ACCOUNTS OF CHEMICAL RESEARCH

VOLUME 1 NUMBER 4 APRIL, 1968

Organocobalt Chemistry of Vitamin B_{12} Model Compounds (Cobaloximes)

G. N. SCHRAUZER

Department of Chemistry, University of California, San Diego, Revelle College, La Jolla, California 92037

Received September 26, 1967

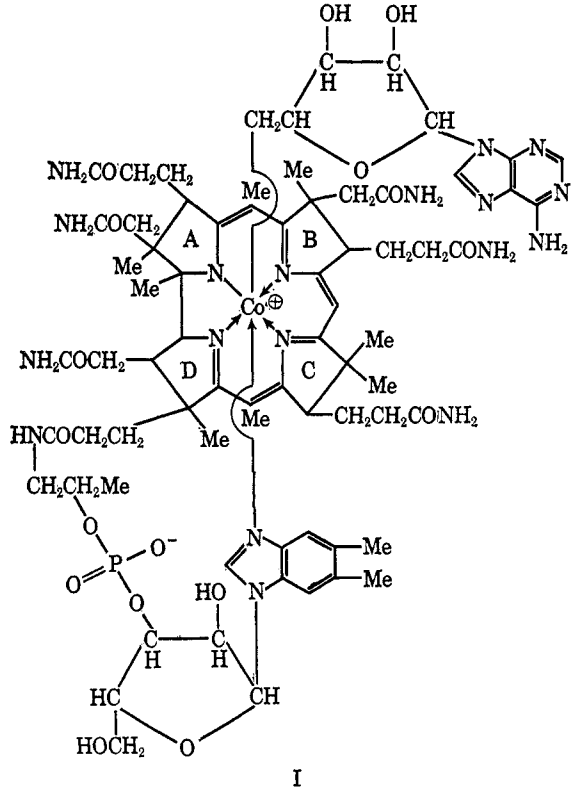
The highly unusual organometallic chemistry of cobalt in vitamin B_{12} and its derivatives can now be studied with surprisingly simple model compounds.

Introduction

Until 1964 only a few compounds with cobalt σ bonds were known, and all proved to be sensitive to heat, air, and protic solvents. For example, some rather labile complex cobalt acetylides were prepared by Nast and Lewinsky in 1955,[1] and in 1958 Hieber, *et al.*, reported methyltetracarbonylcobalt ($CH_3Co(CO)_4$) to be stable only below $-35°$.[2] Heck and Breslow in 1960 similarly obtained a highly reactive allyltetracarbonylcobalt ($C_3H_5Co(CO)_4$).[3,4]

In 1961 Chatt and Shaw described complexes of general composition $CoR_2(phosphine)_2$ which they prepared from bisphosphine adducts of cobalt halides and certain Grignard reagents.[5] Simple alkyl derivatives of this type proved unstable, but the species with R = mesityl, biphenyl, or 2-methylnaphthyl could be characterized. It was observed that stable organocobalt compounds only resulted in this case if the organic group carried bulky *ortho* substituents.

From this history it became fairly generally accepted that compounds with Co–C σ bonds should be rather unstable and reactive, if at all capable of existence. The discovery that a coenzyme of vitamin B_{12} isolated by Barker[6] contained an adenosyl group linked to cobalt by a direct cobalt–carbon σ bond (Crowfoot-Hodgkin),[7] therefore, was rather surprising.



I

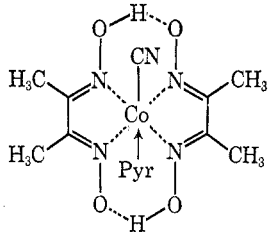
The 5-deoxyadenosyl(5,6-dimethylbenzimidazolyl)-cobinamide I was the first naturally occurring transition metal organic complex to be recognized, and is one of the most stable organocobalt compounds ever reported. Independent of this discovery, syntheses of organocobalamin derivatives were developed in the laboratories of A. W. Johnson (Nottingham), E. L. Smith (Glaxo Research Ltd.), and K. Bernhauer (Stuttgart). Detailed accounts of this and other work on

(1) R. Nast and H. Lewinsky, *Z. Anorg. Allgem. Chem.*, **282**, 210 (1955).
(2) W. Hieber, O. Vohler, and G. Braun, *Z. Naturforsch.*, **13b**, 192 (1958).
(3) R. F. Heck and D. S. Breslow, *J. Am. Chem. Soc.*, **82**, 750 (1960).
(4) R. F. Heck and D. S. Breslow, *ibid.*, **82**, 4438 (1960).
(5) J. Chatt and B. L. Shaw, *J. Chem. Soc.*, 285 (1961).
(6) H. Barker, H. Weissbach, and R. D. Smyth, *Proc. Natl. Acad. Sci. U. S.*, 1093 (1958).
(7) D. Crowfoot-Hodgkin, *Proc. Roy. Soc.* (London), **A288**, 294 (1965).

vitamin B_{12} may be found in ref 8–12. This unusual "organic" chemistry of cobalt in vitamin B_{12} was for some time believed to be a consequence of specific electronic effects of the corrin ligand system on the metal atom. Work was therefore initiated to find cobalt complexes other than corrins capable of forming stable organometallic derivatives which could simulate the principal reactions of the cobalt atom in the complicated corrins.

