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A Survey Paper On: The Chemistry of Vitamin B_{12} and Related Inorganic Model Systems

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Abstract: **Cobaloxime complexes of the type [CoCl(DMGH)2(L)], where DMGH = dimethylglyoxime monoanion, L =tri-ethanol amine and 1,10 phenanthroline, were synthesized. The compounds were formulated on the basis of cobalt and chloride contents, IR and UV-visible spectral analyses and magnetic moment measurement. Cyclic voltammetric technique was also employed to investigate the interaction between Co(II)and the ligands under study.**

Keywords: **Cobaloxime, Vitamin B12, Dimethylglyoxime.**

1. INTRODUCTION

Vitamin B_{12} is an important coordination compound in biology. It is an interesting biomolecule in the sense that no other vitamin contains a metal ion. This is the only naturally occurring organometallic compound found in biology. An intriguing aspect of vitamin B_{12} is the great stability of the metal-carbon bond. A great deal of new and interesting inorganic chemistry has been uncovered while studying systems pertinent to B_{12}.

VitaminB_{12} is one of the naturally occurring coordination compounds in biology. Some of the other important examples are chlorophyll, haemoglobin, myoglobin and cytochromes. The common feature in these biomolecules is that a metal ion is enclosed in a macrocyclicligand. Although vitamin B_{12} is certainly the most complex non-polymeric compound found in nature, it is devoid of protein structure making its biological role relatively easy to understand. Vitamin B_{12} is known to be present in plants, animals and also in bacteria. It plays an important role in the metabolism of nucleic acids and in protein synthesis. It is of critical importance in the reaction by which residues from carbohydrates, fats and proteins are used to

Produce energy in living cells. In humans, deficiency of vitamin B_{12}leads to pernicious anemia.

2. STRUCTURE OF VITAMIN B12

The molecule is octahedral cobalt (III) complex with a 15-membered 4-nitrogen ringligand, called corrin, occupying the equatorial plane. All the sidechains of corrin are made of acetamide and/or propionamide groups.One of themis an isopropanol phosphate residue attached to a riboseand finally terminated by 5, 6-dimethyl benzimidazole, which bindsto the Co(III) ion.The corrin ring resembles a porphyrin ring at first glance but is notfully conjugated and therefore quite different chemically. Besides theequatorial ligand, there are two axial ligands inmost B_{12} derivatives.

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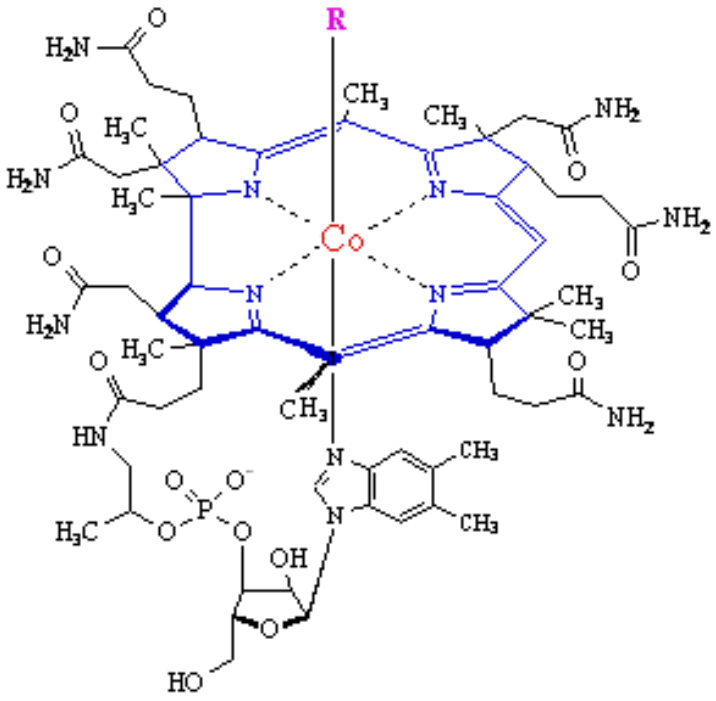

Figure 1. Structural of vitamin B12 derivatives

Vitamin B_{12} is the only known essential biomolecule with a stable metal-carbon bond, that is, it is an organometallic compound. The cobalt can link to: a methyl group - as in methylcobalamin a 5'-deoxyadenosine at the the 5' positon - as in adenosylcobalamin (coenzyme B12 a cyanide group - as in Vitamin B12 - as supplied from drug companies The particular link in the cobalamin has a profound effect upon the mechanism of the enyme reaction.A methyl-nickel intermediate on acetyl-CoA synthase is also known, but only as an intermediate rather than a stable, isolable compound as the three cobalamins.

