions like cobalt, iron, zinc etc.

As you can see here this apoenzyme which is basically high molecular mass mostly protein it determines selectivity and the rate of the reaction. Cofactor is low molecular mass it determine the type of reaction and when you combine both apoenzyme and cofactor it gives rise to holoenzyme which is actually the complete enzyme with full functional behavior.

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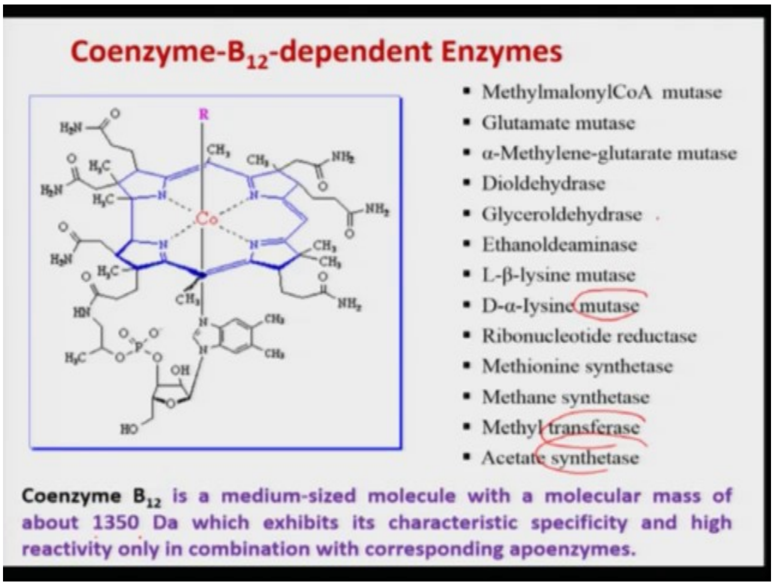

This is plot of coenzyme B_{12} dependent enzyme and as you can see that coenzyme B_{12} is a medium sized molecule with a molecular mass of about 1350 Dalton which exhibits its characteristic specificity and high reactivity only in combination with corresponding apoenzyme. Now, there are several enzymes having this coenzyme B_{12} and some of them are listed here. You see the large number of cobalt containing enzymes synthetase, transferase, reductase, mutase lots of enzymes are present.

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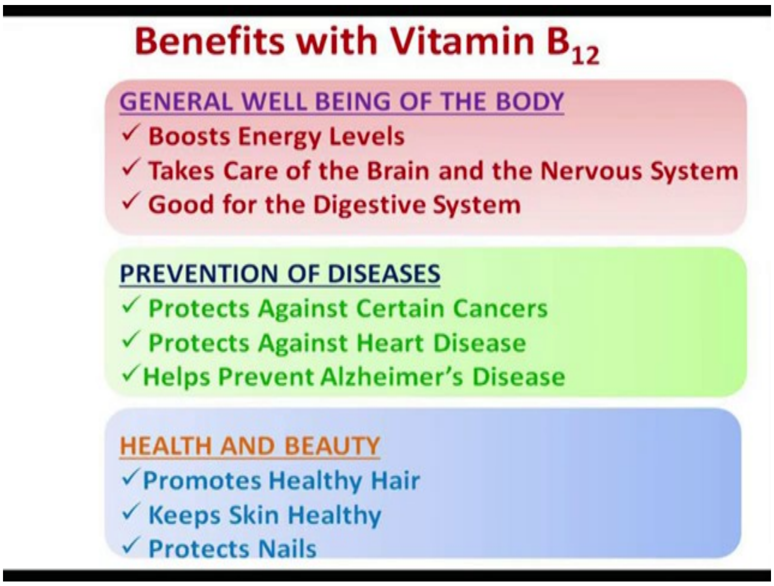

Now, the benefits with vitamin B_{12}: general well being of the body. Particularly boost energy level; it takes care of the brain and nervous system; good for the digestive system. It also prevents us from disease such as protects against certain cancers, protects against heart disease, helps prevent Alzheimer’s disease. It also responsible for some health and beauty – promotes healthy hair, keeps skin healthy, protects nails lots of things which actually are controlled by vitamin B_{12}.