Cobaloximes and Other Cobalamin Model Compounds

Early in 1963 it was observed that bis(dimethylglyoximato)cobalt complexes show many reactions of the cobalt atom in the corrins.[13] In view of their similarity to the cobalamins and for convenience, complexes of this type were named "cobaloximes." The structure of "cyanopyridinecobaloxime" is shown in II. As in



cyano(pyridine)bis(dimethylglyoximato)cobalt(III)
("cyanopyridinecobaloxime")

II

the case of vitamin B_{12} and related corrins it was possible to apply a variety of alkylation procedures to the cobaloximes. It was soon found that the tendency of the ligands to stabilize Co–C bonds is independent of the detailed nature of their vertical π-electron system. All that is required is the presence of a cobalt ion in a sufficiently and optimally strong, essentially planar ligand field. It is obvious that many ligands fall into this class, and we have since found more than a dozen cobalt chelates with similar properties.[14] The coordinating atoms do not have to be necessarily nitrogen but may be cyanide (as in the pentacyanocobaltates),[15,16] or the nitrogen atoms in the ligands may be partially substituted by oxygen. This is the case in a number of Schiff bases derived from salicylaldehyde or acetylacetone.[14,17,18]

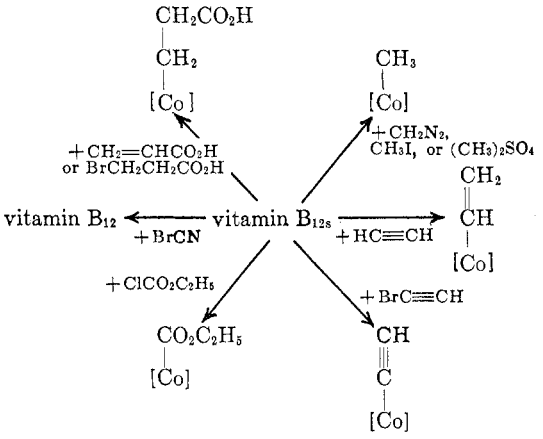
Organocobalt derivatives of cobalt porphyrins were reported by Dolphin and Johnson.[19] It is important to note that the cobalt porphyrins cannot be reduced to the cobalt(I) state under the conditions in which vitamin B_{12s} is obtained. The synthesis[19] of the organocobalt porphyrins therefore had to be conducted in nonaqueous solvents, either by the reaction of the alkali metal derivatives with alkyl halides or by reaction with organomagnesium halides. The inability of the porphyrin ligand to stabilize the Co(I) valence state in aqueous medium limits the usefulness of cobalt porphyrins as models for the corrins and may be one reason why the former were not utilized in chemical evolution.[20]

Generation of Nucleophilic Cobalt Species

Organocobalamins have been synthesized largely *via* reductive alkylation or by the addition of olefinic or acetylenic compounds to a gray-green exceedingly reactive cobalt(I) derivative of vitamin B_{12} which is most frequently referred to as "vitamin B_{12s}." [21,22] Some of its reactions are summarized in Scheme I.

Scheme I

Some Reactions of Vitamin B_{12s}[a]



[a] All of these can also be duplicated with "cobaloxime$_s$."

The elucidation of the nature of vitamin B_{12s} was greatly facilitated by the study of cobaloximes.[23] These can also be reduced to blue or blue-green Co(I) species. Solutions of "cobaloxime$_s$" are extremely oxygen sensitive and only capable of existence at alkaline pH. In acidic solution they decompose to form cobaloxime(II) and hydrogen, in analogy to the behavior of vitamin B_{12s}. Extremely oxygen-sensitive yellow-brown alkali metal derivatives of cobaloximes(I) are obtained by the reaction of cobaloximes(III) with alkali metals in aprotic solvents.[13,23] On dissolution in water, these salts produce solutions with properties typical of cobaloxime. The alkaline pH of these solutions was interpreted as