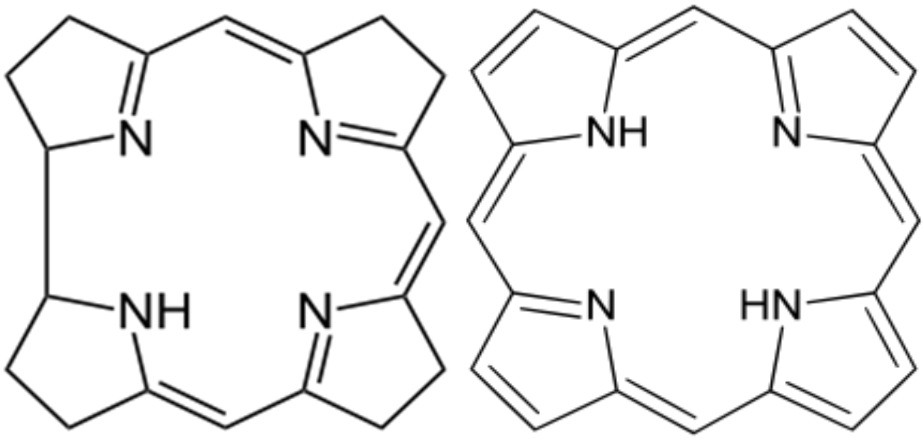

Figure 2. Structural comparisonof corrin and porphyrin

CorrinPorphyrin:

Other organ metals such as the methyl mercury ion are highly toxic; it is interesting that there is an unfortunate connection between CH_3Hg^+ and methylcobalamin.

Cobalamin was purified and its three dimensional structure was elucidated from x-ray crystallography by Dorothy Hodgkin and she was awarded Nobel Prize in chemistry in 1964 for this work.

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3. OXIDATION STATE OF COBALT

The oxidation state of the central cobalt ions range from+1 to +3; Co(I) imparts a gray-green color, Co(II) imparts yellow-to-orange color, and Co(III), which is the most common form, imparts a red color to the B_{12}derivatives,and is known as the "red vitamin." Methylcobalamin and adenosylcobalamin as the coenzyme forms are parts of in vivo enzymes that catalyze the biosynthesis of methionine and the isomerizations with carbon-skeleton rearrangements, respectively. Recent studies revealed that the complex of such corrin ring structures acts on the active center of the dechlorination reaction in anaerobic dependent enzymes.

The additional instability of the coenzyme toward light and acid suggests why the coenzyme form of vitamin B_{12}remained undiscovered for as long as it did. As with vitamin B_{12}, the structure of the coenzyme was elucidated through the crystallographic studies of Hodgkin,S who showed that the general macrocyclic structure and peripheral substituent were the same for both cyanocobalamin and the vitamin coenzyme and also demonstrated, a unique feature of the coenzyme, the covalent bond between cobalt and the 5' carbon of an adenine moiety. This was the first example of a naturally occurring organometallic coenzyme and related alkylcobalamins represent compound.

Indeed to this day the vitamin B_{12} coenzyme and related alkylcobalamins represent the only known organometallic compounds of nature. While the crystallographic studies elucidated the major structural features of the vitamin B_{12}coenzyme,they left open the possibility that the extent of the conjugated chromophore might be different inthe coenzyme from that of B_{12} itself. This difference in the extent of oxidation of the chromophore was suggested by studies on the formation of the coenzymefrom vitamin B_{12} and would have been consistent with the considerable differences in the optical spectra.

The degree of unsaturation of the corrinchromophore was related to, and furthercomplicated by, the oxidation state of the cobaltB_{12}, but which is trivalent (diamagnetic) in vitamin which had been reported to be paramagnetic by someand diamagnetic by others in the coenzyme. At this time the coenzyme had been prepared by an initial reduction of cyano- or hydroxocobalamin followed by alkylation with a suitable derivative of 5/-deoxyadenosine. Thus the mode of the oxidation state of the cobalt, and allowed forformation did not definethe possible reduction of the chromophore during formation of the coenzyme.

