3. VITAMIN B12

The vitamin was isolated from liver after it was found that eating raw liver would alleviate pernicious anaemia. Pernicious anaemia is a blood disorder caused by lack of vitamin B12. Patients who have this disorder do not produce a protein (intrinsic factor) in the stomach that allows the body to absorb vitamin B12. Symptoms include shortness of breath, fatigue, loss of appetite, diarrhea, numbness of hands and/or feet, sore mouth, and bleeding gums. Vitamin B12 is a coenzyme and its deficiency leads to the dissfunction of cobalamin-dependent enzymes such as methylmalonyl-coenzyme A mutase (MCM) and glutamate mutase. Methylmalonyl-coenzyme A catalyses the isomerisation between methylmalonyl-coenzyme A and succinyl-coenzyme A, while glutamate mutase catalyses the reversible interconversion of L-glutamate and L-3-methylaspartate. MCM is also involved in the degradation of several amino acids, odd-chain fatty acids and cholesterol. Hydroxycobalamin, methylcobalamin or cyanocobalamin are now used for treatment of pernicious anaemia.

3.1 Structure of Vitamin B12

In Vitamin B12, the Co atom is coordinated to a corrin ring (macrocyle similar to the porphyrin ring). On one side of the corrin ring, the ligand bonded to Co is a-5,6-dimethylbenzimidazole nucleotide, which is also joined to the corrin ring. The active form of the vitamin, called coenzyme B12, contains an adenosyl group as the sixth ligand, while it is called cyanocobalamin with CN-as the sixth ligand. Vitamin B12 with CN-removed is called cobalamin.

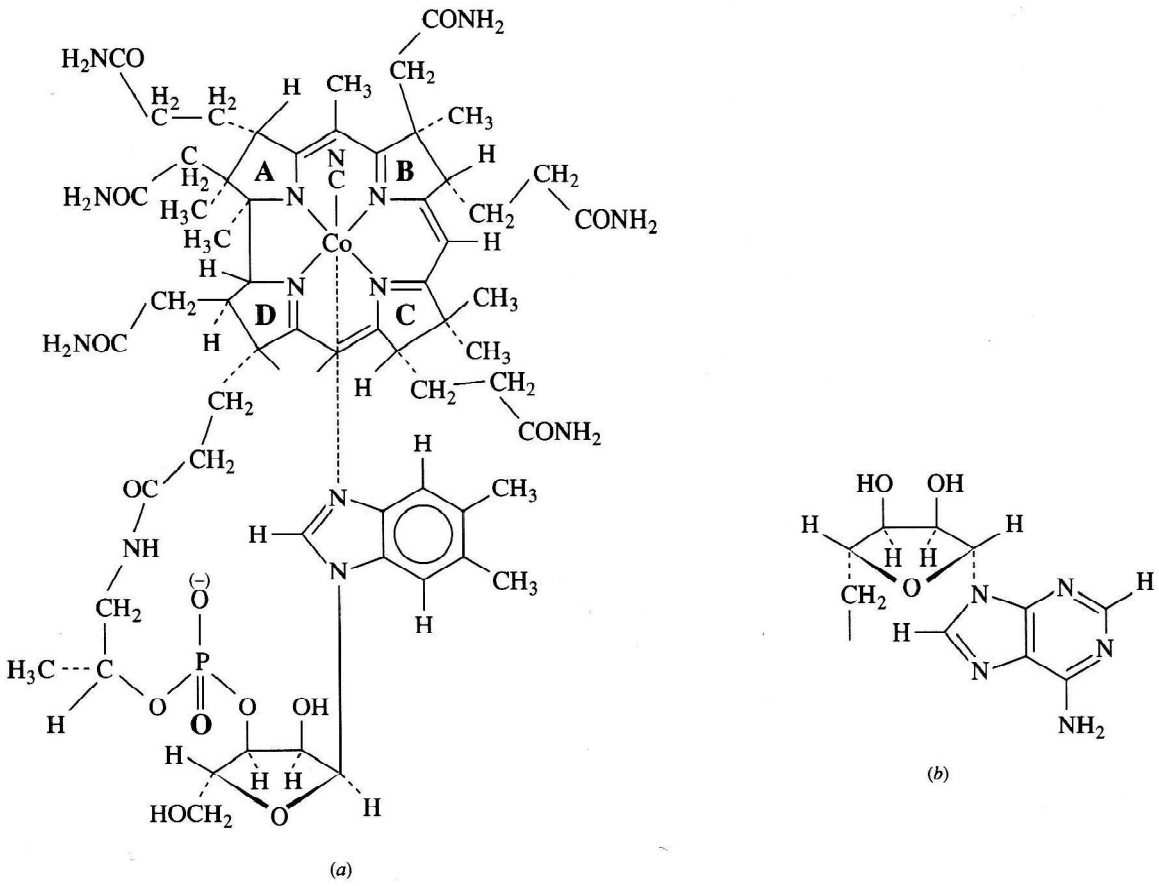

Figure 9: (a) Vitamin B12, (b) The adenosyl group which is present in place of CN-in coenzyme B12.

