Photochemical and Thermal Cobalt–Carbon Bond Cleavage in Alkylcobalamins and Related Organometallic Compounds. A Comparative Study[1]

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Abstract: The homolytic cleavage of the cobalt–carbon bond in alkylcobalamins is compared with the behavior of alkylcobaloximes and cobalt alkyl derivatives of a number of chelates derived from Schiff base ligands such as bissalicylaldehyde–ethylenediimine or bisacetylacetone–propylenediimine. In the anaerobic photolysis of methylcobalamin, methane and ethane are formed. The ethane arises mainly from methyl radical dimerization. Methyl group abstraction from the corrin ligand by the methyl radical, which previously was regarded to be mainly responsible for the ethane formation, accounts for only a small percentage of the total ethane produced. The methane is formed by ligand hydrogen abstraction as well as methyl radical reduction. The methane–ethane ratio depends on the pH, the nature of the axial base, and the solvent. Strongly interacting axial groups such as cyanide completely surpress ethane formation in favor of methane. Ethylcobalamin yields mainly ethylene on photolysis, while olefins are the principal photolysis products from higher alkylcobalamins. The study of the photolysis reactions of alkylcobaloximes revealed surprising parallels with alkylcobalamins, but the corresponding derivatives of the Schiff base chelates duplicated alkylcobalamin reactions less well. The pyrolysis of alkylcobalamins and cobalt alkyl chelates under controlled conditions yields alkyl radicals which either dimerize or undergo hydrogen abstraction, disproportionation, or dehydrogenation. A new method of synthesis of cobalt alkyl derivatives of the Schiff base chelates *via* the Co(I) nucleophiles is described.

The remarkable chemical similarity between cobalamins and cobaloximes is now well recognized to be a consequence of the fortuitous near-identity of the effective coordinating strengths of these chemically unrelated ligand systems.[4–6] Although we have already pointed out that cobalt complexes of a variety of Schiff bases exhibit similar chemical behavior,[6] the properties of these "vitamin B_{12} model compounds" have not yet been directly compared with any of the cobaloximes or the corresponding cobalamin derivatives. In the present paper we report on the photolysis and pyrolysis of alkylcobalt derivatives of vitamin B_{12} (Figure 1) and the chelates shown in Figure 2. We have chosen these homolytic Co–C bond cleavage reactions since they can be achieved under mild conditions in the absence of other reagents. The analysis of the fate of the alkyl radicals was expected to yield important information on the role of the cobalt atom and of the ligands in the radical termination processes. Most compounds used in the present work are known. The synthesis of several new compounds by a new, generally applicable method is described in the Experimental Section. The cobalt alkyls of chelates **4** and **6** are new but closely resemble those of **3** and **5**. All compounds are reasonably air stable and crystalline.

(1) Supported by NSF Grant GB 6174.
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(4) G. N. Schrauzer and J. Kohnle, *Chem. Ber.*, **97**, 3056 (1964).
(5) G. N. Schrauzer, *Accounts Chem. Res.*, **1**, 97 (1968), and references cited therein.
(6) G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, **88**, 3738 (1966).

Anaerobic Photolysis of Methylcobalamin and Methylcobaloximes

The photolability of methylcobalamin is well known.[7] It is generally agreed that methyl radicals and vitamin B_{12r} are initial photolysis products (eq 1). In the presence of air the methyl radicals are oxidized to various products, mainly formaldehyde. These well-known

$$\underset{\text{methylcobalamin}}{\overset{CH_3}{|}\,(Co)} \xrightarrow{h\nu} \underset{\text{vitamin } B_{12r}}{(Co^{II})} + CH_3\cdot \qquad (1)$$

methyl radical reactions will not be discussed here, however. Under anaerobic conditions photolysis is slow, presumably due to extensive recombination, and methane and ethane in the ratio of about 1:2 are formed. An earlier claim[7] that methylcobalamin is stable to light under strictly anaerobic conditions could not be confirmed. The ethane was recently[8] suggested to arise from the methyl radical induced abstraction of a methyl group from the corrin ring (such as at positions C-7, C-12, or C-17), a conclusion based on the apparent low specific radioactivity of the ethane formed in the photolysis of $^{14}CH_3$-cobalamin.[8] The formation of methane in turn was interpreted as resulting from the abstraction of a hydrogen atom on the corrin. Thus the corrin ligand was assumed to play an extensive part in the events following the homolytic cleavage of the Co–C bond.

(7) D. Dolphin, A. W. Johnson, and R. Rodrigo, *Ann. N. Y. Acad. Sci.*, **112**, 590 (1964).
(8) H. P. C. Hogenkamp, *Biochemistry*, **5**, 417 (1966).

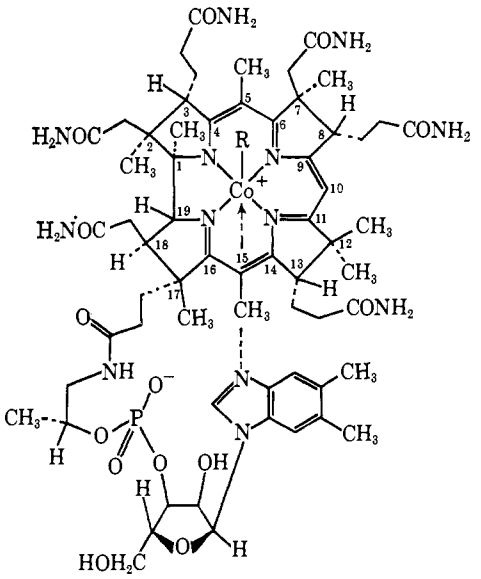


Figure 1. Structure of alkylcobalamins (R = methyl, ethyl, etc.).