(8) E. L. Smith, "Vitamin B_{12}," 3rd ed, Methuen & Co., London, New York, 1965.
(9) K. Bernhauer, O. Müller, and F. Wagner, *Angew. Chem. Intern. Ed. Engl.*, **3**, 200 (1964).
(10) R. Bonnett, *Chem. Rev.*, **63**, 573 (1963).
(11) "Vitamin B_{12} Coenzymes," *Ann. N. Y. Acad. Sci.*, **112**, 2 (1964).
(12) Vitamin B_{12} and Intrinsic Factor, 1st European Symposium, Enke Verlag, Stuttgart, Germany.
(13) G. N. Schrauzer and J. Kohnle, *Chem. Ber.*, **97**, 3056 (1964).
(14) Unpublished work.
(15) J. Halpern and J. P. Maher, *J. Am. Chem. Soc.*, **86**, 2311 (1964).
(16) J. Kwiatek and J. K. Seyler, *J. Organometal. Chem.* (Amsterdam), **3**, 421 (1965); **3**, 433 (1965).
(17) G. Costa, G. Mestroni, and L. Stefani, *ibid.*, **7**, 493 (1967).
(18) G. Costa, G. Mestroni, G. Tauzher, and L. Stefani, *ibid.*, **6**, 181 (1966).
(19) D. Dolphin and A. W. Johnson, *Chem. Commun.*, 494 (1965).
(20) G. N. Schrauzer, *Naturwissenschaften*, **53**, 459 (1966).
(21) R. N. Boos, J. E. Can, and T. B. Coun, *Science*, **117**, 603 (1963).
(22) O. Müller and G. Müller, *Biochem. Z.*, **336**, 299 (1962).
(23) G. N. Schrauzer, R. J. Windgassen, and T. Kohnle, *Chem. Ber.*, **98**, 3324 (1965).

being due to anion hydrolysis[23] (eq 1). The system (1)

$$(Co^{I})^{-} + H_2O \rightleftarrows \overset{H}{\underset{|}{(Co)}} + OH^{-} \quad (1)$$

is complicated by the fact that the Co–H acids are unstable as such and at equilibrium with molecular hydrogen and the corresponding Co(II) compounds. The predominant species in alkaline and neutral solutions therefore is the complex-bound Co(I) ion which is spin paired and formally isoelectronic with low-spin Ni(II). It is five-coordinate, but there is evidence that the axial base component is easily detached. The interaction of the base with the Co(I) complexes (eq 2) is responsible for the characteristic dependence of the color of cobaloximes solutions on the nature of the base B. The high nucleophilicity of the cobalt atom in the

$$(Co^{I})^{-} + B \rightleftarrows \overset{}{\underset{B}{(Co^{I})^{-}}} \quad (2)$$

"s" species is caused by the ligand-modified d_{z^2} orbital which is localized perpendicular to the plane of the molecule. Since the polarographic half-wave potentials for the reduction of Co(III) to Co(II) and Co(I) are strikingly similar, most arguments on cobaloximes also apply for vitamin B_{12s}. In contrast to the cobaloximes, however, vitamin B_{12r} is not readily reduced to vitamin B_{12s} by molecular hydrogen in the absence of a catalyst. This is attributed to steric effects, preventing the close approach of two molecules of the vitamin. For similar reasons vitamin B_{12r} is unable to exist as a diamagnetic dimer.

Vitamin B_{12r} and Cobaloximes(II)

Addition of one electron to vitamin B_{12a} produces the brown "vitamin B_{12r}" which is paramagnetic and sensitive to oxygen. It cannot be alkylated except in the presence of an additional reducing agent. Three types of cobaloximes(II) have so far been prepared. On dehydration of diaquacobaloxime(II) we have obtained the blue-violet, paramagnetic bis(dimethylglyoximato)-cobalt(II),[24] an air-sensitive, hygroscopic compound which readily adds bases to produce either paramagnetic bisadducts or diamagnetic and presumably dimeric monoadducts. The compounds are incompletely reversible oxygen carriers. Vitamin B_{12r} also seems to form a presumably dimeric oxygen adduct.[25] All cobaloximes(II) disproportionate in alkaline solution into a mixture of cobaloxime(I) and cobaloxime(III) but are stable in neutral medium in the absence of oxygen. The tendency to disproportionate may be utilized for the synthesis of organocobaloximes from Co(II) salts, dimethylglyoxime, stoichiometric amounts of base, and the alkylating agent in the absence of a reducing agent; under these conditions the yields can only approach 50% of the total cobalt present. The reaction solution absorbs hydrogen, however, and with this reducing agent the synthesis of organocobaloximes is possible in one stage.[26] Yields are nearly quantitative in many cases.

