

14.8. Bioinorganic Catalysis

14.8.1. Introduction

Additional sections which deal with bioinorganic catalysis are projected for publication in a final Supplementary unit of the *Inorganic Reactions and Methods* series.

14.8.2. Cobalamin Reactions

14.8.2.1. Cobalamin Models

14.8.2.1.1. Formation of the Cobalt-Carbon Bond.

Coenzyme B₁₂¹, methylcobalamin (Fig. 1a and b) and closely related derivatives were the first organometallic compounds to be found in nature. Their complex structures, together with that of vitamin B₁₂ (Fig. 1c), were elucidated by X-ray crystallography².

After isolation of the B₁₂ coenzyme it was realized that the cobalt-carbon (Co—C) bond could be stabilized by other ligands. Many organocobalt compounds were subsequently synthesized and used as models for the alkylcobalamins. The most commonly used are cobaloximes and Costa complexes. The former has two dimethylglyoximate monoanions (dmgH) with a general chemical composition of alkylcobalt(HI) (dmgH)₂(base) (I)³, the latter has a diacetylmonoximeimino diacetylmonoximato imine propane monoanion [(DO) (DOH)pn] with a general chemical composition of a kylcob-

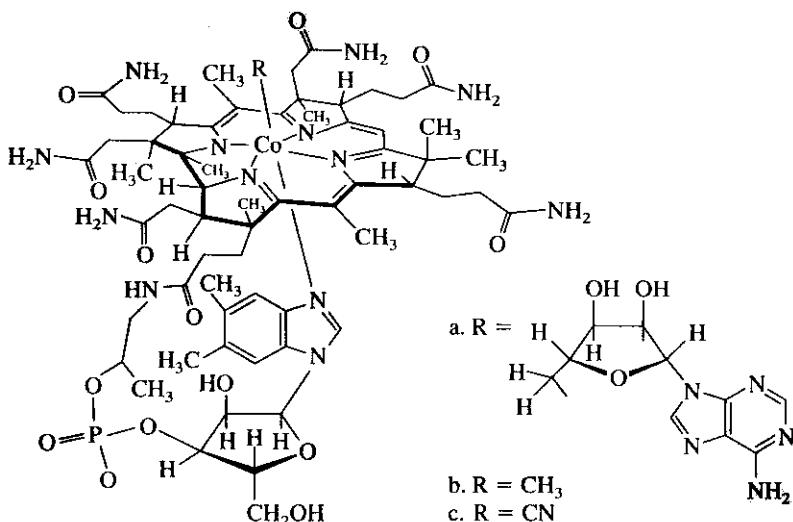


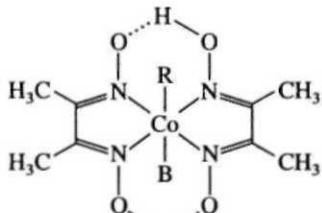
Figure 1. (a) Vitamin B₁₂ coenzyme; (b) methylcobalamin; (c) vitamin B₁₂.

14.8.2. Cobalamin Reactions

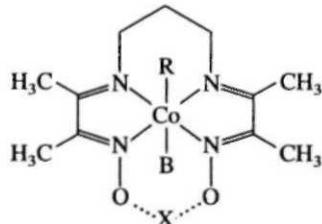
14.8.2.1. Cobalamin Models

14.8.2.1.1. Formation of the Cobalt-Carbon Bond.

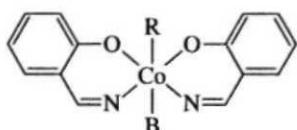
alt(III) $[(DO)(DOH)pn]X$ (2)^{4,5}. Molecular orbital calculations of the cobaloxime and cobalamin based on HMO and modified Wolf-Helmholtz MO techniques indicate that cobalamin and cobaloxime are somewhat similar, but that the cobalt atom in cobalamin has a smaller partial positive charge, which results in a stronger binding of axial ligands and a lower kinetic reactivity of cobaloximes^{6,7}. Nevertheless, cobaloximes continue to be widely studied B_{12} model compounds^{8,9}.