These condlusions appear to be in contradiction to the results of photolysis experiments in the cobaloxime series, where the methane produced was assumed to arise *via* a reductive mechanism, whereas the ethane was concluded to result from methyl radical dimerization. Radical coupling as the mechanism for the ethane formation must be invoked to explain the formation of ethane in the photolysis of the cobalt methyl derivatives of glyoxime, 1,2-cyclohexanedione dioxime, and diphenylglyoxime (Table I). In view of this conflicting evidence the photolysis of methylcobalamin was therefore reinvestigated.

Table I. Photolysis of Four Methylcobaloximes in Water[a]

Ligand	Methane/ethane, mol %
Dimethylglyoxime	59/41
Diphenylglyoxime	59/41
Cyclohexanedione 1,2-dioxime	63/37
Glyoxime	79/21

[a] Axial base, pyridine.

The Origin of Ethane. To establish whether the ethane is formed *via* methyl radical coupling or methyl abstraction, methylcobalamin-d_3 and methylcobaloxime-d_3 were synthesized in 99+ isotopic purity using methyl-d_3 iodide consisting of 99.8% of CD_3I (the impurity being CD_2HI (~0.2%) determined by mass spectrographic analysis). The photolysis of methylcobalamin was carried out under conditions similar to those employed by Hogenkamp, affording methane and ethane in the ratio of 1:2.2. The mass spectrographic analysis of the ethane revealed it to consist of 89% C_2D_6 and 11% $C_2D_3H_3$. No other deuterated ethane derivatives were detectable. Both products were definitely identified by separate, high-resolution mass spectrographic measurements.

Analysis of the ethane produced in the photolysis of methyl(pyridine)cobaloxime-d_3 indicated an identical isotopic composition within the errors of the analysis. No other deuterated ethanes, or deuterium-free ethane, were detectable. The photolysis of both methylcobalamin and methylcobaloxime was repeated in D_2O with the same results (Table II).

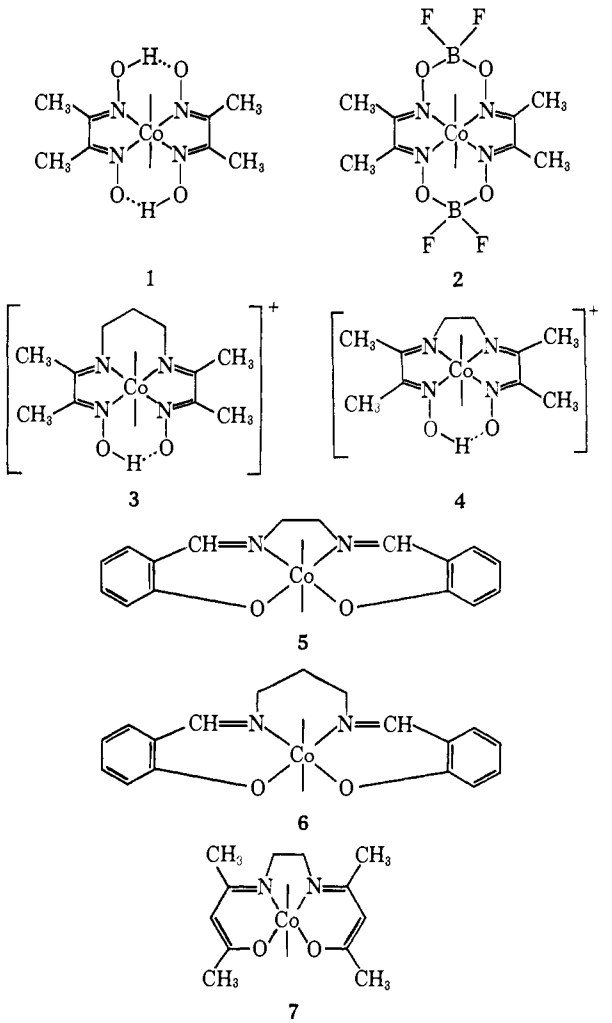


Figure 2. Structures of the cobalt chelates studied. Complexes **3**–**7** will be mainly referred to by the numbers given here. Occasionally **5** will also be named "Co(salen)," for cobalt bis(salicyladehyde)-ethylenediimine.

Table II. Composition of the Ethane Formed on Photolysis of Methylcobalamin-d_3 and Methylcobaloxime-d_3 in H_2O and D_2O

Compound	$C_2D_6/C_2D_3H_3$, % H_2O	D_2O
Methylcobalamin-d_3	89/11	88/12
Methyl(pyridine)cobaloxime-d_3	89/11	89/11

Hence, 95% of the available CD_3 radicals dimerized to ethane-d_6. Ligand methyl group abstraction occurred with the remaining 5%. Since our conditions of irradiation were similar to those employed in ref 8, the apparent low specific activity of the ethane obtained from methylcobalamin-^{14}C was probably due to low counting efficiency. Methyl abstraction or any equivalent process accounting for the formation of ethane composed of one ligand methyl and one cobalt methyl radical thus is only a minor side reaction. The photolysis of methylcobalamin was also studied at different light intensities (50–450 W). The methane/ethane

Table III. Methane and Ethane Formed in the Anaerobic Photolysis of Methylcobalamin and of Methylcobalt Derivatives of the Chelates **1–7** (in Mole Per Cent in the Gas Phase, Corrected for Solubility in Liquid Phase)

Chelate[a]	pH 4	pH 7	pH 9.5	pH 12.5	0.1 *M* KCN	CH_3OH	RSH[b]
Methyl-cobalamin	29/71	30/70	42/59	57/43	100/0	100/0	100/0
1 (Py)[c]	46/54	59/41	61/39	88/12	100/0	95/5	100/0
2 (Py)	30/70	30/70	44/56	73/27	98/2	99/1	100/0
3 (H_2O)	98/2	94/6	95/5	97/3	100/0	100/0	100/0
4 (H_2O)	96/4	93/7	83/17	91/9	100/0	100/0	100/0
5 (H_2O)	69/31	77/23	59/41	82/18	100/0	85/15	100/0
6 (H_2O)	89/11	86/14	93/7	97/3	100/0	100/0	100/0
7 (H_2O)	~99/1	~96/4	~100/0	~100/0	~100/0	~100/0	~100/0

[a] Ligand numbers as in Figure 1. [b] Mercaptoethanol, 1 *M* aqueous solution. [c] Axial base component in parentheses.

