

Vitamin B₁₂

PG Third Semester

Bioinorganic Chemistry-V

Lecture 13

**Bapan Saha
Assistant Professor, Chemistry
Handique Girls' College
Guwahati-01**

Contents

- Structure and function of vitamin B12
- Mechanism of 1,2-shift reaction

Books/References used and suggested

- Bioinorganic Chemistry by Bertini, Gray, Lippard and Valentine
- Inorganic Biochemistry by Cowan
- Bioinorganic Chemistry by A. K. Das
- Oxford Chemistry Primer by Fenton

Vitamins

- ❖ Organic nutrients required (small quantity) for several biochemical functions.
- ❖ Cannot be synthesized in body.
- ❖ Must be acquired from diet.
- ❖ Two classes

Water soluble: B-complex, Vit C (ascorbic acid)

Fat soluble: Vit A (retinol), Vit D (calciferol), Vit E (tocopherol)

- ❖ Vitamin C and Vitamin E function as antioxidant.
- ❖ Both excess and deficiency intake of Vitamin can be potentially harmful.

Vitamin B₁₂ : Cyanocobalamin

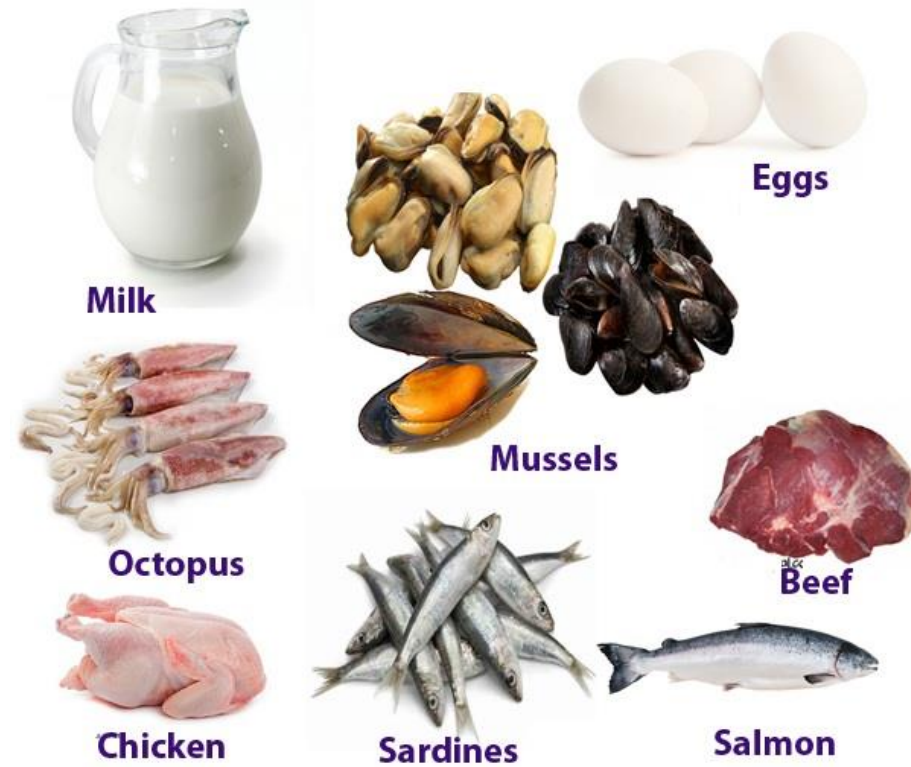
- ❖ First naturally occurring organometallic compound (the only vitamin with metal)
- ❖ Produced by micro-organisms (bacteria) and fungi, and not by higher plants
- ❖ Dietary intake for adult is 2-3µg/day.
- ❖ Pregnancy and lactation 6 µg/day
- ❖ Body stores vitamin B₁₂ of about 3-4 mg, primarily in liver (sufficient enough for 3 years if its dietary intake is ceased).
- ❖ Vitamin B₁₂ is relatively stable and little is lost during cooking.
- ❖ Cyanocobalamin: anti-pernicious anemia factor

Sources of Vitamin B₁₂

Foods of animal origin (red meat, liver, fish, eggs, seafood, dairy products)

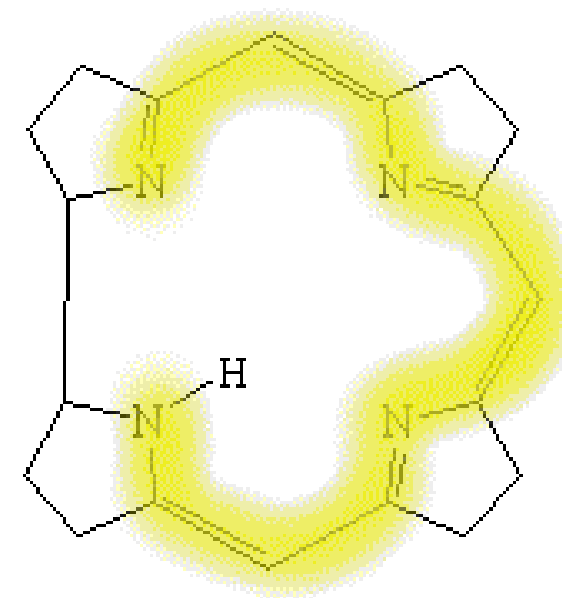
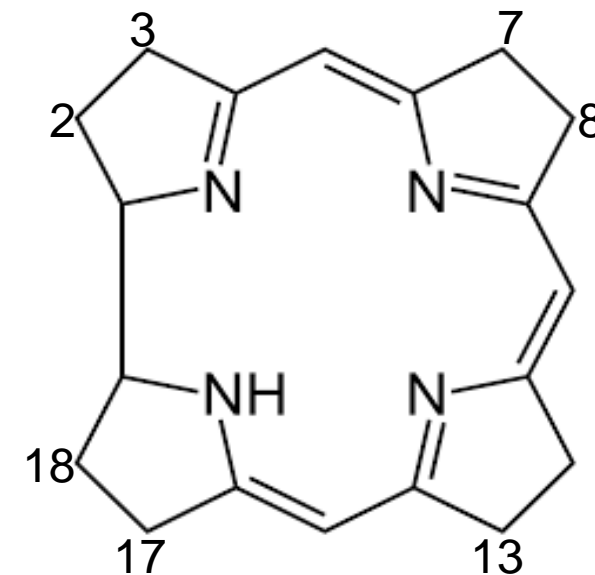