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And, you can see here lots of good food having vitamin B_{12}. There are certain fish item, meat items, eggs, a lot of other cheese which are having large amount of vitamin B_{12}.

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Symptoms of having vitamin B_{12} deficiency in humans: you can have headache, you can have eye problem, you can have pernicious anaemia as reflected in the tongue because of vitamin B_{12} deficiency in our body.

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And, if you do not have sufficient vitamin B_{12} we go to the doctor. Doctor will prescribe various medicines to supplement the deficiency of B_{12}. Some of these medicines are shown over here.

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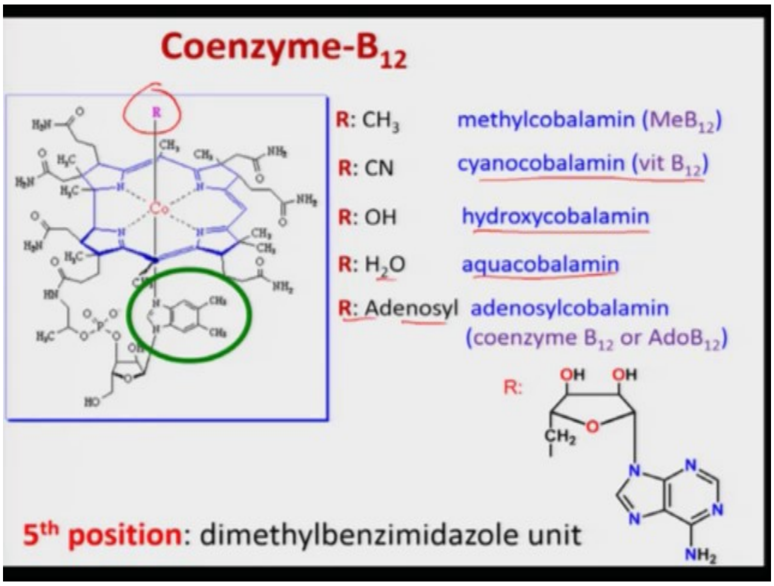

Now, coming back to this coenzyme B_{12}, and as you can see this R, once you change this R, the name also changes. For example, when R is $-CH_3$ it is called methylcobalamin; R is cyanide it is actually cyanocobalamin, which is vitamin B_{12}; R is OH hydroxocobalamin; R is a H_2O aquacobalamin; R is adenosyl you can see this is adenosylcobalamin. This is the R value which is actually a cofactor in the native enzyme.

This fifth position this axial ligand it is dimethylbenzimidazole unit which is very peculiar. It only present in vitamin B_{12}, no other enzyme have this axial ligand.

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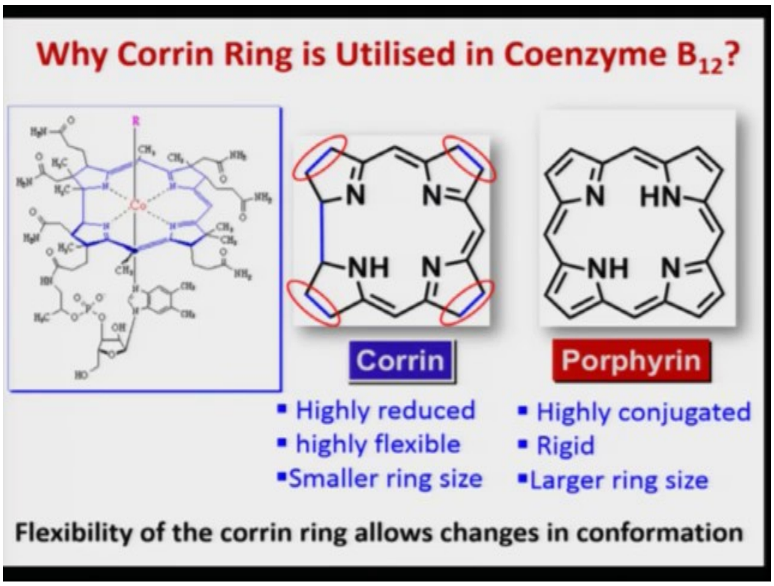

As you can see that this macrocycle which is present in the coenzyme B_{12} is a very peculiar, it is called corrin. So, I have actually compared here corrin and a popular macrocycle called porphyrin which you have seen in so many enzymatic system. For example, cytochrome P450, catalase, peroxidase indeed our haemoglobin, myoglobin all have this porphyrin ring.