These questions were resolved when it was shown that both the extent of the conjugated chromophore and the oxidation state of the cobalt were the samefor both B_{12} and the B_{12} coenzyme.

Thus the catalytic reduction of hydroxocobalamin(B_{12b}) with hydrogen and platinum oxide gave vitaminB_{12r}. B_{12r} had previously been assigned as a cobalt(II) complex, and this was confirmed when 0.5mol of hydrogen was consumed during the formation of B_{12r}.

Note- r stands for reduced and s for super-reduced

hydroxocobalamin Co(III)B_{12b} ½ H_2 ⟶ Co(II) + H B_{12r}

Similarly the reduction of methylcobalamin (identicalin oxidation state with that of the coenzyme) also consumed 0.5 mol of hydrogen, when reduced, to give 1 mol of methane and 1 mol of B_{12r}.

methylcobalamin½ H_2 ⟶ methane + B_{12r}.

From the equations it is clear that the coenzyme andB_{12} share the same oxidation state for cobalt (III) andachromophore of the same oxidation state, with the result that the coenzyme and the analogous alkylcobalamins can formally be considered as carbanions coordinated to trivalent Cobalt.

Further reduction of B_{12r} gives a green complex; B12s.Vitamin B_{12s} is rapidly oxidized by both oxygen and water at a pH below 8. One mole of B_{12b} and 1mol of B_{12s} gives 2 mol of B_{12r}, establishing B_{12s} as amonovalent cobalt complex. B_{12s} is a powerful nuc1eophileand reacts with a variety of alkylatingagents to give the corresponding alkylcobalamin.This oxidative addition to electrophiles provides aconvenient route to both alkyl- and acylcobalamins and provides a convenient, and commercial, route to the coenzyme.

Recently Schrauzer has presented evidence whichsupports this formulation.

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There are three routes for the cleavage of the cobalt-carbon bond of alkylcobalamins:

$$R\text{-}Co(III) \rightarrow R + Co(II) \quad (B_{12r})$$
$$R\text{-}Co(III) \rightarrow R^{+} + Co(I) \quad (B_{12s})$$
$$R\text{-}Co(III) \rightarrow R^{-} + Co(III) \quad (B_{12a})$$

4. NATURE OF THE CARBON–COBALT BOND

The successful determination of the molecular structure of coenzymeB_{12} provided an unexpected surprise in that it contained an apparently stable carbon–cobalt bond. This is the only naturally occurring organometallic compound. An intriguing aspect of the B_{12} system is the great stability of the carbon–cobalt bond. Although alkyl–cobalt bond in alkyl coalmines is surprisingly stable, it can be cleaved and transferred into a number of other chemical species. During their action involving model systems the initial Co(II)species is oxidized to Co(III), while the original alkyl Co(III) species is reduced to Co(II). The initial Co(II) species usually has an equatorial ligand with more electron withdrawing groups. Therefore, this is an organometallic example of electron transfer reaction mediated by group transfer.

Biochemical Function:

B_{12} functions in biological systems as a coenzyme. That is, it binds to an appropriate non active enzyme (the apoenzyme) to form the biologically active 'enzyme-coenzyme complex'. B_{12} becomes part of the active site of the catalytically functional unit. Generally, B_{12}dependent enzymes are classified into two different categories, namely, (a) those using coenzyme B_{12} (5´-deoxy- adenosyl) as the cofactor and (b) those using methylcobalamin as cofactor.

The enzymes using coenzyme B_{12} as cofactor carry out a catalytic reaction which involves transfer of a hydrogen atom. Therefore these enzymes are sometimes referred to as hydrogen transfer enzymes. The second categories of B_{12} dependent enzymes, which usemethylcobalamin as cofactor, are involved in the metabolism of one carbon fragments.

The important coenzyme B_{12} dependent enzymes are glutamatemutase, methylmalonylCoAisomerase, dioldehydrase, ethanolamineammonialyase and ribonucleotidereductase. Methionine synthetase, methane synthetase and acetate synthetase depend on the activity of methylcobalamin.

Model Compounds:

Study of model compounds involves the design, synthesis, structure determination, physical measurements and reactions of simple coordination compounds. Through studies on model compounds some insight into the workings of the natural system is sought. An additional objective is to mimic in a simple system the catalytic function of a metalloenzyme for industrial or biomedical or synthetic purposes. Current attempts to mimic catalytic properties of vitamin B_{12} by certain cobalt complexes exemplify this aspect.