VITAMIN B12 RICH FOODS

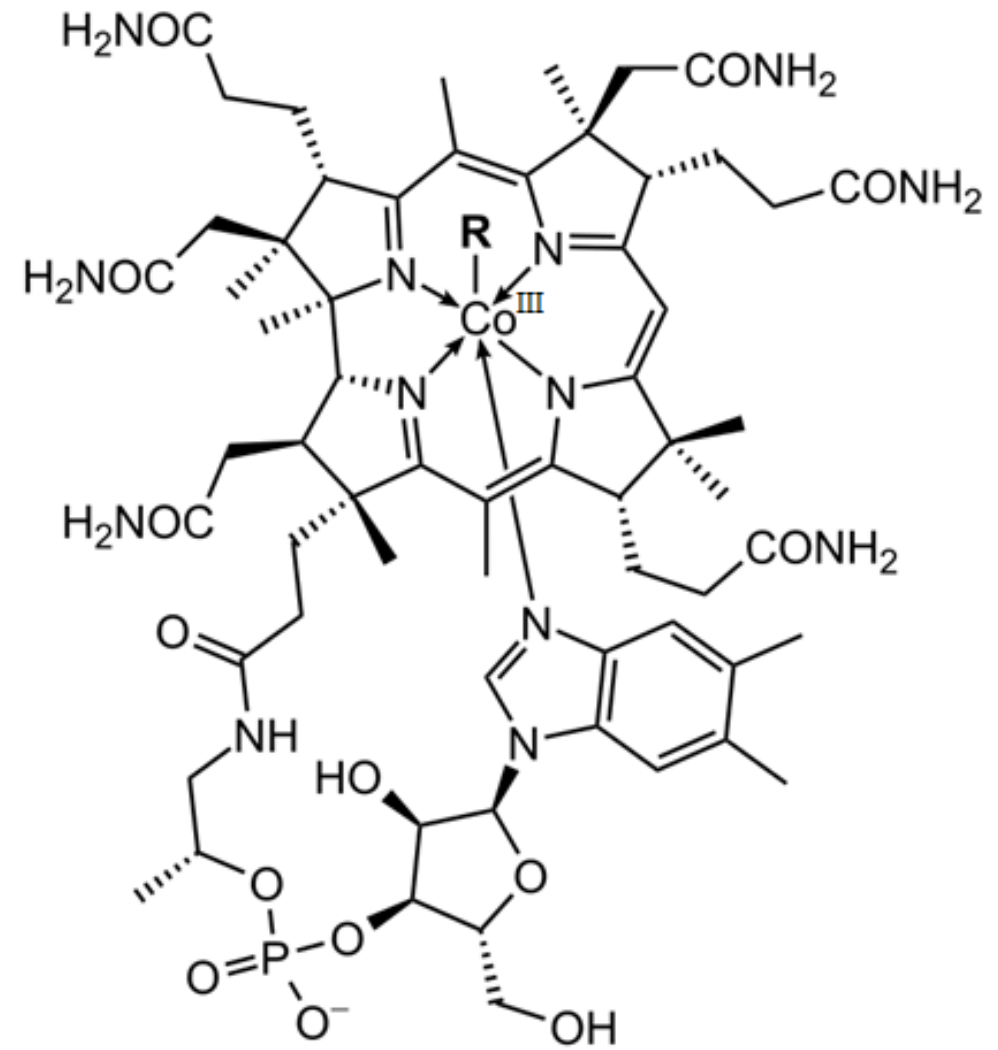


Structure of Vitamin B₁₂

- ❖ D. C. Hodgkin, Noble Prize 1964
- ❖ Six coordinated, Planar Co(III) corrin ring (tetrapyrrole),
- ❖ Corrin is similar to porphyrin with one methylidyne linkage (-CH=) between two of the pyrrole type ring is missing, contracting the ring.
- ❖ π -delocalization disrupt, making corrin ring flexible and adopt different conformations required for biochemical function
- ❖ At 2, 7 & 18 positions - three acetamide, -CH₂CONH₂
- ❖ At 3, 8 & 13 positions - three propionamide, -(CH₂)₂CONH₂
- ❖ At 1, 2, 5, 7, 15 & 17 positions – one Me and at 12 – two Me