And, this corrin and porphyrin if you look at their difference you see that corrin is highly reduced, highly flexible because it is saturated and the ring size is much smaller. In contrast, porphyrins are highly conjugated and flat molecules and ofcourse, it is a rigid because it is due to a extended conjugation and the cavity size also is larger than the corrin. So, this flexibility of the corrin rings actually allows the change in conformation which indeed is necessary for its reactivity.

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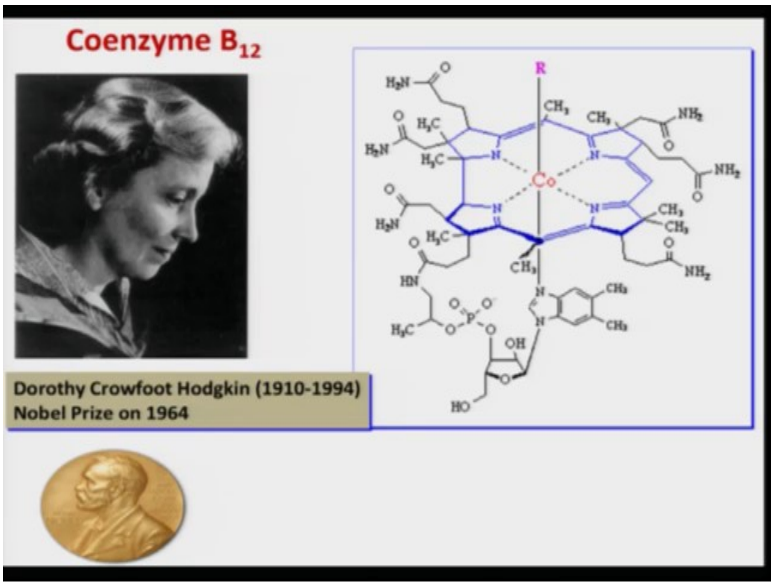

This is coenzyme and this complicated molecule was first structurally characterized by Dorothy Hodgkin and she got Nobel Prize because of that in 1964. Please note that this is the first molecule where cobalt-carbon bond was established. At that time there was no evidence of such bond.

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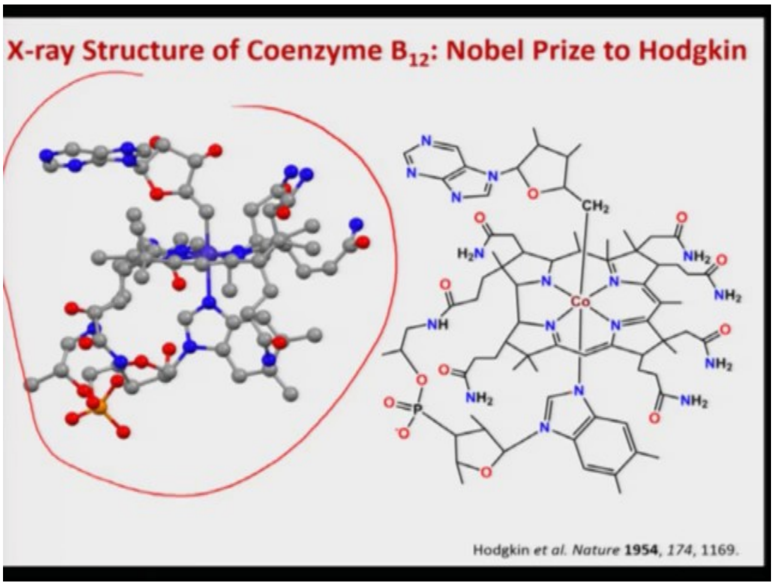

And, this is the X-ray structure which leads to Hodgkin a Nobel Prize you see that cobalt-carbon bond and then this X-ray structure of this coenzyme B_{12} is shown over here and now you know exactly what is in fifth position, what is in sixth position, how the rings looks like what is the distance angle every all details you can see from the X-ray structure. And, this complicated molecule corrin which is having nine chiral centres has been then realized after looking at this X-ray structure.