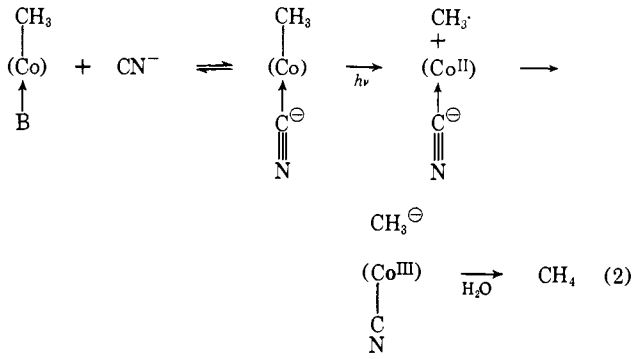
ratio was found not to depend on the light intensity or the length of irradiation. From this evidence it is concluded that the ethane indeed is formed *via* the dimerization of methyl radicals and not by another process, *e.g.*, the abstraction of the cobalt-bound methyl group by the photochemically generated methyl radicals. If the latter mechanism of ethane formation were important, the methane/ethane ratio would have to be time dependent due to the continuously decreasing concentration of methylcobalamin during the photolysis. Another experiment which eliminates the abstraction of alkyl groups attached to cobalt by free methyl radicals will be described in a later section.

The Formation of Methane and pH Dependence. The anaerobic photolysis of methylcobalamin in D_2O yielded methane consisting of 66% CH_3D and 34% CH_4 at pH 7.0. The amount of CH_3D formed depends on a variety of factors. Thus in the presence of some air, only 28% CH_3D formed. A strong pH dependence of the deuterium incorporation was also noted. At pH 4.0 the methane obtained from methylcobalamin contained only 5% CH_3D. At pH 12.5 in D_2O the methane produced consisted of 98% CH_4 and 2% CH_3D. These results indicate that ligand hydrogen abstraction and methyl radical reduction are competitive pH-dependent processes.

Photolysis of Related Methylcobalt Complexes

The methane/ethane ratios observed for all complexes under study at various pH values and other data are summarized in Table III. Methylcobalamin, methyl(pyridine)cobaloxime, and the methyl pyridine derivative of chelate **2** produce comparable amounts of ethane on photolysis. The remaining chelates yield more methane in almost all cases. The most important factors influencing the methane and ethane formation are described below.

Effect of Axial Bases. Since 75% of the total free methyl radicals produced in methylcobalamin photolysis dimerize to ethane, and thus only a small fraction is reductively converted to methane, an attempt was made to increase methyl radical reduction by changing the axial base component. The photolysis of methylcobalamin and of the other methylcobalt chelates was therefore carried out in dilute aqueous solutions of KCN. Cyanide, at low concentration, displaces the 5,6-dimethylbenzimidazole ligand in methylcobalamin without cleaving the Co–C bond. The coordination of the cobalt atom by cyanide increases its electron density and thus should favor the reduction of the methyl radicals to carbanions (eq 2).



(2)

The photolysis of methylcobalamin and of all model compounds in the presence of 0.1 *M* KCN *yields methane to the virtual exclusion of ethane.* The CH_3D formed in the photolysis of methylcobalamin in 0.1 *M* KCN solution in D_2O amounted to 70% (as compared to 2% in solutions of the same pH but without cyanide). Methyl radical reduction was also increased in the photolysis of cyanide containing solutions of methylcobaloxime, although hydrogen abstraction from the ligands is more competitive in this case. Thus at pH 12.5, 15.8% of the total methyl radicals produced in the photolysis of methyl(pyridine)-cobaloxime are converted to CH_3D. At the same pH, but in cyanide–D_2O solution, 29% of all available methyl radicals are recovered as CH_3D. The photolysis of methylcobaloximes with various axial base components gave methane/ethane ratios (summarized in Table IV). Photolysis of a *suspension* of methyl(tri-

Table IV. Effects of Axial Bases on the Methane–Ethane Ratio in the Anaerobic Photolysis of Methylcobaloximes (Mole Per Cent Ratios)

Axial base	Methane/ethane
H_2O[a]	46/54
Pyridine[a]	59/41
Aniline	56/44
Triphenylarsine	48/52
Triphenylstibine	56/44
Cyclohexyl isocyanide	66/34
Triphenyl phosphite	84/16
Benzimidazole	87/13
Triphenylphosphine	100
Tributylphosphine	100
Cyanide[b]	100

[a] In H_2O solution, pH 7 buffer. [b] In 0.1 *M* KCN; all other complexes were irradiated as suspensions in aqueous pH 7 buffer.

butylphosphine)cobaloxime in D_2O afforded mainly methane (99+%) and traces of ethane. The methane

contained 3% CH_3D; hence ligand hydrogen abstraction accounts for most of the methane produced in the photolysis of the insoluble complexes.

Effect of pH. The methane/ethane ratios of the chelates other than cobaloximes are also somewhat pH dependent. The effects are relatively insignificant, however, and will not be discussed further.