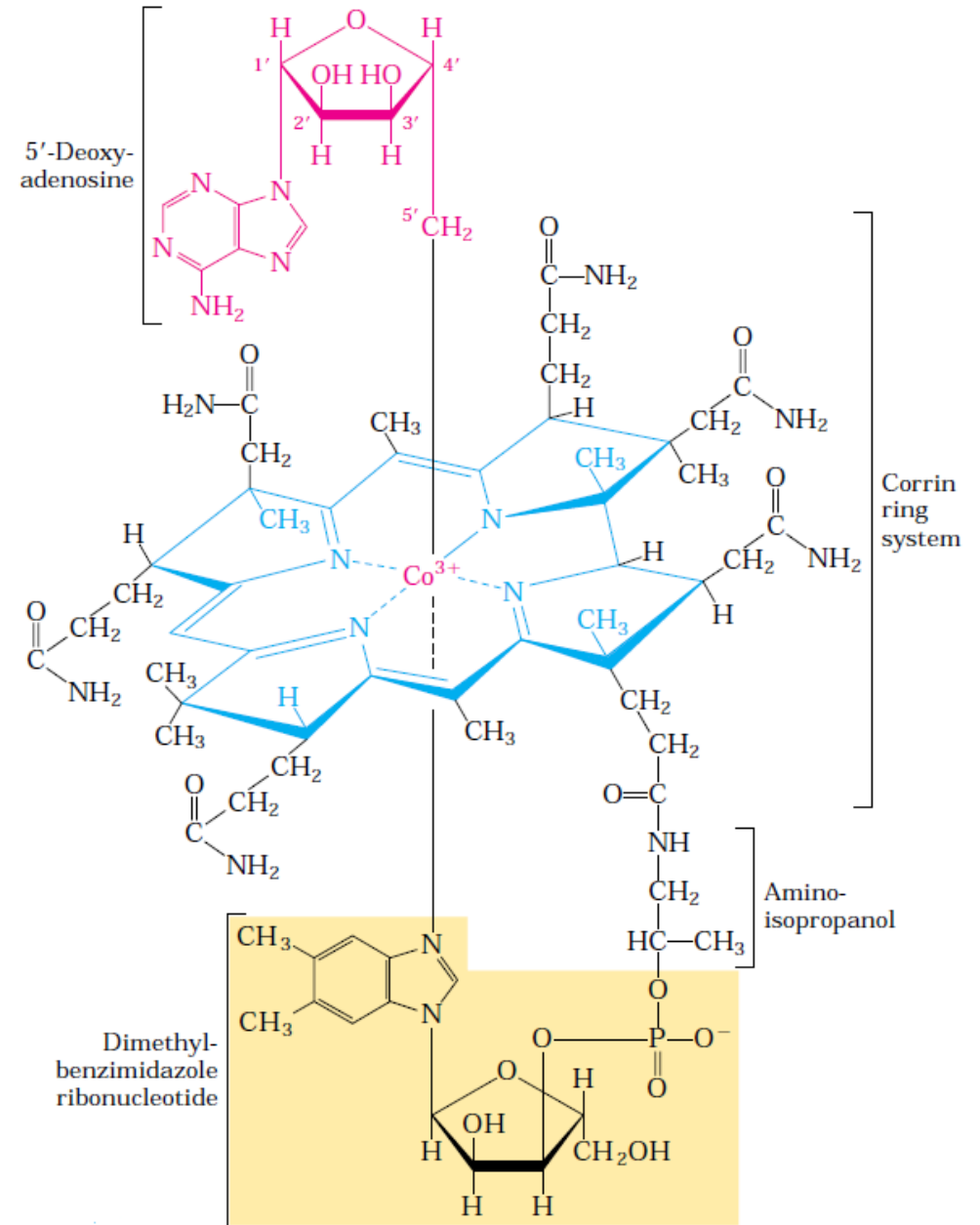
- ❖ At 17 position, one N-substituted propionamide (isopropyl connected to unusual ribonucleotide with 5,6-dimethylbenzimidazole group)
- ❖ Fifth coordination site is occupied by N-atom from imidazole ring of 5,6-dimethyl benzimidazole group (phosphate, ribose sugar and organic base)
- ❖ Sixth coordination site is occupied by CN^- ion (in biological system, H_2O molecule is loosely bound to Co-center)
- ❖ Inclusion of CN is an artifact & does not exist in nature