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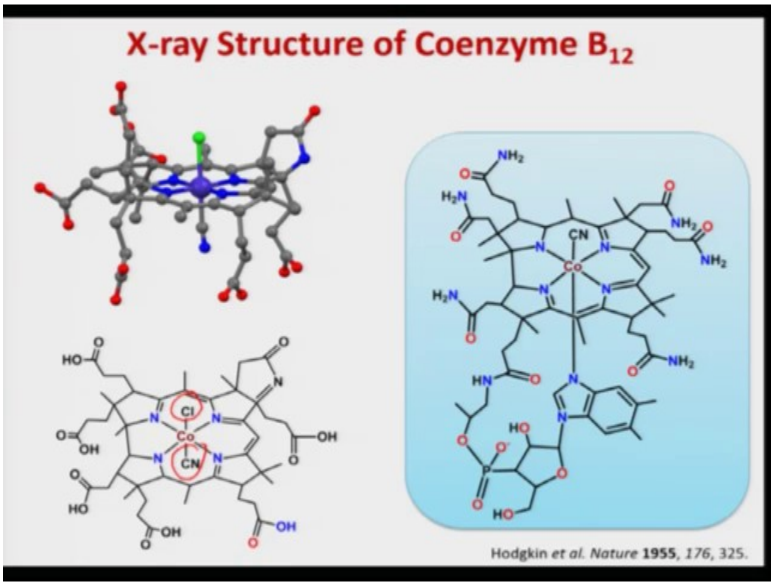

And, also she did some of this derivative. One of such derivatives is shown over here, where these axial ligand are chloride and cyanide. And, so, it is now known well established that what is the extra structure of coenzyme B_{12}.

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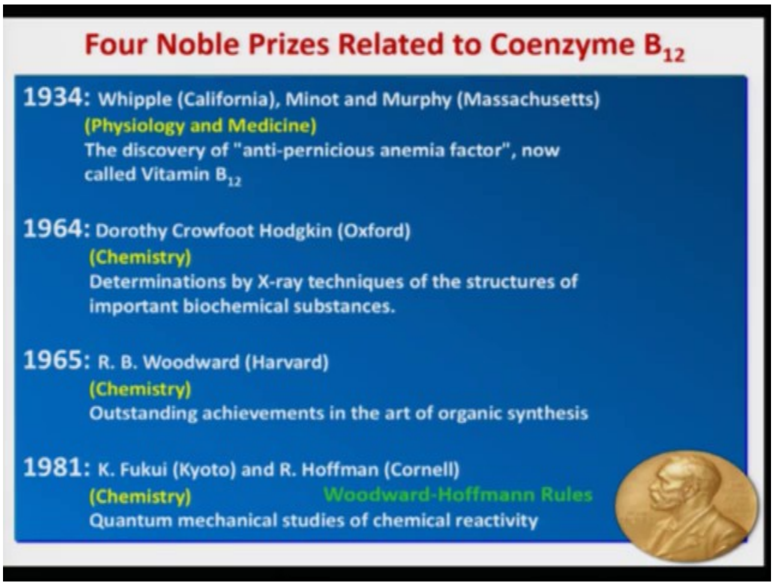

Indeed it is such a important molecule, four Nobel Prizes related to coenzyme vitamin B_{12}. 1934 – Whipple Minot and Murphy first got this Nobel Prize on this topic because of the discovery of anti-pernicious anaemia factor, now called vitamin B_{12}. 1964 – Dorothy Hodgkin from Oxford, got the Nobel Prize and this is because of the X-ray structure of this important biomolecules. 1965 – Woodward got his Nobel Prize for its outstanding achievements in the art of organic synthesis. It is such a complicated molecule he would able to synthesize this. 1981 – Fukui and Hoffman got also Nobel Prize due to quantum mechanical studies of chemical reactivity.