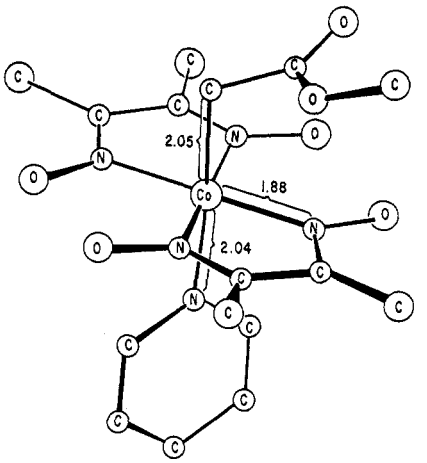


Figure 1. Structure of O-methyl-(Co–C)-carboxymethyl[bis-(dimethylglyoximato)pyridine]cobalt.[27] (Hydrogen atoms are not shown.)

Structure of a Substituted Alkylcobaloxime

The first structure determination of a substituted alkylcobaloxime was recently completed by Lenhert.[27] The structure resulting for methyl(carboxymethyl)-(pyridine)cobaloxime is shown in Figure 1. The observed in-plane Co–N bond lengths and the Co–C distance are the same as those in coenzyme B_{12} within the errors of the determination. The Co–N(pyridine) bond length is somewhat shorter than the Co–N(5,6-dimethylbenzimidazole) distance in the coenzyme but identical with that observed in cyanocobalamin. This suggests that the cobalt atom may have a slightly greater positive charge in the cobaloxime, causing a somewhat stronger attachment of the axial base component.

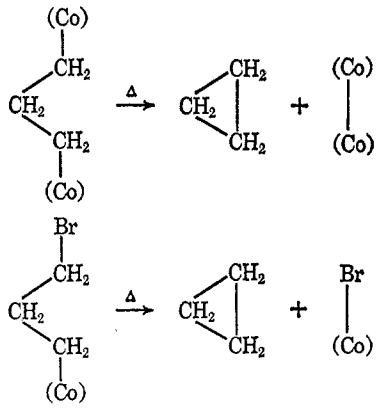
Since the dimethylglyoxime moiety imposes less steric restrictions than the corrin ligand, the stability of cobaloximes is frequently greater than that of the corresponding cobalamins. Secondary alkylcobaloximes can be prepared and isolated without difficulty, but the existence of corresponding cobalamin derivatives is still doubtful.

Properties and Reactions of the Co Alkyls

Simple alkylcobaloximes are among the most stable transition metal organic compounds known. They remain unchanged usually up to about 200° and show remarkable resistance to concentrated nonoxidizing acids and bases. However, cleavage of the Co–C bond occurs on exposure to light. The initial products of the photochemical Co–C bond cleavage are alkyl radicals whose subsequent reactions depend on a variety of factors which are currently being investigated in detail. In water under anaerobic conditions methyl-

(24) G. N. Schrauzer and R. J. Windgassen, *Chem. Ber.*, **99**, 602 (1966).
(25) B. Jaselskis and H. Diehl, *J. Am. Chem. Soc.*, **80**, 2147 (1958).
(26) G. N. Schrauzer and R. J. Windgassen, *ibid.*, **88**, 3738 (1966).
(27) G. Lenhert, *Chem. Commun.*, 980 (1967).

cobaloxime yields a mixture of methane and ethane. Ethylcobaloxime, however, yields mainly ethylene. If generated in benzene, the methyl radicals from methylcobaloxime add to the solvent, yielding toluene.[26] In water in the presence of oxygen formaldehyde is the main product of methylcobaloxime photodecomposition. The *thermal decomposition* of methylcobaloximes yields methane and very little ethane. Thermolysis of higher alkylcobaloximes produces mainly olefins and small amounts of paraffins. Cobaloximes with bulky alkyl groups attached to the cobalt are thermally less stable. Particularly striking is the difference in the thermal stability of α- and β-phenylethylcobaloximes (decomposition point 90 and 175°, respectively). It is of interest that the thermal decomposition of the binuclear cobaloxime as well as that of 3-bromo(*n*-propyl)-cobaloxime afford cyclopropane (eq 3).