Solvent Dependence. The rate of methylcobalamin photolysis has been correlated previously with the homolytic reactivity of the alcohol α-hydrogens assumed to be abstracted by the methyl radicals.[9] Pinacol from the photolysis of solutions of methylcobalamin in isopropyl alcohol has also been observed.[9] Accordingly, we find methane to be the nearly exclusive product of methylcobalamin photolysis in alcoholic solvents. In a 1:1 D_2O–isopropyl alcohol mixture still 25% CH_3D is formed indicating a competition between the reductive and the homolytic process of methane formation. In 1:1 D_2O–acetone mixtures the methane formed contained only 0.2% CH_3D. Deuterium incorporation in 1 *M* solutions of mercaptoethanol in D_2O was 86%. Similar results were obtained with methylcobaloxime as the source of methyl radicals (Table III).

Effect of Ligand Structure. Whereas methylcobaloxime derivatives (with water, pyridine, and a number of other axial bases) yield methane and ethane on photolysis in ratios comparable to methylcobalamin (Tables III and IV), most other cobalt chelates form consistently more methane under the same conditions. The greater tendency of methane formation is evidently caused by the presence of the ethylenediimine and propylenediimine groups, which furnish additional abstractable ligand hydrogen. Deuterium incorporation in the methane is in all cases lower than in methylcobalamin or methyl(pyridine)cobaloxime (Table V).

Table V. Deuterium Incorporation in the Photolysis of Methylcobalt Derivatives of Chelates **1**–**7** in D_2O, pH 7

CH_3Co derivative of chelate no.	Axial base	% CH_3D in CH_4	% CH_3D absolute[a]
Methylcobalamin	Dimethylbenzimidazole	66	11.7
1	Pyridine	22	10
1	H_2O	7	2.1
2	Pyridine	25	5.3
3	H_2O	10	8.9
4	H_2O	7	6.1
5	H_2O	2	1
6	H_2O	2	<1
7	H_2O	~1	<1

[a] Per cent deuterium incorporation per methyl radical converted into methane and ethane.

Methyl Radical Transfer Reaction. Although the slow rate of methylcobalamin photolysis under anaerobic conditions is suggestive of a high rate of recombination, the scavenging ability of the cobalt atom in vitamin B_{12r} has not yet been demonstrated. To verify eq 3, a solution of methylcobaloxime was photolyzed in the presence of an equivalent amount of vitamin B_{12r} at pH 6.5. After irradiation, the reaction solution was examined by paper chromatography. The presence of methylcobalamin could be demonstrated by comparison of the R_f values. The spot of vitamin B_{12a} showed considerable trailing, however, indicating that the reaction of vitamin B_{12r} with the methyl radicals was accompanied by side reactions (hydrogen abstraction). When methylcobalamin was photolyzed in the presence of an equivalent amount of vitamin B_{12s}, photolysis was very rapid and only methane was formed.

$$\underset{\text{methylcobaloxime}}{CH_3\text{–Co}} + \underset{\text{vitamin } B_{12r}}{Co^{II}} \xrightarrow{h\nu} \underset{\text{cobaloxime(II)}}{Co^{II}} + \underset{\text{methylcobalamin}}{CH_3\text{–Co}} \quad (3)$$

Anaerobic Photolysis of Higher Alkylcobalamins and Related Chelates

Ethylcobalt Derivatives. The anaerobic photolysis of ethylcobalamin is faster than that of methylcobalamin, yielding mainly ethylene (99%) with detected traces of ethane and butane. The conversion of the ethyl radical to ethylene is accompanied[10] by a reduction of the B_{12r} produced to the +I state which under the reaction conditions slowly decomposes into vitamin B_{12r} and hydrogen (eq 4).

$$CH_3\text{–}CH_2\text{–Co} \xrightarrow{h\nu} CH_3CH_2\cdot + Co^{II} \longrightarrow CH_2{=}CH_2 + \left\{ (Co^{I})^{\ominus} \underset{H_2O}{\rightleftharpoons} H\text{–Co} \rightleftharpoons Co^{II} + \tfrac{1}{2}H_2 \right\} \quad (4)$$

Ethylene is also the principal photolysis product of all ethylcobalt chelates (Table VI). Some ethane and butane but only traces of ethanol (detected in the liquid phase) are formed. The ethylene/ethane ratio is almost independent of pH. In 0.1 *M* KCN solution, however, consistently more ethane (up to 70% relative to ethylene) is produced. A large increase in the amount of ethane formed is observed in 1 *M* mercaptoethanol. In methanol or 2-propanol solvents the increase in ethane formation is relatively small. Ethylcobalt(salen) is of interest as it reproducibly yields the largest relative amounts of *n*-butane of all the chelates (~10% relative to ethylene). Ethyl(pyridine)-cobaloxime produced 1.6% of butane; the remaining ethylcobalt chelates formed amounts below 1% under the same conditions (H_2O, pH 7). Photolysis of ethylcobaloxime in D_2O gave ethylene consisting of 93% of C_2H_4, 5% of C_2H_3D, 0.9% of $C_2H_2D_2$ and approximately 0.4% of C_2HD_3. This suggests that slow exchange of the ethylene protons occurs with the solvent under the conditions of photolysis.

Joint Photolysis of Methyl- and Ethylcobalamin. The photolysis of a mixed solution of methyl- and ethylcobalamin was studied to obtain evidence for or against the possible abstraction of cobalt-bound ethyl (or methyl) groups, *e.g.*

(9) R. Yamada, S. Shimizu, and S. Fukui, *Biochim. Biophys. Acta*, 124, 195 (1966).

(10) R. Yamada, S. Shimizu, and S. Fukui, *ibid.*, **124**, 197 (1966).