You all familiar with this Woodward – Hoffmann rule and this is based on this coenzyme B_{12}. They have established and now it is very popular rule for pericyclic reactions.

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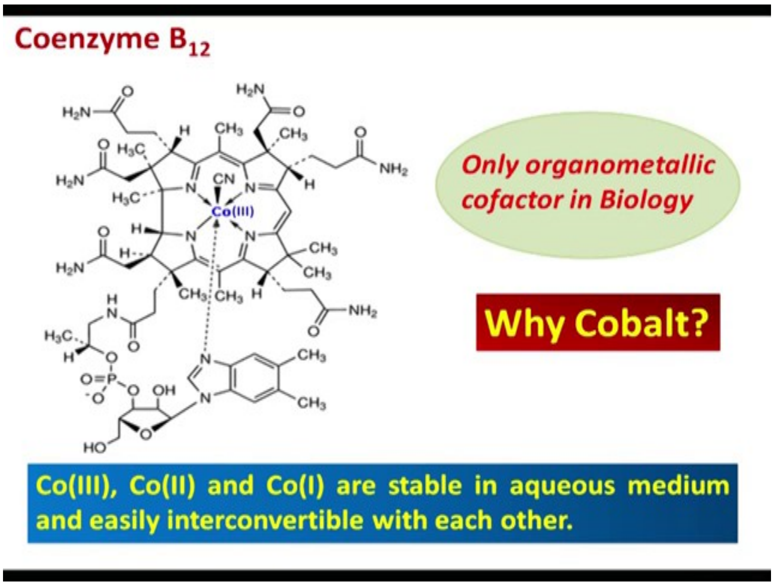

Now, coming back to coenzyme B_{12}, as you can see that this is the only organometallic cofactor known in biological system and this is also only vitamin having a metal ion and this is very important for our life. Now, question is that why nature selected cobalt out of so many elements in a periodic table? Please note, that cobalt is only metal where cobalt III, cobalt II and cobalt I are stable in aqueous medium and they are easily inter-convertible with each other.

No other metal can have this kind of behaviour. Say for example, if you take copper; say Cu(III) is highly oxidized. If you take iron, Fe(I) is very difficult to get it is stability in presence of oxygen. Now, corrin macrocycle also is necessary because you see that Co(I) porphyrin is not that stable in under oxygen. But corrin all these three oxygen states are achievable, they are very stable in aqueous medium and easily inter-convertible to one another and we will see that this is why nature utilized cobalt in its macrocycle core.

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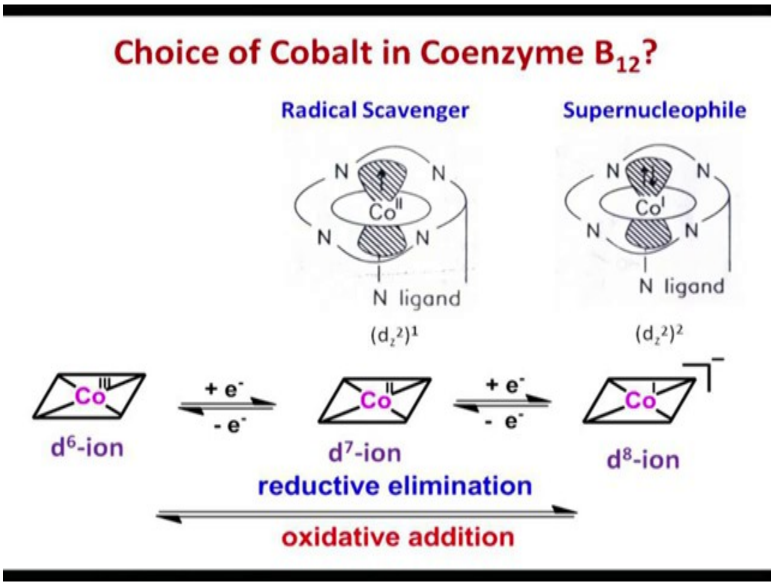

