

The chemistry of cobaloxime complexes of Vitamin B₁₂ derivative and Its related inorganic model compounds

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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 derivative, dimethylglyoxime

Introduction

Vitamin B₁₂ 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 B₁₂ 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 B₁₂.

Vitamin B₁₂ 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 macrocyclic ligand. Although vitamin B₁₂ 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 B₁₂ 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 B₁₂ leads to pernicious anemia.

Materials and Method

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 them is an isopropanol phosphate residue attached to a ribose and finally terminated by 5, 6-dimethyl benzimidazole, which binds to the Co(III) ion. The corrin ring resembles a porphyrin ring at first glance but is not fully conjugated and therefore quite different chemically. Besides the equatorial ligand, there are two axial ligands in most B₁₂ derivatives and structure are shown in figure-1.

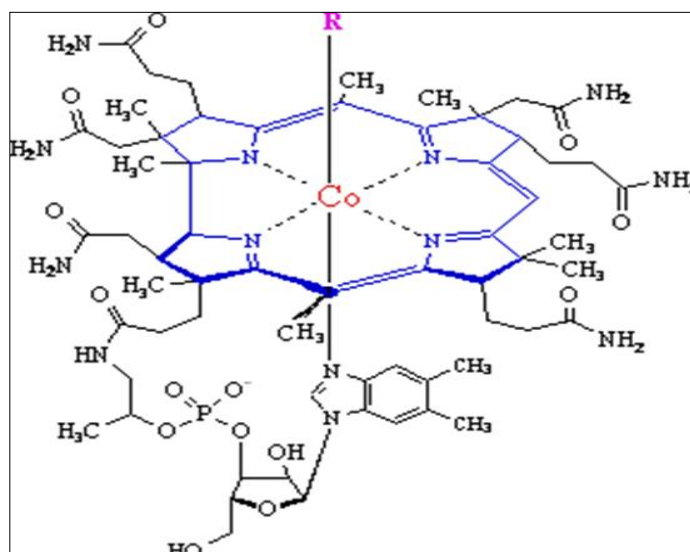


Fig 1: Structural of vitamin B₁₂ derivatives

The Vitamin B₁₂ 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 enzyme 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 are shown in Figure-2.

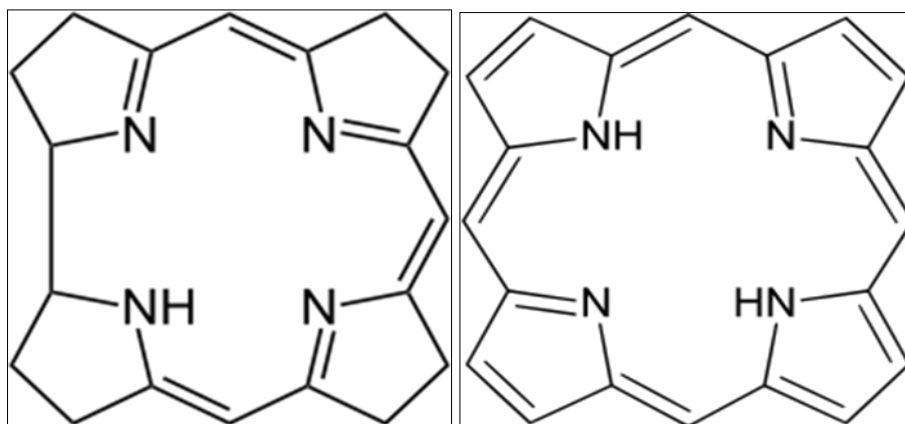


Fig 2: Structural comparison of corrin and porphyrin

Corrin Porphyrin: 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

Results and Discussion

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 B₁₂ 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 B₁₂ remained undiscovered for as long as it did. As with vitamin B₁₂, the structure of the coenzyme was elucidated through the crystallographic studies 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 B₁₂ coenzyme and related alkylcobalamins represent the only known organometallic compounds of nature. While the crystallographic studies elucidated the major structural features of the vitamin B₁₂ coenzyme, they left open the possibility that the extent of the conjugated chromophore might be different in the

coenzyme from that of B₁₂ itself. This difference in the extent of oxidation of the chromophore was suggested by studies on the formation of the coenzyme from vitamin B₁₂ and would have been consistent with the considerable differences in the optical spectra.

The degree of unsaturation of the corrin chromophore was related to, and further complicated by, the oxidation state of the cobalt B₁₂, but which is trivalent (diamagnetic) in vitamin which had been reported to be paramagnetic by some and 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 for formation did not define the 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 same for both B₁₂ and the B₁₂ coenzyme. Thus the catalytic reduction of hydroxocobalamin (B_{12b}) with hydrogen and platinum oxide gave vitamin B_{12r}. B_{12r} had previously been assigned as a cobalt(II) complex, and this was confirmed when 0.5 mol of hydrogen was consumed during the formation of B_{12r}.