Table VI. Anaerobic Photolysis of Ethylcobalamin and the Ethylcobalt Derivatives of Chelates 1–7[a]

Chelate[b]	pH 4	pH 7	pH 12.5	0.1 *M* KCN	CH_3OH	RSH[c]
Ethylcobalamin	100/0	100/0	100/0	75/25	100/0	40/60
1 (Py)[d]	100/0	97/3	95/5	51/49	92/8	11/89
1 $P(n\text{-}C_4H_9)_3$	88/12	100/0	100/0	70/30	100/0	40/60
2 (Py)	100/0	100/0	100/0	70/30	100/0	40/60
3 (H_2O)	97/3	97/3	96/4	71/29	70/30	38/62
4 (H_2O)	100/0	99/1	99/1	76/24	99/1	40/60
5 (H_2O)	99/1	99/1	89/11	76/24	92/8	40/60
6 (H_2O)	99/1	96/4	96/4	95/5	82/18	10/90
7 (H_2O)	60/40	69/31	70/30	30/70	92/18	10/90

[a] Ethylene/ethane ratio in mole per cent in gas phase, corrected for solubility. Amounts of *n*-butane detected are mentioned in the text but not included here. [b] Numbering of ligands as in Figure 1. [c] 1 *M* mercaptoethanol solution. [d] Axial base component in parentheses.

$$\begin{array}{l} CH_3 \\ | \\ CH_2 \\ | \\ (Co) \end{array} + CH_3\cdot \longrightarrow + CH_3{-}CH_2{-}CH_3 + (Co^{II}) \qquad (5)$$

The experiment was furthermore expected to give information on the relative rate of methyl- and ethylcobalamin photolysis. Propylene, ethane, methane, and ethylene were formed in the molar ratio of 1:0.9:0.65:36.0 (at pH 6.5, unbuffered); no propane was detected. The rate of ethylcobalamin photolysis is thus approximately 15 times that of methylcobalamin under the same conditions. The propylene resulted from the addition of the methyl radical to ethylene and the subsequent dehydrogenation of the propyl radical.

$$\begin{array}{l} CH_3 + C_2H_5 \\ | \quad\quad | \\ (Co) \quad (Co) \end{array} \xrightarrow{h\nu} \begin{array}{l} CH_2{=}CH_2 + \\ [H] + CH_3\cdot \end{array} \longrightarrow \begin{array}{l} CH_2{=}CH_2, \\ C_2H_6,\ CH_4 \\ CH_3{-}CH{=}CH_2,\ [H] \end{array} \qquad (6)$$

Propylcobalt Derivatives. The photolysis of propylcobalamin and the corresponding derivatives of cobaloximes in aqueous solutions gave mainly propylene and little propane, but the cobalt(salen) derivatives yielded propylene (80%) and approximately 10% each of propane and of *n*-hexane. Isopropylcobaloxime afforded propylene, isopropylcobalt(salen) a 3:1 mixture of propylene and propane, respectively. Tetramethylethane was not detected.

Thermal Homolysis

Methylcobalamin decomposes between 215 and 225° yielding approximately equal amounts of methane and ethane. The methane/ethane ratio is time dependent, however, since more methane is formed at early stages of pyrolysis. This suggests that abstractable hydrogen is consumed before methyl radical dimerization becomes significant. In the presence of air more ethane is formed (observed CH_4/C_2H_6 = 13/87). The methylcobalt derivatives of chelates **1–4**, **6**, and **7** yielded mainly methane, but methylcobalt(salen) produced methane plus a significant amount of ethane (Table VII). Ethylene is the main product of ethylcobalamin pyrolysis and of the ethyl derivatives of chelates **1** and **2**. In all other ethylcobalt chelates studied the amounts of ethane formed were consistently greater. The amount of butane was below 1% in all cases except with ethylcobalt(salen), which again yielded a significant amount (~8%) of the radical dimerization product. The pyrolysis of *n*-propylcobalamin and the propylcobalt derivatives of **2** and **3** yielded propylene exclusively.

Table VII. Pyrolysis of Methyl- and Ethylcobalamin and Related Alkylcobalt Chelates, Mole Per Cent Ratios, Observed in Gas Phase (Argon) Pyrolysis, Temperature 200–225°

Chelates	Pyrolysis products[a]: R = methyl Methane/ethane	Pyrolysis products[a]: R = ethyl Ethylene/ethane/butane
Cobalamin	46/54	99/0.5/0.5
1 (Py)	95/5	100/Tr/Tr
1 $(P(n\text{-}C_4H_9)_3)$	100/0	98/2/Tr
2 (Py)	99/1	99/Tr/Tr
3 (H_2O)	100/Tr	93/6/1
4 (H_2O)	100/Tr	92/8/Tr
5 (H_2O)	25/75	80/18/2
6 (H_2O)	100/0	63/37/Tr
7 (H_2O)	100/0	98/2/Tr

[a] Tr, trace.

The formation of *n*-hexane was observed in the case of *n*-propylcobalt(salen). Pyrolysis of the corresponding isopropyl derivative gave only propylene, however, and no tetramethylethane.

Discussion

Reactions of the Methyl Radicals. The four most important reactions of the methyl radicals generated photochemically (excluding the recombination) are shown in Table VIII, together with the approximate relative rates of product formation in H_2O, pH 7. Assuming identical stationary concentrations of methyl radicals in all the experiments, some interesting conclusions concerning the reactions of the radicals with the ligands are possible.

Thus vitamin B_{12} *is the most inert ligand system of all chelates studied* with respect to hydrogen abstraction by photochemically produced methyl radicals. The cobaloximes, in comparison, are somewhat better hydrogen donors, but the chelates **4–7** exceed cobalamins and cobaloximes by far with respect to their relative tendency to undergo hydrogen abstraction. This is due to the presence of the ethylene- and propylenediimine moieties in these systems, which undergo hydrogen abstraction more rapidly than, *e.g.*, the dimethylglyoxime methyl hydrogen.