So, again coming back this cobalt, this Co(III) which is a d^6 ion basically it is converts to Co(II) after one electron addition and then it becomes Co(I). So, d^6, d^7, d^8 and d^8 is as you know that it is you can have oxidative addition; d^6 you can have reductive elimination convert in to d^8. So, all these things you can play with that.

And, also Co(II) it is a d^7 ion and this one unpaired electron is in d_{z^2} orbital as shown over here. This is called radical scavenger, is a radical basically in character, and Co(I) this d_{z^2} orbital contains 2 electron although they are paired.

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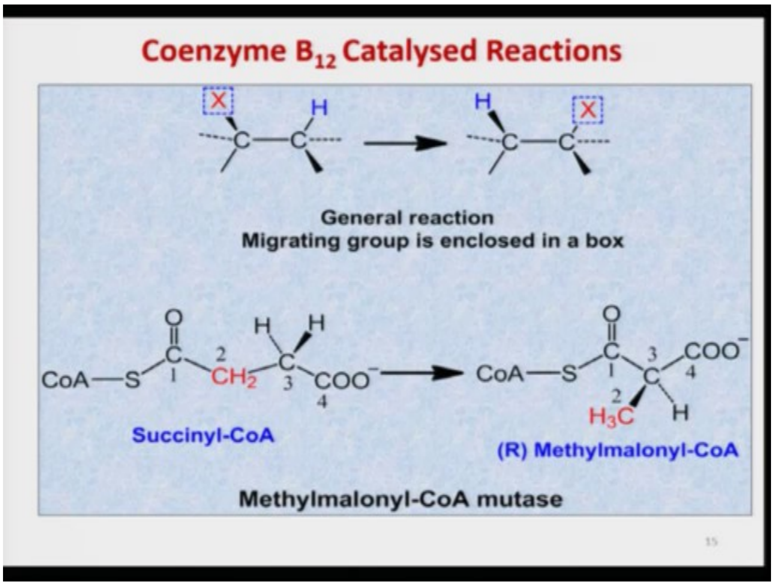

As I have already said that coenzyme B_{12} catalyzes lots of chemical reactions and the specificity and reactivity depends on the proteins around the coenzyme. Now, the basic chemical transformation that these coenzyme B_{12} catalyze is the migration of group. As you can see that this X comes to 1,2 shift. This comes over here and proton goes over here, this migration of the group.

And, the next example you see that the CH_2 group had been migrated and converted to the methyl. This is what is happening in methylmalonyl coenzyme A mutase. So, basically groups are getting migrated from one carbon to another carbon in these reactions.

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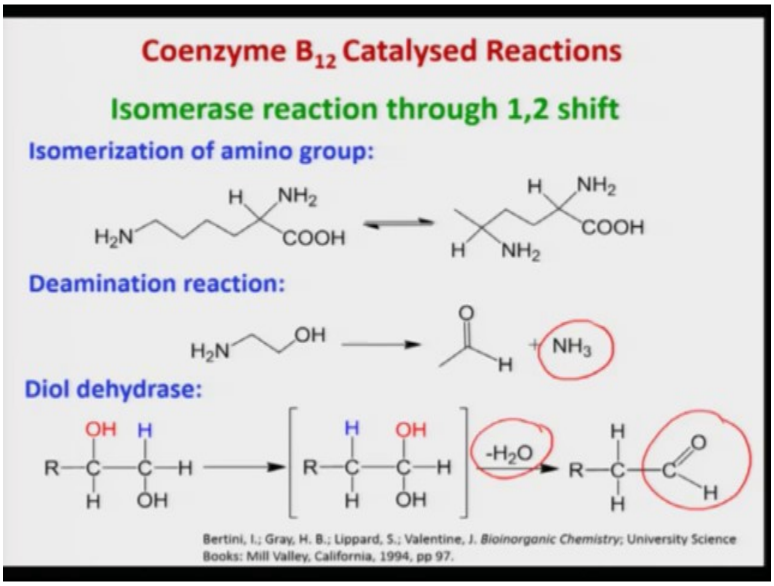