R = 5'-deoxyadenosyl, CH_3 , OH, CN

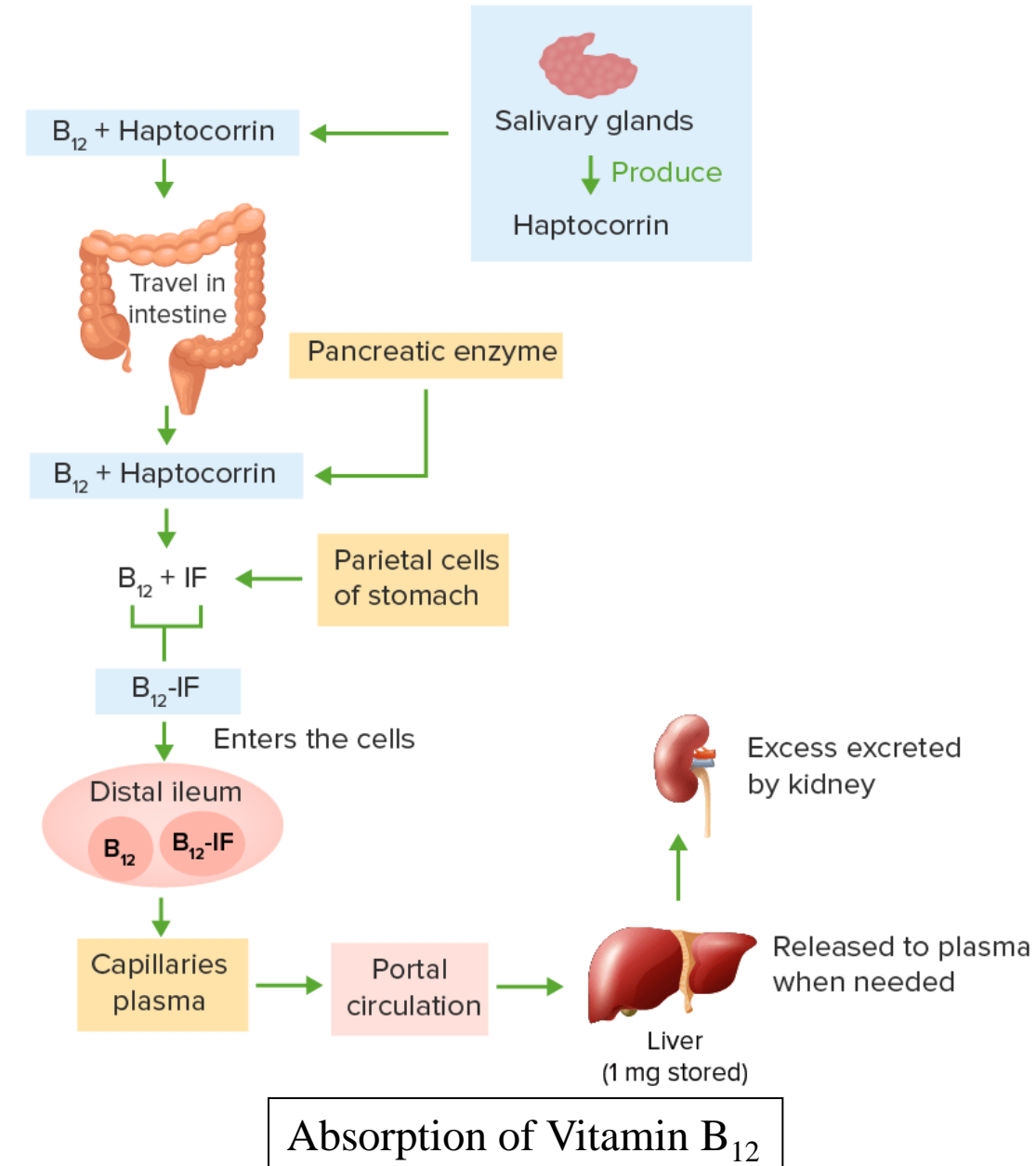
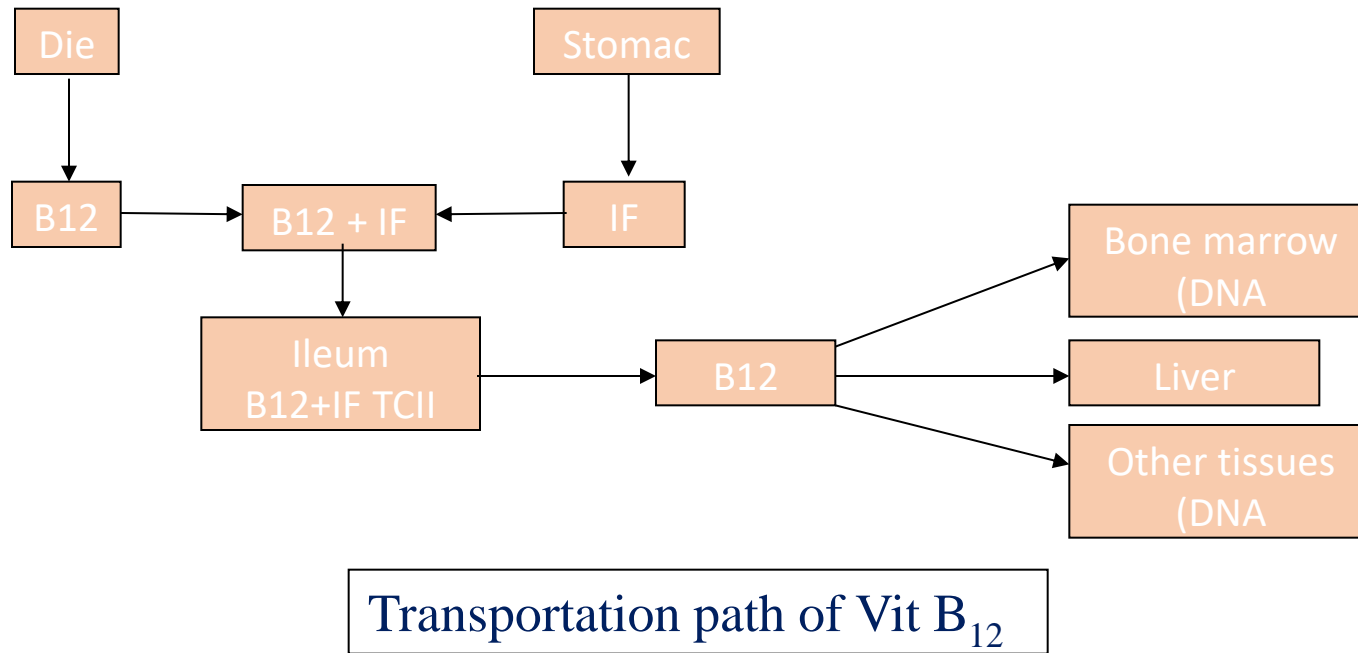
Structure of Vitamin B₁₂ coenzyme

- ❖ D. C. Hodgkin, Noble prize 1964
- ❖ Structure is similar to Vitamin B₁₂
- ❖ Sixth coordination site is occupied by 5'-deoxyadenosyl ligands.
- ❖ Acts as prosthetic group in different enzyme
- ❖ It is a diamagnetic orange red crystal



Transport and metabolism of Vitamin B₁₂

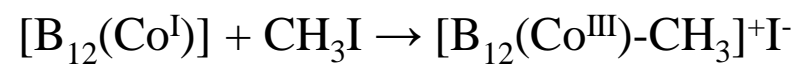
- ❖ Two important proteins involved in the transport process
- ❖ From diet to ileum (Intrinsic factor [IF-a glycoprotein, MW=4500]).
- ❖ From ileum to tissues (Transcobalamin I, II, III [TCII]).