(3)

cyclopropane formation

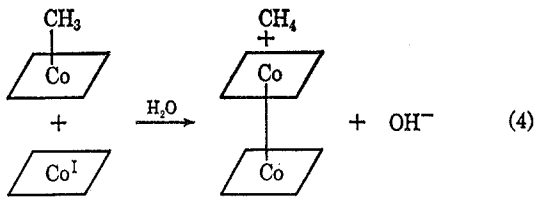
A mixture of butadiene with butenes is obtained as the hydrocarbon chain pyrolysis product of tetramethylene(pyridine)dicobaloxime. The decomposition temperatures of various alkylcobaloximes vary little with the nature of the axial base, although the phosphine adducts are somewhat more stable than those of nitrogen bases. Aquamethylcobaloxime can be dehydrated to a red, air-stable, and weakly hygroscopic anhydride which is insoluble in all noncoordinating solvents and probably associated in the solid state. This indicates that the axial base component is not essential for Co–C bond stabilization.[26]

Alkylcobalamins, on the whole, behave on photolysis similarly to alkylcobaloximes. In the case of methylcobalamin the methane and ethane formation has been interpreted as the result of hydrogen and methyl group abstraction from the corrin ligand.[28] Recent work indicates, however, that the anaerobic photolysis of methylcobalamin in dilute solutions produces ethane mainly *via* methyl radical coupling, just as does methylcobaloxime.

Chemical Cleavage of Cobalt–Carbon Bonds

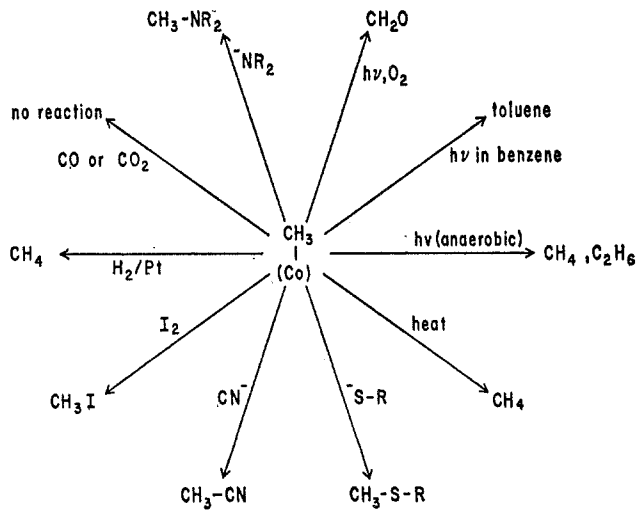
Carbon–cobalt bond cleavage in alkylcobaloximes can be effected by a number of nucleophiles, mainly CN^- and SR^-. During the substitution the base component in the sixth coordination position is displaced by the nucleophile, but this does not seem to produce an accelerating effect on the bond cleavage reaction. The reaction with cyanide is very slow, and a large excess of CN^- is required. Weaker nucleophiles (azide, thiocyanate, or iodide), but also methyllithium, fail to cleave the Co–C bond in alkylcobaloximes. Bond cleavage occurs under reducing conditions in the presence of a catalyst. Polarographic measurements indicate that the first reduction step is irreversible, presumably due to the Co–C bond cleavage which occurs at this point.[26] One may describe this process by assuming that the electron occupies the antibonding component of the Co–C bond molecular orbital. Electron transfer into this orbital would be facilitated if the sixth coordination position were free. Indeed it is observed that aquoalkylcobaloximes are more readily cleaved than the phosphine-substituted derivatives. Similarly, methylaquocobalamin is reduced by borohydride under conditions where methylcobalamin (with the dimethylbenzimidazole ligand occupying the sixth coordination position) is attacked only very slowly.

The reductive cleavage is autocatalyzed by the reduced cobaloxime formed in the process. A solution of methylcobaloxime and cobaloxime slowly evolves methane, and dimeric cobaloxime(II) is deposited[26] (eq 4). The reactions of methylcobaloxime are summarized in Scheme II. Many of them are also typical of methylcobalamin. The Co–C bonds in the alkylcobaloximes and cobalamins are essentially covalent; the protons do not undergo any deuterium-exchange reactions and show neither acidic nor basic properties.