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

$$\text{B}_{12b} \xrightarrow{\text{Co(III)}\frac{1}{2}\text{H}_2} \text{Co(II)} + \text{H}$$

Similarly the reduction of methylcobalamin (identical in 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}.

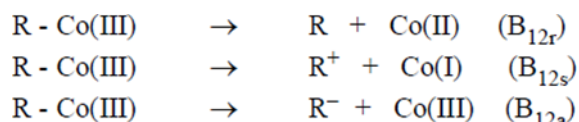
$$\text{methylcobalamin} \xrightarrow{\frac{1}{2}\text{H}_2} \text{methane} + \text{B}_{12r}$$

From the equations it is clear that the coenzyme and B₁₂ share the same oxidation state for cobalt (III) and chromophore 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; B_{12s} . Vitamin B_{12s} is rapidly oxidized by both oxygen and water at a pH below 8. One mole of B_{12b} and 1 mol of B_{12s} gives 2 mol of B_{12r} , establishing B_{12s} as a monovalent cobalt complex. B_{12s} is a powerful nucleophile and reacts with a variety of alkylating agents to give the corresponding alkylcobalamin. This oxidative addition to electrophiles provides a convenient route to both alkyl- and acylcobalamins and provides a convenient, and commercial, route to the coenzyme.

Recently Schrauzer has presented evidence which supports this formulation.

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



Nature of The Carbon-Cobalt Bond: The successful determination of the molecular structure of coenzyme B_{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 cobalamins 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.

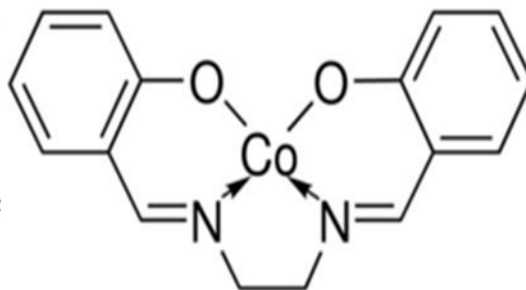
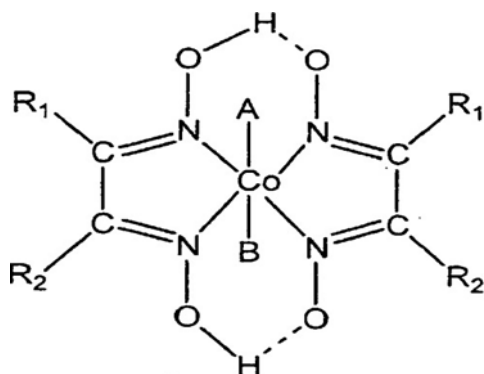
Biochemical Function: B_{12} functions in biological systems as a coenzyme. That is, it binds to an appropriate non active enzyme (the apoenzyme) to form the biologically active „enzyme-coenzyme complex“. B_{12} becomes part of the active site of the catalytically functional unit. Generally, B_{12} dependent 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 use methylcobalamin as cofactor, are involved in the metabolism of one carbon fragments. The important coenzyme B_{12} dependent enzymes are glutamate mutase, methylmalonyl CoA isomerase, diol dehydrase, ethanolamine ammonia lyase and ribonucleotide reductase. 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 (dimethylglyoximate) 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 vitamin B_{12} .

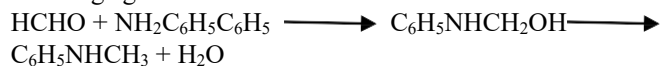
1. Bis (dimethylglyoximate) cobalt, $Co(dmg)_2$
2. N, N'-ethylene bis (salicylideneiminate) cobalt, $Co(Salen)$



Similarities between Vitamin B_{12} 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 and B_{12s} has contributed to an understanding of the latter. It

appears that the close similarity between cobalamins and cobaloximes is due to the 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 methylate homocysteine, although the reaction is not reversible. However, demethylation is possible, provided it is first converted to the S-adenosyl derivative. Both vitamin B₁₂ coenzymes and cobaloximes also catalyse reduction reactions involving the synthesis of N-methyl groups from formaldehyde and amines in the presence of a reducing agent.



Differences between Vitamin B₁₂ and model compounds

: Although inorganic model complexes exhibit nearly the same coordination chemistry as B₁₂ itself, some differences do exist. For example, some of the model compounds can be alkylated simultaneously in both axial positions while B₁₂ cannot be alkylated similarly due to the large size of the corrin ligand. The second example is the inability of B₁₂ to dimerize while model compounds can exist as dimers. The above differences in behavior are due to the great deal of steric hindrance in the coenzyme not duplicated by the cobaloximes. This is important in Co-C homolysis, a vital factor for the catalytic behavior of vitamin B₁₂.

Conclusions

The reactions of model compounds to mimic the functions of vitamin B₁₂, thus far succeeded in matching the chemical properties and structural features of vitamin B₁₂. 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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