And, there are some more reaction isomerase reactions through 1,2 shift and you can see that even this amino group also getting migrated to another carbon. It is also deamination reactions where it liberates NH_3 groups. And diol dehydrase also, where you can see that 1,2 shift and after that the elimination of water leads to an aldehyde group. Now, all this chemical transformation is believed to go through a radical pathway. So, I will now show how coenzyme B_{12} catalyze chemical reaction.

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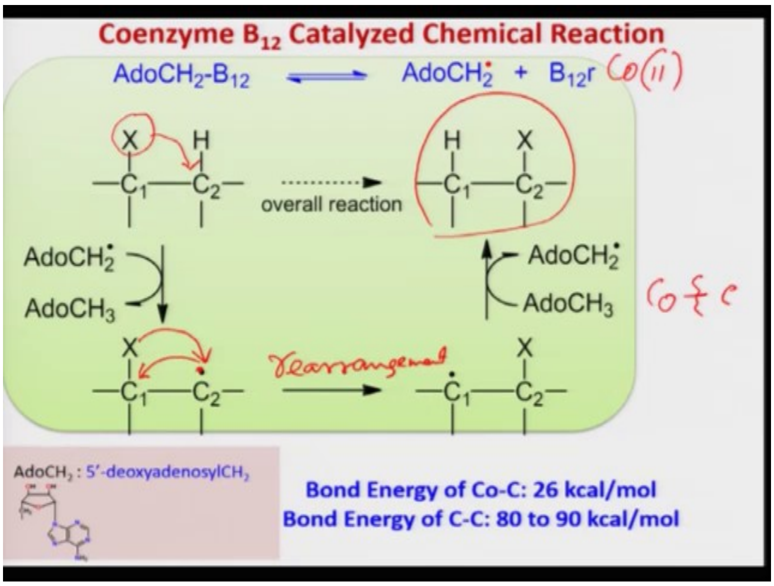

So, as you can see this ado B_{12} first undergo a homolytic cleavage. Cobalt-carbon bond gets undergo a cleavage and forming that ado-CH_2 radical plus reduced B_{12}; that means, which is actually Co(II). Now, this radical actually responsible for all these transformations which are happening, I will show how this radical is responsible for that.

Now, this is an overall reaction which is shown over here as you can see that this X group migrates from C1 to C2 unit and this is the product. Now, how this migration is possible using this radical ion? Now, this adenosine radical actually abstract the proton forming a C2 radical and this C2 radical undergo a rearrangement undergo a rearrangement and this radical comes from C2 to C1. It is migrate from C2 to C1 and there and then X comes from C1 to C2. And, this radical abstract another proton from adenosine CH_3 and then it gives this product.

So, as you can see that formation of the radical is very crucial. Can this radical you can generate just by a cleaving C-C bond as well? Yes, you can. However, if you look at this bond energy of C-C bond it is 80 to 90 kcal/mol; whereas, if you use cobalt you reduce dramatically the bond energy and it is only 26 kcal/mol. So, just light or thermally you can cleave this cobalt-carbon bond and form this radical species and thereby you can do miracle in your catalytic reactions.

I have discussed coenzyme B_{12} dependent enzymes today, and highlighted their role in catalyzing a large variety of chemical transformations in biology. You also have seen and enjoyed the beauty of natures design in the B_{12} and the selection of cobalt and the corrin macrocycle there in. The importance of cobalt carbon bond has been highlighted here which indeed responsible for a large number of chemical transformations in biology.

I do hope you all enjoy looking at the role of inorganic elements in biology. In my next few lectures, I will show you the beauty of natures design in controlling the chemical processes that are responsible for our survival in this earth.

Thank you.