It is remarkable although probably fortuitous that the photolysis of methylcobalamin and methylcobaloxime yields ethane containing the same amount (~5%) of ligand methyl groups. The four cobaloxime methyl groups and the five allylic corrin methyl groups at C-1, C-7, C-12, and C-17 are available for abstraction, *or the release by another mechanism.* The coin-

Table VIII. Relative Rates of Product Formation in the Anaerobic Photolysis of Methylcobalamin and Methylcobalamin and Methylcobalt Chelates in Water, pH 7

Reaction	Compounds: Methylcobalamin	1(Py)	1(H_2O)	2(Py)	3(H_2O)	4(H_2O)	5(H_2O)	6(H_2O)	7(H_2O)
(a) $CH_3\cdot + \cdot CH_3 \rightarrow C_2H_6$	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
(b) $CH_3\cdot \xrightarrow[(Co^{II}),H_2O]{} CH_4$	0.15	0.18	0.03	0.06	0.8	0.5	0.04	~0.07	~0.1
(c) $CH_3\cdot + (H)_{lig} \rightarrow CH_4$	0.07	0.54	0.33	0.17	8.0	6.0	1.6	3	~10
(d) $CH_3\cdot + (CH_3)_{lig} \rightarrow C_2H_6$	0.05	0.05	*a*	*a*	*a*	*a*			*a*

[a] Not determined.

cidence in the methyl group incorporation suggests that the C–C bond energies are nearly the same in both cases. The rates of methyl radical reduction vary with the nature of the axial base component. In the photolysis of methylcobalamin cyanide causes a significant increase in the amount of methane formed by methyl radical reduction. This is plausibly explained by the effect of the cyanide ion onto the charge density of the cobalt atom. Cyanide or pyridine causes an increase in methyl radical reduction in the photolysis of methylcobaloxime, but the relative rates of ligand hydrogen abstraction increase as well.

Presumably this is because any change in the electron density on the metal also affects the charge density in the ligands, as is evident, *e.g.*, from the dependence of the C=N stretching frequencies[6] of the cobaloxime moiety on the axial base component.

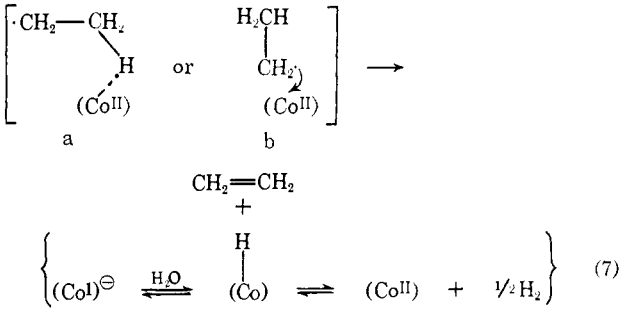
The inertness of the corrin ligand toward hydrogen abstraction suggests that the number of abstractable hydrogen atoms in the molecule is small. Which of the hydrogens are abstracted is not known. The tertiary allylic hydrogen atoms at C-3, C-8, C-13, and C-19 of the corrin ligand would appear to be likely candidates.[8]

The greater relative rates of ligand hydrogen abstraction observed for the chelates **3**, **4**, **5**, and **6** conclusively demonstrate the effect of the secondary hydrogens of the propylenediimine and ethylenediimine groups in the ligands.

At least two additional reactions of methyl radicals are possible and should be mentioned at this point. These are methyl radical trapping by the ligands, and hydrogen abstraction from the methyl group attached to cobalt. Whereas all available evidence suggests that the latter is at best of minor importance, some evidence for methyl radical trapping by the corrin ligand exists.[8] Additional work is required to establish fully the extent of this process. The formation of methane with high deuterium incorporation in the photolysis of methylcobaloximes and methylcobalamin in mercaptoethanol–D_2O solution and the observed abstraction of hydrogen from alcohols or acetone by photochemically generated radicals from methylcobalt chelates are in accord with the known properties of methyl radicals in the presence of thiols or in solvents with labile hydrogen.

The pyrolysis of methylcobalamin and of the methylcobalt chelates produced results which again demonstrate the importance of the ligands as hydrogen donors. Thus methylcobalamin and methylcobalt(salen) both produce the largest relative amounts of ethane. The conspicuous time dependence of the methane/ethane pyrolysis ratio (methane is mainly formed in the early stages of pyrolysis of methylcobalamin) is evidently again a consequence of the small number of abstractable hydrogen atoms in the corrin.

Reactions of the Higher Cobalt Alkyl Complexes. The ionization potential of the ethyl radical (−8.76 eV) is lower than that of methyl (−9.93 eV).[11] Accordingly, ethyl radicals reduce vitamin B_{12r} or cobaloximes(II) to the univalent state, whereas methyl radicals partly oxidize the Co(II) complexes to the Co(III) derivatives. The first ionization potential of the cobalt(II) ion in vitamin B_{12r} and the cobaloximes(II) thus must be between −8.7 and −9.9 eV. The ethyl radical is oxidized to ethylene, a reaction which could either be a metal-assisted hydrogen abstraction or a concerted electron transfer deprotonation (eq 7).



(7)

The observed deuterium incorporation into the ethylene on photolysis of ethylcobaloxime in D_2O indicates that reaction 7 is partially reversible. Whereas we favor 7b, a distinction between the two mechanisms (7a and 7b) is probably immaterial since both could take place simultaneously. Photolysis of the ethylcobalt compounds in the presence of cyanide ion evidently affects the Co(II) complex ions sufficiently to yield increased amounts of ethane, although ethylene production is still extensive. A part of the ethane probably arises from ethyl radical reduction and disproportionation, but most of it from ligand hydrogen abstraction. Oxidation of ethyl radicals to carbonium ions is not important (alcohol formation is negligibly small in all cases, as evidenced from the analysis of the photolysis solutions). This contrasts the observed behavior of alkyl radicals in the presence of oxidizing metal ions such as Cu^{2+},[12a] where ethanol is the main product.