Biochemical function of Vitamin B₁₂

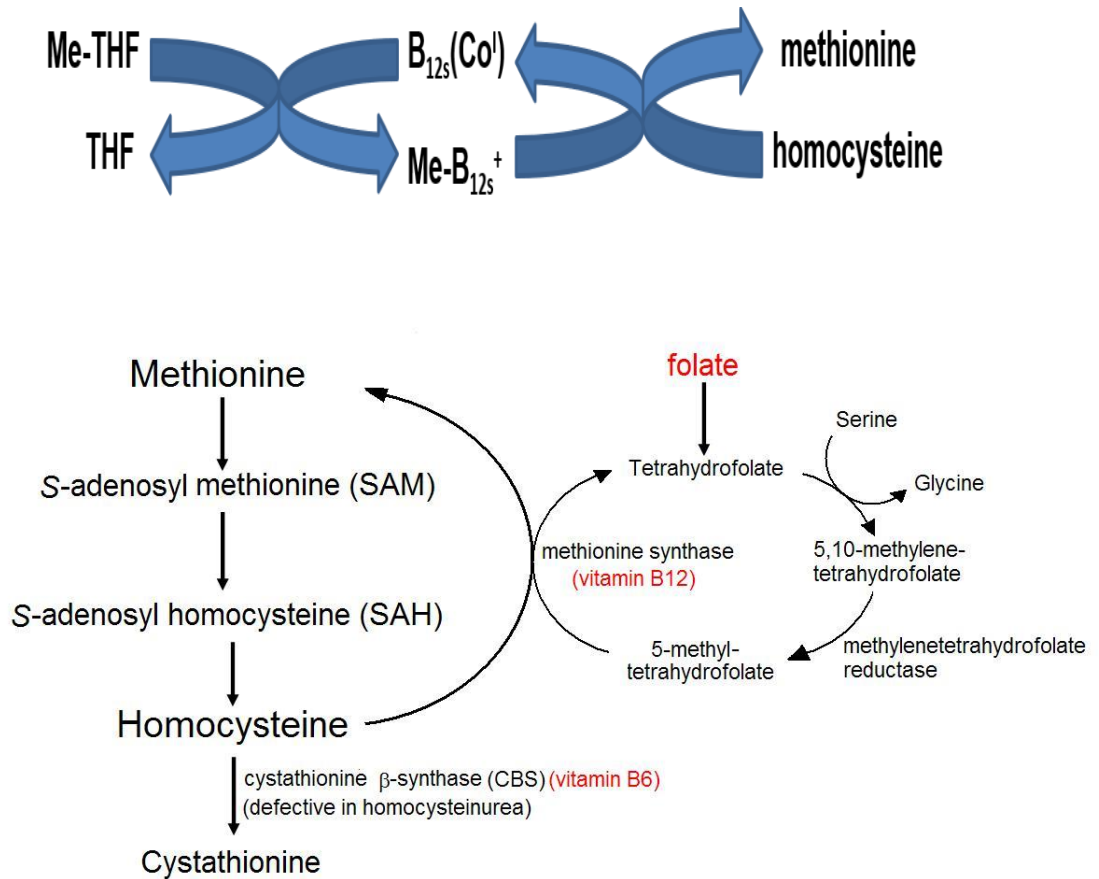
- ❖ Vit B₁₂ plays a significant role in one carbon transfer reactions, important in
 - 1) DNA and Fatty acid synthesis and energy production
 - 2) Biosynthesis of amino acids such as serine, methionine, glycine etc.
- ❖ Enzymes that require Vit B₁₂ as cofactor (essential in addition to enzyme)
 - 1) Methylmalonyl-coA mutase: Isomerization of methyl malonyl CoA from odd number of carbon containing fatty acids which is an essential step for catabolism of fatty acids.
 - 2) Methionine synthase: Synthesis of Methionine from Homocysteine
- ❖ Vit B₁₂ may be reduced by one electron (Vit B_{12r}) or two electrons (Vit B_{12s}) to form Co(II) and Co(I) respectively. In biological condition, the two electron reduction is accomplished by NADH (nicotinamide adenine dinucleotide + H) and flavin adenine dinucleotide (FAD).

❖ Vit B_{12s} is strongly nucleophilic and readily undergoes alkylation via oxidative addition

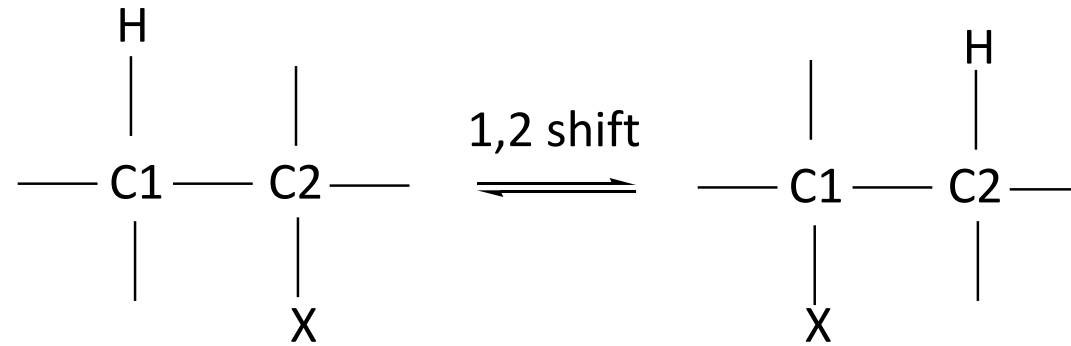


Synthesis of Methionine from Homocysteine

- ❖ This step is important in intracellular synthesis of folate coenzyme.
- ❖ Both Vit B₁₂ and folic acid are involved
- ❖ Vit B₁₂ acts as a co-enzyme (methylcobalamin, MeCo) for methyltransferase
- ❖ Vit B₁₂ accepts Me group from CH₃THF to give methylcobalamin
- ❖ MeCo participates in biomethylation in biosynthesis of methionine (terminal step)
- ❖ Me transfer from methylcobalamin involves cleavage of Co-C bond.