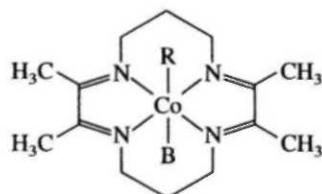
$RCo(dmgh)_2B$
1



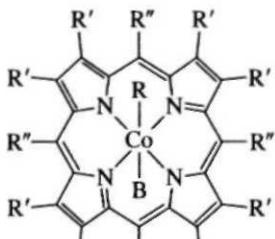
$RCo[(DO)(DOH)pn]B$
2



$RCo(salen)B$
3



$RCo(tim)B$
4



$RCo(Porp)B$
5

$R' = \text{alkyl}, R'' = \text{H}$
 $R' = \text{H}, R'' = \text{aryl}$

Costa-type model compounds, however, have been shown to be a closer mimic of the B_{12} electrochemical behavior than the cobaloximes, or any other model compounds¹⁰⁻¹². Hence, they are used more widely as models in kinetic studies relevant to the mechanisms of catalysis mediated by B_{12} , which involve electron transfer processes¹³⁻¹⁵. The nonplanarity of the equatorial ligand of $(DO)(DOH)pn$, caused by propylene group pucker^{16,17}, also appears to mimic the distortion in the corrin ring.

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14.8.2.1. Cobalamin Models

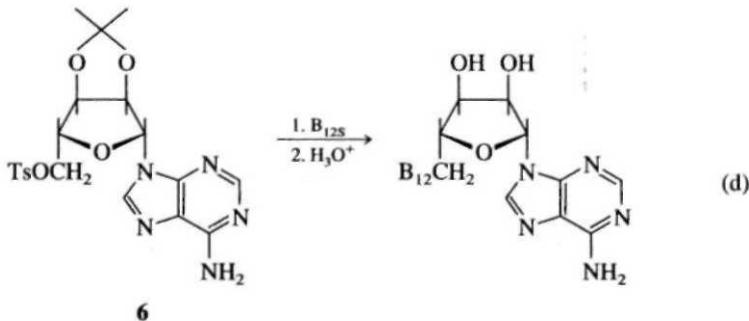
14.8.2.1.1. Formation of the Cobalt-Carbon Bond.

Imine bases (Schiff bases)¹⁸ such as bis(salicylaldehyde)ethylene diamine (salen) (**3**), are planar tetradeinate ligands used less widely as models of B₁₂. Tetraazamacrocyclic ligands, such as 2,3,9,10-tetramethyl-1,4,8,11-tetraaza-cyclotetradeca-1,3,8,10-tetraene (tim) (**4**)¹⁹⁻²² and porphyrins²³ (**5**) are similar. These compounds stabilize the three oxidation states of cobalt: +3, +2, and +1, each of which can form a Co—C bond.

Reactions of Co(III) with carbanions, Co(II) with alkyl radicals, and Co(I) with electrophilic reagents give a Co—C bond²⁴:



Both cobaloxime(I) and cob(I)alamin have been described as very strong nucleophiles²⁵⁻²⁶. Nucleophilicity (*n*) has been defined as $n_{\text{MeI}} = \log(k_Y/k_{\text{MeOH}})$, where k_Y and k_{MeOH} are the second-order specific rate constants for attack by a nucleophile Y and methanol, respectively, on the substrate CH₃I at 25°C in methanolic solution. The observed values of *n* are 14.4 for cob(I)alamin and 14.3 for cobaloxime(I). For comparison, *n* for MeO⁻ is 6.3. Because of their high nucleophilicity, these Co(I) complexes react with many alkylating agents, a commonly used method for the formation of the Co—C bond. The B₁₂ coenzyme is prepared by reaction of B_{12s} with the tosylate **6** followed by removal of the protecting group [equation (d)]²⁷.



Dicyanocobyrinic acid heptamethyl ester (Fig. 2) is useful because of its relative simplicity compared to cobalamins, and because of its high solubility in organic solvents. It is prepared by reaction of vitamin B₁₂ with MeOH/H₂SO₄ and then with KCN²⁸. Like B₁₂ and cobaloximes²⁹, it is reduced to Co(I) with NaBH₄ and alkylated by alkyl halides²⁸.