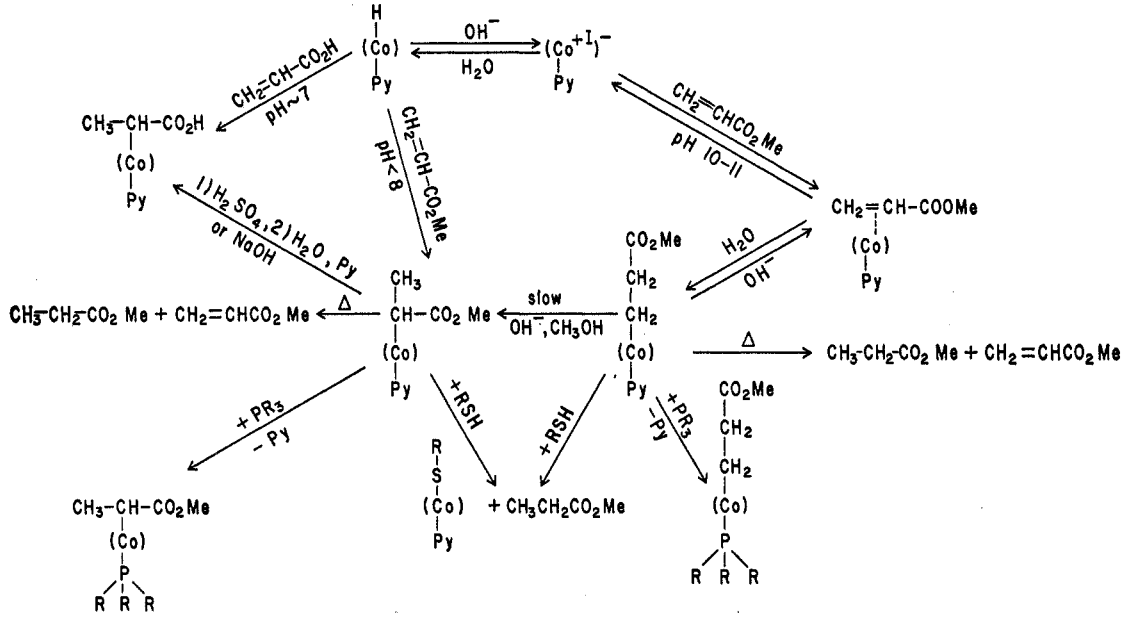
(4)

Scheme II
Some Reactions of Methylcobaloxime



(28) H. P. C. Hogenkamp, *Biochemistry*, 5, 417 (1966).

Scheme III
Reactions of Carbomethoxyethylcobaloximes[a]



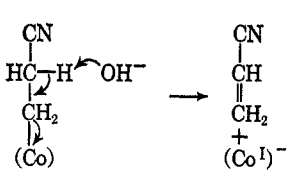
[a] Dioxime ligands symbolized by parentheses.

Reactions and Properties of α-Substituted Alkylcobaloximes

The introduction of an electronegative substituent in the α position of an alkylcobaloxime has little effect on the gross chemical properties except that reductive cleavage of the Co–C bond occurs more readily. Carboxymethylcobaloxime (decomposition point 200–210°) has a pK_a of 7.14 (25°) and hence is a weaker acid than acetic acid (pK_a = 4.75, 25°). This has been attributed to a proximity effect. The esters of the "cobaloximeacetic acids" are surprisingly stable. Warm, concentrated sulfuric acid (!) is required for their hydrolysis. Thermal decomposition of the ester produces esters of acetic acid as the main product of Co–C bond cleavage; the free acid yields acetic acid and only very little methane and CO_2. This shows that the attachment to cobalt does not facilitate decarboxylation.[29a]

Reactions of β-Substituted Alkylcobaloximes

Electronegative substituents in the β position of ethylcobaloximes introduce alkali sensitivity caused by an elimination of the type shown in eq 5.[29a] Reaction



(5)

5 has also been reported for the corresponding cobalamin derivative.[29b]

The synthesis of the substituted alkylcobaloximes from vinyl compounds is of interest since the type of isomer formed depends on the pH of the reaction solution. At pH 10–11 the β isomer is obtained exclusively, but at pH 7–9 the α isomer is produced. The formation of the latter has been attributed to the presence of the Co–H "acid" whereas the reaction in the more strongly alkaline medium involves the Co^I nucleophile.[29b] The reactions of carbomethoxyethylcobaloximes are summarized in Scheme III.

The β isomers undergo a remarkable rearrangement into the α compounds in mildly alkaline solutions. The rearrangement is not intramolecular although it may involve the formation of a labile π-bonded intermediate. It has not yet been verified for cobalamin derivatives, but it has been suggested that an isomerization of the type mentioned above could play a part in the methylmalonyl–succinyl-CoA and the glutamic–methylaspartic mutase enzymes.[29a]

The β-hydroxyalkylcobaloximes[30] also exhibit a number of unusual properties. Of particular importance is that the hydroxyalkyl derivatives are sensitive to both acids and bases. With acids, *olefins* and cobaloximes(III) are formed. Protonation of the hydroxyl group followed by elimination of water and olefin from the oxonium ion appears to be the mechanism of acid cleavage. The alkali decomposition apparently involves the initial formation of a cobaloxime alkoxy anion. This species could either decompose into olefin oxide plus cobaloxime(I) or undergo a hydride shift to produce aldehydes or ketones plus the reduced cobaloxime.[30] Only the latter reaction appears to occur, since the β,β-dimethyl-β-hydroxyethylcobaloxime does not decompose in alkaline solution. An al-

(29) (a) G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, **89**, 1999 (1967); (b) R. Barrett, H. P. C. Hogenkamp, and R. H. Abeles, *J. Biol. Chem.*, **241**, 1483 (1966).