(11) Values taken from A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(12) (a) H. E. De La Mare, J. K. Kochi, and F. F. Rust, *J. Am. Chem. Soc.*, 85, 1437 (1963). (b) The Co(II)/Co(I) reduction potentials of cobalt complexes may be used as another criterion for the classification of cobalamin model compounds. The potentials of chelates **1–4** are close to that of the vitamin B_{12r}/B_{12s} couple (~−0.60 V in the presence of 1 atm of H_2 and a platinum catalyst). The potentials of chelate **5–7** are ≥−0.8 V; they are therefore more difficult to reduce to the Co(I) nucleophiles (see Experimental Section) than cobalamins or cobaloximes.

Ethyl radical dimerization to *n*-butane occurs only to a minor extent in most cases but is significant in the photolysis and pyrolysis of ethylcobalt(salen). This is indicative of the relative inertness of the cobalt(salen) system to ethyl radicals, and of the high Co(II)/Co(I) reduction potential.[12b]

Homolysis of *n*-propylcobalt(salen) similarly afforded some *n*-hexane (in addition to propylene and propane). The isopropyl derivatives of cobaloxime and of cobalt(salen) both yielded only propylene in photolysis and pyrolysis. Oxidative deprotonation of the isopropyl radical is clearly favored over all other processes due to its low ionization potential (−7.89 eV).

Summary

Alkyl radicals generated in the photolysis or pyrolysis of alkylcobalamins, alkylcobaloximes, or the cobalt alkyl derivatives of Schiff base chelates undergo subsequent termination reactions depending on the ligands, the axial bases, the solvent, and the nature of the radical involved. Although all model chelates showed some similarities to the alkylcobalamins, the cobaloximes displayed analogies to a degree not shared by any of the other model compounds studied.

Experimental Section

Synthesis of the Alkylcobalt Compounds. All alkylcobalamins were synthesized according to eq 8 using $NaBH_4$ as the reducing agent. The alkyl derivatives of the cobaloxime chelates **1–3** are

$$(Co^{III}) \xrightarrow{2e\ (NaBH_4)} (Co^{I})^- \xrightarrow[(H_2O)]{R-X} \overset{R}{\underset{|}{(Co)}} + X^- \qquad (8)$$

accessible under the same conditions.[4-7,13] However, the analogous compounds of chelates **4–7** could at first not be obtained in protic solvents, since the Co(I) nucleophiles of these chelates do not form under conditions normally employed for the reduction of vitamin B_{12} or the cobaloximes. The reduction and subsequent alkylation were possible in nonaqueous media, *e.g.*, in diglyme or pyridine, using sodium amalgam as the reducing agents.[14-16] This behavior is reminiscent of that displayed by cobalt porphyrins, which similarly cannot be reduced to the Co(I) state in aqueous solvents.[17] This, however, is simply due to the higher Co(II)/Co(I) reduction potential of these complexes, which causes the instability of the Co(I) nucleophiles in neutral or mildly alkaline solutions.[18,19]

Accordingly, the reduction of the chelates **5–7** is possible under *alkaline conditions*. The cobalt(salen) derivatives **5** and **6**, for example, are reduced to the Co(I) state only at the pH of at least 13. Under the conditions normally employed for cobaloxime reduction, hydrogen evolution is observed and formation of the Co(I) nucleophiles does not take place. Sodium borohydride–palladium and Raney nickel alloy are useful reducing agents. Sodium borohydride alone, or hydrogen (the latter even in the presence of noble metal catalysts), proved ineffective. Reduction of chelate **4** is already possible at pH ~10, even with hydrogen. Reduction of **7** is incomplete even at pH ≥13. However, the amount of Co(I) derivative produced is sufficient to permit the synthesis of alkylcobalt derivatives of this chelate.

Methyl- and Ethylcobalt Derivatives of Chelate 4. A solution of 60.0 g of butanedione monoxime and 18.0 g of ethylenediamine in 1 l. of benzene was boiled under reflux for 1 hr. The water from the reaction was collected as formed in a Dean–Stark trap. The product, bis(butanedione monoxime)ethylenediimine, precipitated on cooling and was recrystallized from ethanol. To a solution of 11.2 g (0.05 mol) of the above ligand with 11.9 g of $CoCl_2 \cdot 6H_2O$ in 300 ml of methanol there was added 8.0 g (0.1 mol) of 50% NaOH solution under nitrogen. After 10 min a solution of 8.0 g of 50% NaOH and 1.0 g of $NaBH_4$ in 30 ml of water was added. The solution turned deep blue. Subsequently, 15 g of methyl or ethyl bromide (dissolved in 50 ml of ethanol) was added. The blue color of the solution was discharged within a few seconds and the solution was filtered. After adding 10 ml of acetone (to destroy excess $NaBH_4$) the filtrate was diluted with 1 l. of water. To one-tenth of this solution there was added 1.0 g of sodium tetraphenylboron in 50 ml of water. The complex tetraphenylboronate was collected by filtration and washed with water.

Anal. Calcd for CH_3–Co(Lig)·$H_2O^+B(C_6H_5)_4^-$, $C_{34}H_{39}N_4O_3BCo$: C, 65.70; H, 6.33. Found: C, 65.65; H, 6.56. *Anal.* Calcd for C_2H_5–Co(Lig)·$H_2O^+B(C_6H_5)_4^-$, $C_{35}H_{41}N_4O_3BCo$: C, 66.10; H, 6.51. Found: C, 66.05; H, 6.50.