The organometallic chemistry of cobalt in vitamin B_{12} and its derivatives is unusual and interesting. This may be paralleled quite remarkably in many cases by simple model compounds. The most commonly mentioned B_{12}model system is bis (dimethylglyoximato) cobalt complex. These complexes are often referred to as cobaloximes. The common feature of the different models is that each possesses a very strong equatorial ligand field. Even porphyrins have been used as models for vitamins B_{12}. Cobalt porphyrins can be converted into organic derivatives by demetallation reaction, but they cannot be reduced to the cobalt (I) state in aqueous solution. The reduction is usually carried out with a Grignard reagent in non-aqueous solution.

Some important model compounds of vitaminB_{12}.

i) Bis (dimethylglyoximecobalt, $Co(dmg)_2$

ii) N, N-ethylene bis (salicylideneiminato)cobalt, Co(Salen)

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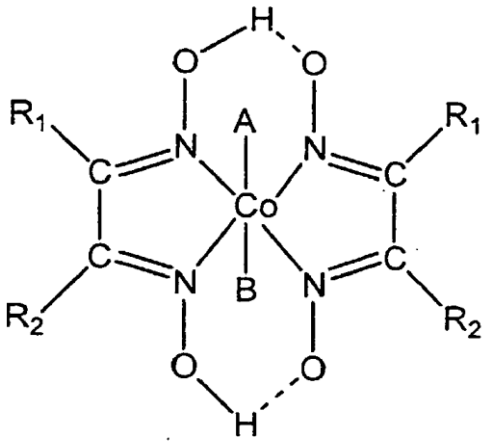

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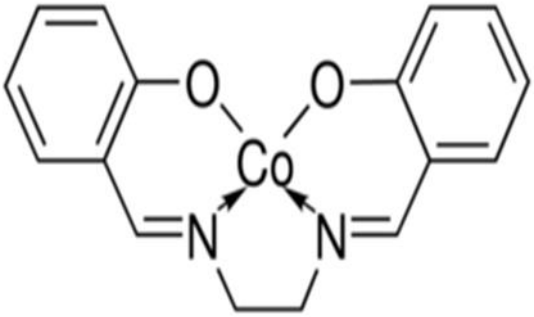

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Similarities between Vitamin B12 and Model Compounds:

Model compounds, for example, cobaloximes show very many of the reactions of the cobalt atoms in corrins. They too add on axial groups and form stable organo derivatives readily, and also they can be reduced to Co(I) species. The comparison between cobaloximes andB_{12s} has contributed to an understanding of the latter. It appears that the close similarity between cobalamins and cobaloximes is due tothe presence of an in-plane ligand of similar strength and is independent of the axial ligands. This is supported by spectroscopic and theoretical studies. The crystal structure of a substituted alkyl cobaloxime shows that the Co-N (in plane) and Co-C bond lengths are very similar to those found for the coenzyme.

Methylcobaloximes (and some other model compounds) will similarly methylatehomocysteine, although the reaction is not reversible. However, demethylation is possible, provided it is first converted to the S-adenosyl derivative.

Both vitaminB12 coenzymes and cobaloximes also catalyse reduction reactions involving the synthesis of N-methyl groups fromformaldehyde and amines in the presence of a reducing agent.

$$HCHO + NH_2C_6H_5C_6H_5 \longrightarrow C_6H_5NHCH_2OH \longrightarrow C_6H_5NHCH_3 + H_2O$$

5. DIFFERENCES BETWEEN VITAMIN B12 AND MODEL COMPOUNDS

Although inorganic model complexes exhibit nearly the same coordination chemistry as B_{12} itself, some differences do exist. Forexample, some of the model compounds can be alkylated simultaneously in both axial positions while B_{12} cannot be alkylatedsimilarly due to the large size of the corrin ligand. The second example is the inability of $B_{12}$to dimerize while model compounds can exist as dimers. The above differences in behavior are due to the great deal of steric hinderance in the coenzyme not duplicated by the cobaloximes. This is important in Co-C homolysis, a vital factor for the catalytic behavior of vitamin B_{12}.

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6. CONCLUSIONS

The reactions of model compounds to mimic the functions of vitaminB_{12}, thus far succeeded in matching the chemical properties and structural features of vitamin B_{12}. However, more work remains to be done in reproducing the catalytic functions and on the applications of model compounds to natural systems. The subject continues to be a vibrant topic of research in bio-inorganic chemistry.

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