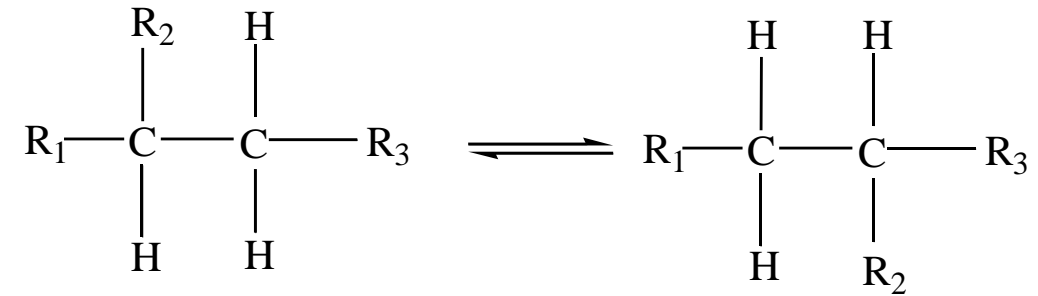
1,2-shift reaction



X = group with C/N

- ❖ An enzymic reaction of B₁₂ having 5'-deoxycobalamin as the prosthetic group.
- ❖ Reaction of B_{12s} with ATP results in the formation of Co-C bond between adenosyl and Co, forming B₁₂ coenzyme.
- ❖ It is very effective in inducing 1,2-shift, very important in metabolism (C-C, C-N and C-O bond cleavage).
- ❖ The shift is followed by internal condensation to give the final product.

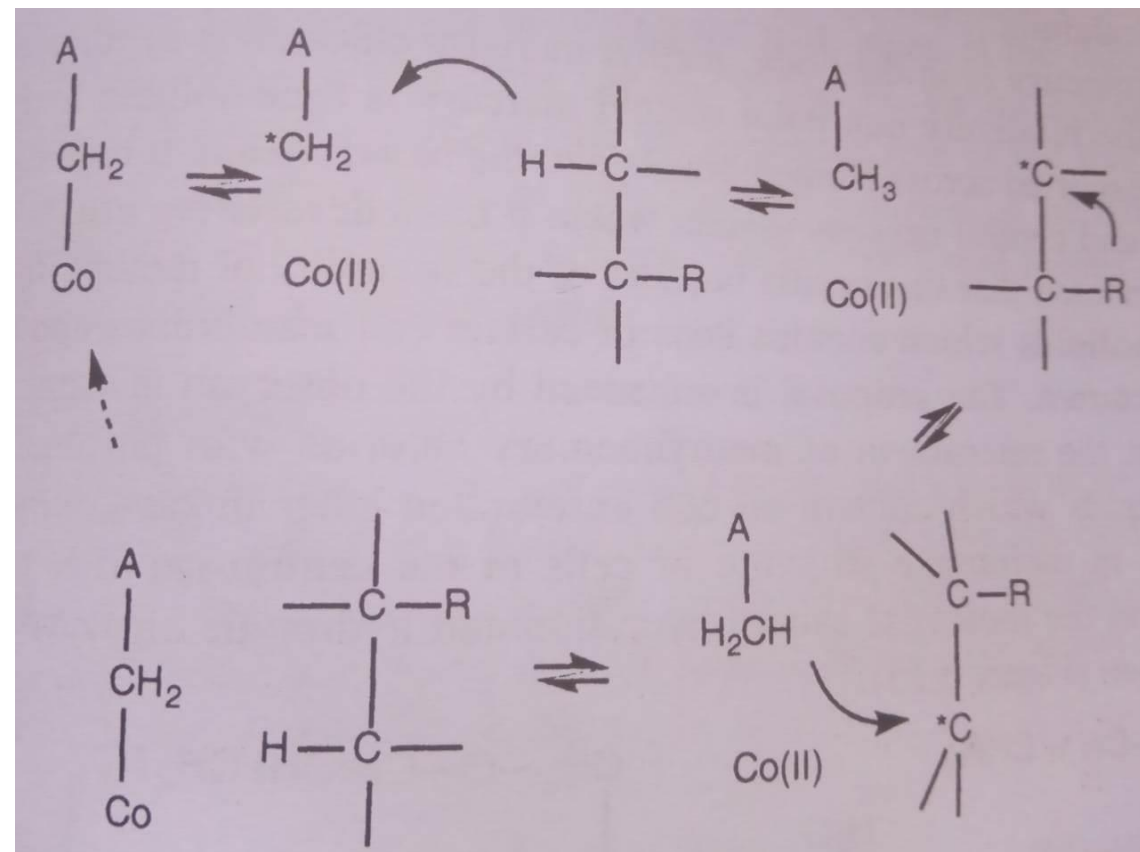
Representative of 1,2-shift reactions

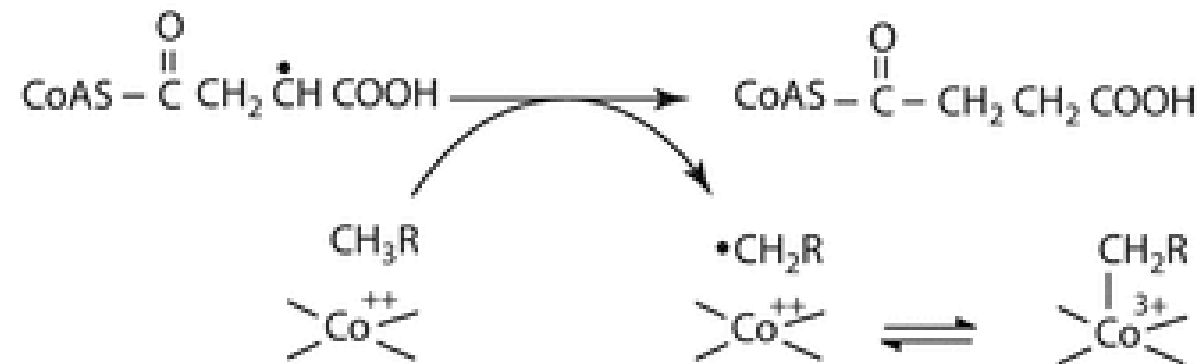
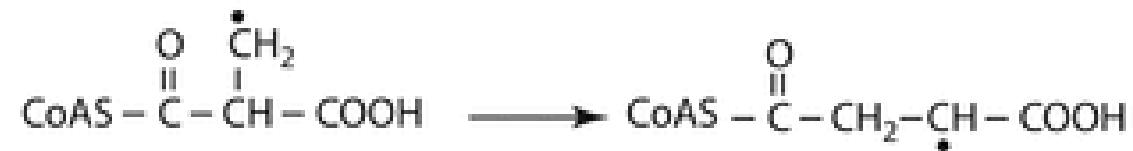
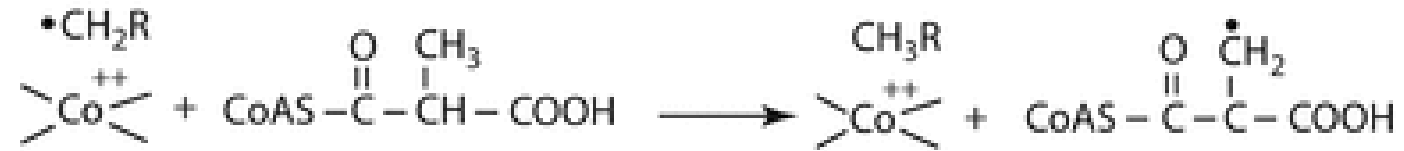