(30) G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, **89**, 143 (1967).

ternative mechanism, the abstraction of a β proton through interaction with the OH^- ion, must be ruled out since alkoxyalkylcobaloximes are completely alkali stable. The conversion of glycol derivatives into aldehydes by means of organocobalt intermediates (eq 6)

$$H_2O + CH_2{=}CH_2 + (Co^{III}) \xleftarrow{H^+} \underset{(Co)}{\overset{CH_2OH}{\overset{|}{CH_2}}} \xrightarrow{OH^-} CH_3CH{=}O + (Co^{I})^- \quad (6)$$

has been suggested as a possible way by which coenzyme B_{12} functions in a diol dehydrase of *Aerobacter aerogenes*.[30] Work with the enzyme system[31] is in progress to test this hypothesis.

At this point it should be mentioned that hydroxyethylcobalamin produces ethylene with acids and that it also decomposes in alkali to produce vitamin B_{12s} albeit more concentrated NaOH is required than in the case of the cobaloxime derivatives.

Compounds with Cobalt–Sulfur Bonds

Thioproteins, dihydrolipoic acid, and other thiols in alkaline solution reduce vitamin B_{12a} to the "r" and "s" forms and hence may be common biological reducing agents of the vitamin. Mercaptocobalamins with Co–S bonds seem to be the intermediates in this reduction, but they are relatively unstable and difficult to isolate. A number of mercaptocobaloximes have therefore been synthesized to determine the properties of the Co–S bond in these and the related cobalamin derivatives.[32] Mercaptocobaloximes are stable in mildly acidic solution, but Co–S bond cleavage occurs in alkaline medium yielding a mixture of cobaloxime(III) and cobaloxime$_s$, plus the corresponding amount of dialkyl disulfide. Cobaloximes catalyze the oxidation of mercaptans to disulfides as well as the reverse process in complete analogy to vitamin B_{12}. It is of interest that mercaptocobaloximes (as well as the mercaptocobalamins) can be directly converted into alkyl derivatives provided that excess thiol and alkylating agent are present and the pH of the reaction solution is adjusted to remain close to neutrality. The reaction may be represented by eq 7. With stoichiometric amounts

$$\underset{(Co)}{\overset{CH_3}{\overset{|}{S}}} + 2CH_3SH + 2CH_3I + 2OH^- \longrightarrow \underset{(Co)}{\overset{CH_3}{\overset{|}{}}} + CH_3SSCH_3 + CH_3SCH_3 + 2I^- + 2H_2O \quad (7)$$

of methyl iodide, alkylation of the mercaptide ion and not cobalt takes place[31] (eq 8).

$$\underset{(Co)}{\overset{SR}{\overset{|}{}}} + CH_3I \xrightarrow[pH\,7]{} CH_3SR + \underset{(Co)}{\overset{I}{\overset{|}{}}} \quad (8)$$

Methyl Group Transfer Reactions and Some Comments to Methionine Biosynthesis

It has recently become apparent that methylation–demethylation reactions of the cobalt atom in vitamin B_{12} occur in biological systems. It therefore appeared to be of interest to establish the chemical relationships between the various methyl donors and acceptors present in the systems. The transfer of methyl groups from cobalt to mercaptide ions takes place readily in mildly alkaline solution. Biochemically of importance is the formation of methionine from methylcobalamin and homocysteine, a reaction which has been verified both enzymatically and nonenzymatically[33] (eq 9).

$$\underset{(Co)}{\overset{CH_3}{\overset{|}{}}} + \text{homocysteine} \longrightarrow (Co^{I})^- + \text{methionine} + H^+ \quad (9)$$

Methylcobaloximes behave like the cobalamin derivative except that they react somewhat more slowly, possibly because of a slight difference in the effective ligand strength.[32] Reaction 9 is irreversible, but a demethylation of methionine is possible by converting it to the S-adenosyl derivative (eq 10). Reaction 10

$$(Co^{I})^- + \text{S-adenosylmethionine} \longrightarrow \underset{(Co)}{\overset{CH_3}{\overset{|}{}}} + \text{S-adenosylhomocysteine} \quad (10)$$