3.2 Stabilization of the Co-C Bond

The coenzyme contains a Co-C s bond and is a cobalt(III) compound. Thermochemical data indicate that transition-metal-carbon bonds are considerably stronger (100-200 kJ/mol) than had been realized earlier, though still somewhat weaker than M-F, M-OR or M-Cl bonds (300-400 kJ/mol). Alkyls are therefore good s donors and are capable of stabilizing high oxidation states such as Co(III). The instability of metal alkyls thus is of kinetic rather than thermodynamic origin, and so the species can be stabilized by blocking reaction pathways. Hence, ligands that are strongly bonded, and occupy all coordination sites stabilize the alkyls.

Co(III) in cobalamin is a d6 system and with ligands such as the corrin nitrogens and the imidazole nitrogen (a strong ligand field will result), the ion will form strong s and p bonds with the ligands.

The bonding of the alkyl group at the sixth position completes the octahedral coordination sphere.

3.3 Co-C Bond Cleavage

There are three possible ways in which the Co-C bond can be broken in alkylcobalamines:

• Heterolytic bond cleavage:

Co(III)-R ---------- Co(III) + :R-(carbanion) (1)

• Homolytic bond cleavage:

Co(III)-R ----------Co(II) + •R (alkyl radical) (2)

• Heterolytic bond cleavage:

Co(III)-R ----------Co(I) + R+ (carbocation alkyl moiety) (3)

(2) and (3) are one step reductive elimination processes which are reversible under physiological conditions via oxidative addition of alkyls from alkyl halides.

3.4 Models of B12

The cobalt complex of dimethylglyoxine is an effective model for B12. The reactions shown by adenosyl and alkyl cobaloxime derivatives, which resemble those of B12, include methyl group transfer, reduction and rearrangements.

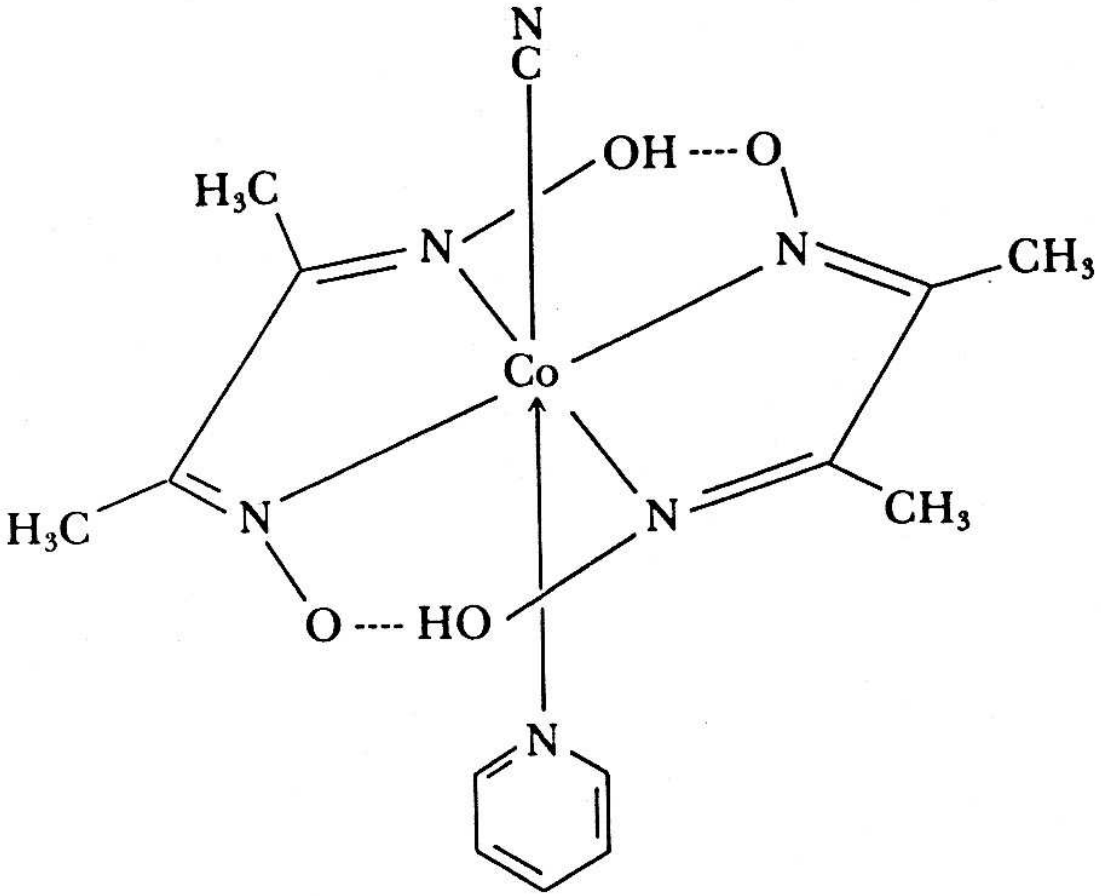

Figure 10: Picture of pyridine cobaloxime.

Tutorial 3

(a) The existence of a relatively inert bond between Co(III) and a primary alkyl ligand (in alkylcobalamins) under physiological conditions is quite remarkable. Interrogate this statement with regards to the coordination chemistry involved.

(b) Discuss the possible ways for the cleavage of the Co-C bond.