	R ₁	R ₂	R ₃
Diol dehydratase	CH ₃	OH	OH
Ethanolamine deaminase	H	NH ₂	
Glutamate mutase	H	CH(NH ₂)COOH	COOH
Methylmalonyl CoA mutase	H	CO-CoA	COOH
Glycerol dehydratase	CH ₂ OH	OH	OH

Mechanism of 1,2-shift/isomerase reaction

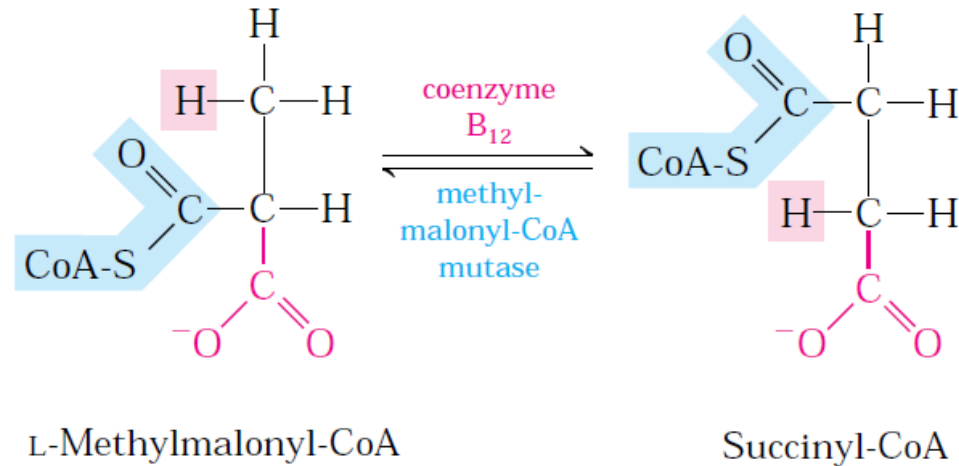
- ❖ Proposed to occur via a radical pathway.
- ❖ Homolytic cleavage of the Co-deoxyadenosine bond yields B12r and deoxyadenosyl radical that abstracts H-atom from the substrate to give 5'-deoxyadenosine and substrate radical
- ❖ Rearrangement of the substrate radical takes place with enzymic intervention and then abstraction of H-atom from 5'-deoxyadenosine to shift it to its new position in the product.
- ❖ The deoxyadenosyl radical formed reacts with B12r to generate the coenzyme.