Alkylcobaloximes can be prepared directly from Co(II) chloride and dimethylglyoxime. However, more reproducible results and purer products are obtained when the pre-formed bromobis(dimethylglyoximato)(dimethyl sulfide)cobalt(III) is reduced with NaBH₄ and then alkylated³⁰. Dimethyl sulfide is easily exchanged, so other base-substituted cobaloximes may be prepared³⁰.

Reaction of Co(I) with alkylating agents is generally described as a nucleophilic substitution (S_N2):

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14.8.2.1. Cobalamin Models

14.8.2.1.1. Formation of the Cobalt-Carbon Bond.

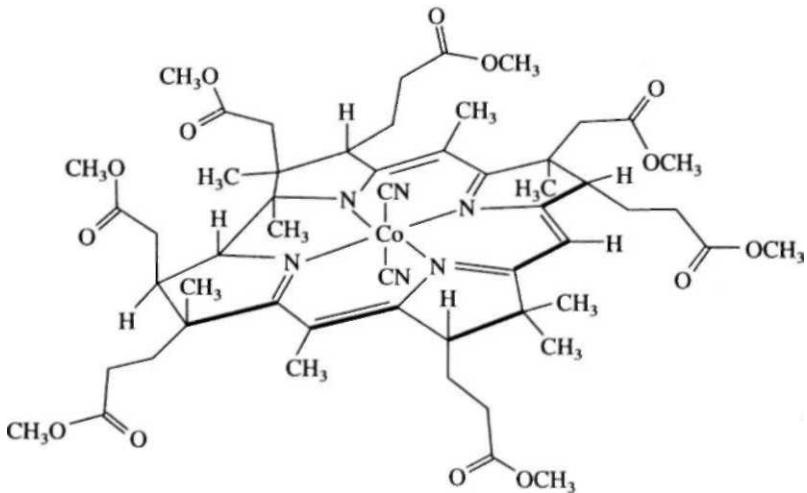
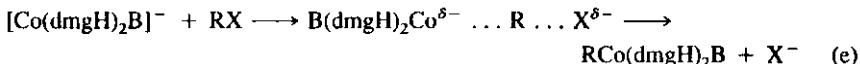
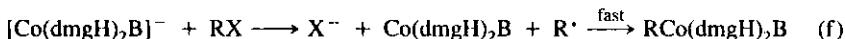


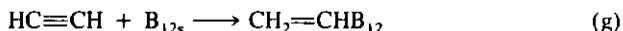
Figure 2. Dicyanocobyrinic acid hcptamethyl ester.



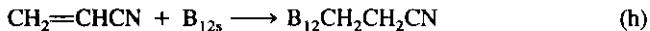
However, electron transfer has been observed with both B_{12s} and cobaloxime(I)³¹⁻³⁹:



Cobaloxime(I) and B_{12s} add to acetylenes⁴⁰⁻⁴² yielding the α - and β -carbon substituted isomer or mixtures of both:



Addition to electron deficient olefins gives predominantly the β -carbon substituted isomer⁴⁰:



Reduction of Co(II) or Co(III) to Co(I) in the presence of acid⁴³ or reduction of Co(II) with hydrogen at pH 7 gives hydridocobalt complexes⁴⁴⁻⁴⁶. The Co(I) and hydridocobalt species are in equilibrium:



Hydridocobalamin decomposes readily to B_{12r} and hydrogen, the stability of hydridocobaloximes depends on the axial base present. Strong π -acceptor bases stabilize the complexes⁴⁷. Hydridotri-n-butylphosphinatocobaloxime has been characterized. Hydriopyridinatocobaloxime is unstable.