may occur under certain conditions of methionine biosynthesis. The transport of methyl groups from sulfonium-type compounds to cobalt may constitute a step in the final stages of methane biosynthesis in certain microorganisms. The transfer of the methyl group from 5-methyltetrahydrofolic acid to cobalt appears to occur in methionine biosynthesis of certain strains of *Escherichia coli*, but another enzyme has been characterized which produces methionine without a requirement for vitamin B_{12}. Methyl group transfer from nitrogen to cobalt would necessitate the cleavage of a N–C bond. The reaction was shown to occur enzymatically.[34] All attempts to verify a direct transfer reaction of this type in nonenzymatic model systems to date have remained unsuccessful. On the basis of purely chemical and empirical considerations we therefore concluded that the *direct* transfer of the methyl group of 5-methyltetrahydrofolic acid to cobalt is unlikely, especially since it was demonstrated that a number of N-methylated compounds readily transfer a methyl group to thiols, but under a variety of different reaction conditions failed to undergo nitrogen-to-cobalt transfer. In the enzyme it is possible that the methyl group of 5-methyltetrahydrofolic acid is at first transferred to another acceptor on the enzyme protein before the methylation of the cobalt atom can occur.

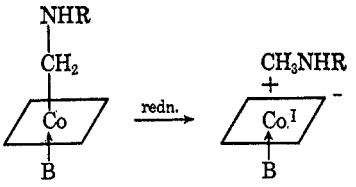
(31) R. H. Abeles and H. A. Lee, *Ann. N. Y. Acad. Sci.*, **112**, 695 (1964).
(32) G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, **89**, 3607 (1967).
(33) J. R. Guest, S. Friedman, D. Woods, and E. L. Smith, *Nature*, **195**, 340 (1962).
(34) R. Taylor and H. Weissbach, *Biochem. Biophys. Res. Commun.*, **27**, 398 (1967).

Catalytic Reactions with Vitamin B_{12} and Cobaloximes: Reductive Methylation

Among the various reduction reactions catalyzed by vitamin B_{12} or by cobaloximes the synthesis of N-methyl groups from formaldehyde and amines will be mentioned.[35] Whereas formaldehyde itself is not reduced by vitamin B_{12r}, amines are reductively methylated by it in the presence of catalytic or stoichiometric amounts of vitamin B_{12r} or cobaloximes and a reducing agent, *e.g.*, molecular hydrogen (eq 11). With cobaloximes in

$$CH_2{=}O + C_6H_5NH_2 \rightleftharpoons C_6H_5NHCH_2OH \xrightarrow[(Co)]{H_2} C_6H_5NHCH_3 + H_2O \quad (11)$$

stoichiometric amounts it has been possible to isolate intermediate complexes (such as shown in eq 12) which release the N-methylated base on reductive cleavage under very mild conditions.[35] S-Methyl groups could



(12)

be synthesized similarly from formaldehyde and mercaptans. On the basis of these findings it was suggested[32,35] that vitamin B_{12} could act as the catalyst in the *de novo* synthesis of labile methyl groups. This catalytic action of vitamin B_{12} would be rather specific for the production of methyl groups from the formaldehyde oxidation level. Ethyl groups, for example, cannot be made this way effectively, both for steric and for electronic reasons. The presently known 5,10-methylenetetrahydrofolate reductases are flavin enzymes and evidently do not require vitamin B_{12}.[36] At the time when a vitamin B_{12} involvement in the *de novo* synthesis of methyl groups was proposed, all available evidence seemed to contradict this idea. In particular, it appeared that 5-methyltetrahydrofolic acid would in fact accumulate in vitamin B_{12} deficient subjects.[37] In the meantime it was observed, however, that at least in some forms of vitamin B_{12} deficiency there is also an accumulation of formyl folates and other *precursors* of 5-methyltetrahydrofolic acid.[38-40] This has been interpreted to suggest an impairment in the reduction of hydroxymethyl to methyl groups.[40] Our demonstration of the catalytic effect of vitamin B_{12} and related compounds in the reductive synthesis of methyl groups from the formaldehyde (hydroxymethyl) level shows that the involvement of the vitamin in biological methyl group synthesis is possible in principle and should stimulate further research.

Concluding Remarks

The purpose of the present account was to outline the main features of an area of organometallic chemistry which will continue for some time to yield unusual organocobalt compounds and new reactions and mechanistic concepts. In the past years we have not ceased to be amazed by the multitude of reactions of the bis(dimethylglyoximato)cobalt chelates, especially since the first and simplest "cobaloximes" were known since Tshugagev's time. The most important aspect of this work lies in the recognition of the surprising similarities of the reactions of cobaloximes with those of cobalamins. We feel strongly that the continuing study of the simple models will contribute to the final elucidation of the exact functions of the B_{12} coenzymes.

The author wishes to acknowledge his appreciation to his graduate students (J. Kohnle, G. Kratel, J. W. Sibert, and Mrs. L. P. Lee), and mainly to Dr. R. J. Windgassen. The work is supported by the National Science Foundation.

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