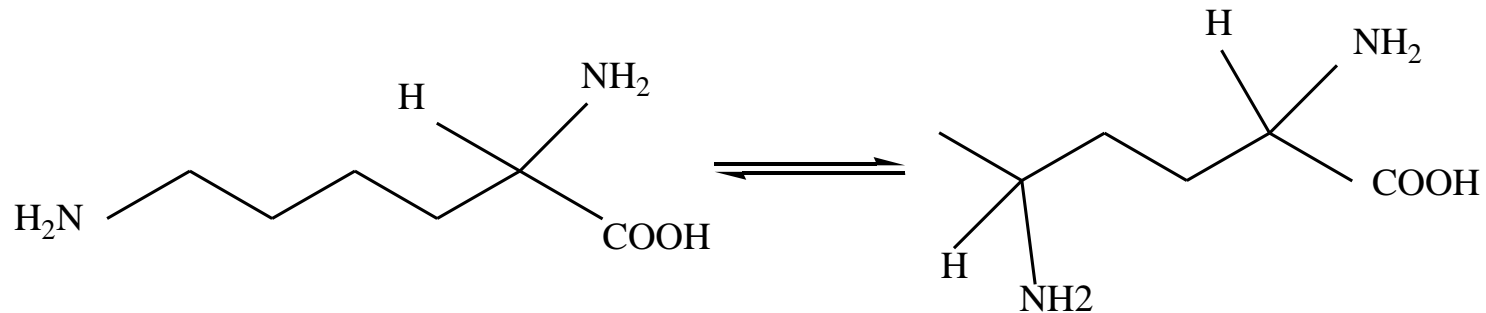


Some Examples

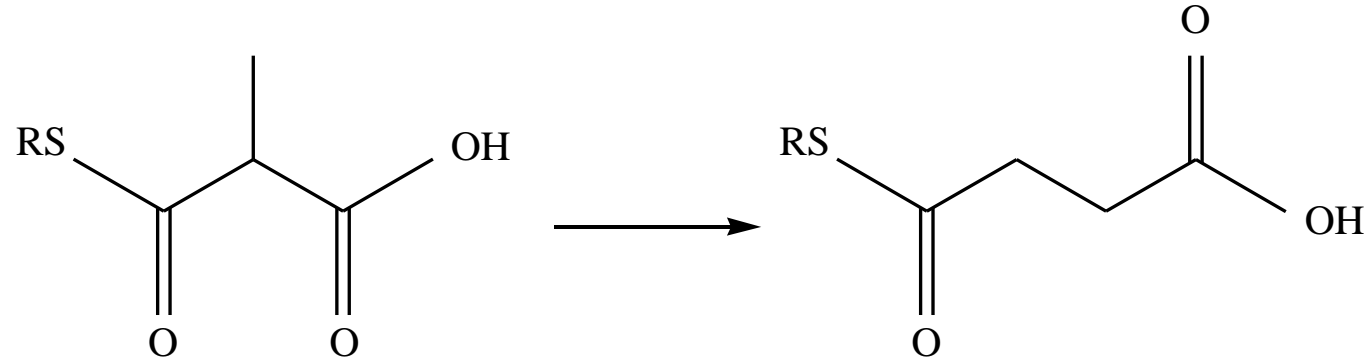
1. Vit B₁₂ is important in conversion/isomerization of methylmalonyl CoA to succinyl CoA in Krebs cycle. In this reaction B₁₂ acts as co-enzyme for methylmalonyl Co A mutase. This is important substrate in Heme synthesis



2. Isomerization of an amino group from a primary to secondary carbon



3. Insertion of CH₂ group




- ❖ Free radical reaction, homolytic cleavage of Co-C bond giving Co(II) atom and 5'-deoxyadenosyl radical (B12 r)
- ❖ 5'-deoxyadenosyl radical abstracts a H-atom from Me group
- ❖ Migration of -C(O)SR group followed by return of H-atom from 5'-deoxyadenosyl to the substrate
- ❖ Regeneration of 5'-deoxyadenosyl radical and formation of Co-C bond giving back the coenzyme.

Factors in favour of Vit B₁₂ for its usefulness in biochemical functions

1. Existence of three oxidation states Co^I, Co^{II} and Co^{III} which are stable in aqueous phase
2. d⁶/d⁸ (16e-/18e-) systems are ideal for oxidative addition and reductive elimination.
3. Flexibility of Corrin ring allows changes in conformation which is crucial in reducing Co(III) to Co(I)

Vitamin B₁₂ Deficiency

- ❖ Liver can store up to six years worth of vitamin B₁₂, hence deficiencies are rare.
- ❖ Upto 50% of vegetarians are Vit B₁₂ deficient
- ❖ About 40% have low normal levels of Vit B₁₂
- ❖ Vit B₁₂ deficiency develops as a result of a lack of intrinsic factor in the stomach leading to malabsorption of the vitamin.



Symptoms of Vitamin B-12 Deficiency Include:

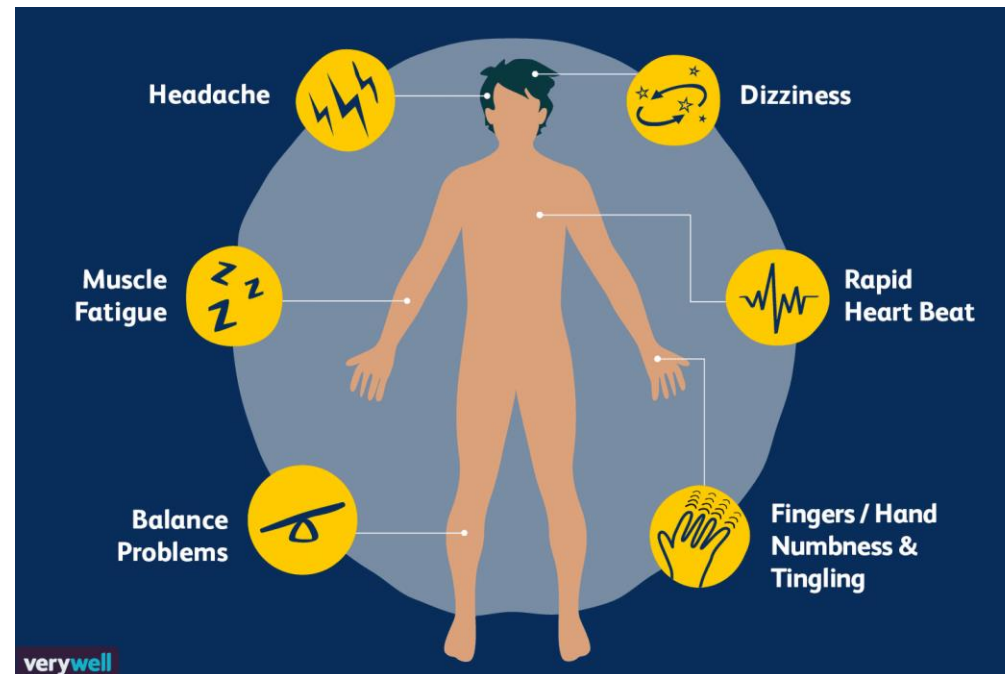
- > Low Energy / Fatigue
- > Sexual Problems / Infertility
- > Depression / Anxiety
- > Muscle Pain
- > Irritability
- > Hearing & Vision Problems
- > Mood Disorders
- > Memory Loss

Studies Have Also Linked B-12 Deficiency to:

- > Alzheimer's / Dementia
- > Learning Disorders in Children
- > Autoimmune Disease
- > Cardiovascular Disease
- > Cancer

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- ❖ **Pernicious anaemia:** Pernicious anemia is failure of the absorption of Vit B₁₂ (through gut wall) rather than dietary deficiency. A disease characterized By Gastric parietal atrophy leading to decreased secretion of intrinsic factor and other gastric juices. This results an increase in excretion of methylmalonic acid as the body fails to convert it to succinic acid.
- ❖ Neurological complications (Neuro psychiatrique symptoms).
- ❖ Gastrointestinal symptoms



Treatment of Vitamin B₁₂ Deficiency

- ❖ Simple blood test
- ❖ Folic acid and Vit B₁₂ both must be given to halt CNS Symptoms
- ❖ To administer Vit B₁₂ injection and take Vit B₁₂ supplements