In protic solvent at neutral to slightly acidic pH, hydridocobalt(III) species react with alkyl halides to give alkyl Co(III) species at a compatible rate to the corresponding Co(I) complex⁴⁷. The stereochemistry of addition to olefins and alkynes changes as the

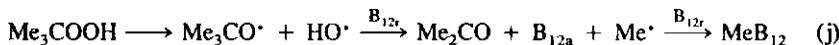
14.8.2. Cobalamin Reactions

14.8.2.1. Cobalamin Models

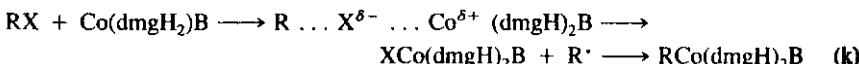
14.8.2.1.1. Formation of the Cobalt-Carbon Bond.

pH is lowered from neutral to acidic because the reactive species changes from the Co(I) to Co(III)-H complex. The hydrido complex gives only α -substituted alkylcobaloxime^{40,47}. Hydridocobalamin is more reactive than hydridocobaloxime and reacts with unactivated olefins, a kyl halides, acyl halides and acetylene⁴⁸⁻⁵⁰. Both primary and secondary alkyl cobalamin, previously inaccessible via B_{12s} , are now prepared from hydridocobalamin⁴⁸.

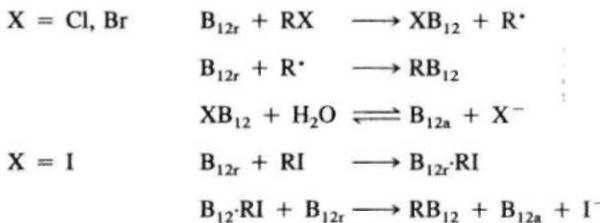
Cobaloxime(II) and B_{12r} couple with alkyl radicals to form organocobalt compounds^{51,52}:



Cobalt(II) also abstracts a halogen atom from alkyl halides to form halocobalt compounds and an alkyl radical which reacts with Co(II)⁵³:



The reaction rate increases as the stability of the leaving organic radical increases. The bond dissociation energy and axial ligand are also important factors⁵⁴. Since equimolar amounts of organo and halo complexes form and separation is often difficult, this synthetic method is employed only when no other alternative is available. However, halocobaloxime can sometimes be recycled by reduction to the Co(II) state using Zn wool until all Co(II) complex is converted to the corresponding organocobalt(III)^{55,56}. The mechanism for reaction of B_{12r} with a kyl halides⁵⁷ is shown in scheme 1.



Scheme 1.

Reaction of alkyl Grignard and other organometallic reagents with Co(III) species was originally used for formation of the Co—C bond³, in particular for the preparation of alkylcobalamin analogues⁵⁸.

Bromopyridinatocobaloxime and B_{12} react with electron-rich olefins, e.g., vinyl ethers, to form organocobalt compounds^{59,60}.

(L. Y. XIE, P. F. ROUSSI, D. H. DOLPHIN)

1. The skeleton of vitamin B_{12} (i.e., the porphyrin nucleus minus C-20) is called corrin. The compound containing the corrin nucleus is called a corrinoid. The compound containing the cobalt atom and the standard side chains in the free acid form is called cobyrinic acid, but cobyrinic acid when the side chains are at positions a, b, c, d, e, g, are in the amide form. Cobyrinic acid substituted with D-1-amino-2-propanol at position f is called cobinic acid. The substituted cobyrinic acid is called cobinamide. Cobinic acid substituted with D ribofuranose-3-phosphate at position 2 of the aminopropanol is called cobamic acid; the substituted cobinamide is called cobamamide. Many B_{12} vitamins and derivatives in which the heterocyclic base is 5,6-dimethylbenzimidazole are given the trivial name cobalamin; see D. Dolphin, ed., B_{12} Wiley-Interscience, New York, 1982.

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14.8.2.1. Cobalamin Models

14.8.2.1.1. Formation of the Cobalt-Carbon Bond.

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 24. B_{12a} = aquo or hydroxocobalamin(III); B_{12r} = aquo or hydroxocobalamin(II); B_{12s} = aquo or hydroxocobalamin(I).
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14.8.2. Cobalamin Reactions

14.8.2.1. Cobalamin Models

14.8.2.1.2. Cleavage of the Cobalt-Carbon Bond.

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