Alkyl Derivatives of Cobalt(salen) (5). To a solution of 14.4 g (0.2 mol) of salicylaldehyde in 800 ml of methanol there was added 6.0 g (0.1 mol) of ethylenediamine followed by 23.8 g (0.1 mol) of $CoCl_2 \cdot 6H_2O$. After the cobalt salt had dissolved, 16.0 g (0.2 mol) of 50% NaOH solution was added under nitrogen. There was next added a solution of 30.0 g of 50% NaOH and 2.0 g of $NaBH_4$ in 50 ml of water, followed by 2 ml of a solution of 2% $PdCl_2$ in 1 *M* KCl. After 5 min the solution was green and the cobalt(salen)(II) had dissolved. Upon the addition of 20 ml of methyl iodide the green color was promptly discharged. After 10 min of stirring the reaction mixture was filtered. The filtrate, on dilution with water, afforded black crystals of methyl(aquo)cobalt(salen), yield 20.6 g (56%).

By the same procedure a number of alkyl- and substituted alkylsalcomins have been prepared (Table IX).

Methyl- and Ethylbis(salicyladehyde)ethylenediiminecobalt (Chelate 6). Salicyladehyde (14.4 g, 0.2 mol) was dissolved in 250 ml of methanol. Propylenediamine (7.4 g) dissolved in 500 ml of methanol was added dropwise under stirring. To the yellow solution of the ligand 24.0 g of $CoCl_2 \cdot 6H_2O$ (0.1 mol) was added and stirring was continued until all of the cobalt salt dissolved. Next 16 g of 50% NaOH solution was added. After 10 min of stirring under argon an additional 25 g of 50% NaOH solution was added and stirring was continued until no further color change of the brown solution was observed (approximately 10 min). To the solution of the chelate, 1 g of $NaBH_4$ dissolved in 10 ml of methanol was added, and the reduction was initiated by adding 5 ml of 2% palladium chloride solution. The reaction mixture turned green, whereupon 15 ml of methyl iodide (or 10 ml of ethyl bromide) was added, and stirring under argon was continued for 5 min. After filtration, the reaction solution was diluted with the twofold volume of water, and the product precipitated. It was collected by filtration, washed with water, and dried under vacuum. Both complexes begin to decompose on heating above 180°, and lose H_2O on drying.

Anal. Calcd for the methyl derivative, CH_3–Co(Lig)·H_2O, $C_{18}H_{21}N_2O_3Co$: C, 58.07; H, 5.69. Found: C, 58.45; H, 5.47%. *Anal.* Calcd for the ethyl derivative, C_2H_5–Co(Lig)·H_2O, $C_{19}H_{23}N_2O_3Co$: C, 59.07; H, 6.00. Found: C, 58.60; H, 6.00.

Methyl and Ethyl Derivatives of Bis(acetylacetone)ethylenediiminecobalt (7). Bis(acetylacetone)ethylenediimine was prepared according to Martell, Belford, and Calvin[20] and recrystallized from toluene. To 350 ml of methanol 2.24 g of the ligand and 2.38 g of $CoCl_2 \cdot 6H_2O$ were added. The reaction mixture was stirred under argon until all had dissolved. Subsequently, 1.6 g of 50% NaOH solution dissolved in 10 ml of methanol was added, followed after 5 min by another 4.1 g of 50% NaOH solution in 15 ml of methanol. $NaBH_4$, 1 g, in 10 ml of H_2O and then 2 ml of 2% $PdCl_2$ solution were added and stirring was continued until the solution turned dark brown. At this point 4 ml of methyl iodide or ethyl bromide was added (all operations under argon). Stirring was continued for 15 min. Next, 10 ml of acetone was added and the reaction solution filtered. After the addition of 500 ml of water the solution was allowed to stand in a refrigerator for 10 hr. The solid residue was collected and redissolved in 30 ml of benzene. After filtration the solution was evaporated at room temperature in a stream of nitrogen, affording orange crystals which partially turned green due to loss of the axially bound water. The complexes were identical with those obtained by reductive alkylation in anhydrous medium.

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Table IX. Analyses of Alkylcobalt Derivatives of Cobalt(salen), by Alkylation in Aqueous Medium

Alkyl group	Axial base	Formula	Calcd, % C	Calcd, % H	Calcd, % Co	Found, % C	Found, % H	Found, % Co
CH_3	H_2O	$C_{17}H_{19}N_2O_3Co$	57.11	5.62		57.05	5.66	
C_2H_5	H_2O	$C_{18}H_{21}N_2O_3Co$	58.07	5.69		58.21	5.70	
n-C_3H_7	H_2O	$C_{19}H_{23}N_2O_3Co$	59.07	6.00	15.25	58.83	5.91	14.87
i-C_3H_7	H_2O	$C_{19}H_{23}N_2O_3Co$	59.07	6.00	15.25	59.12	5.91	15.10
$CH_2C(CH_3)_3$	H_2O	$C_{21}H_{27}N_2O_3Co$	60.88	6.57	14.22	60.84	5.52	14.61
$CH{=}CH_2$	Py	$C_{23}H_{22}N_3O_2Co$	64.04	5.15	13.66	63.88	5.01	13.37
CH_2Cl	H_2O	$C_{17}H_{18}N_2O_3Co$	51.99	4.62	15.01	52.18	4.56	14.79

Photolysis Procedure. Solutions of the alkylcobalt complexes containing 10–20 mg of the crystalline solids in 1.5 ml of water or buffer solutions (Clark and Lubs) were prepared in test tubes which were sealed off with rubber serum caps. They were made anaerobic by first evacuating them with an oil pump and permitting the solution to boil. Subsequently the tubes were filled with argon (99.998% purity) to about 5 lb above atmospheric pressure. The photolysis light source was two 150-W GE projector spot lamps which were placed at a distance of 20 cm from the sample tubes. During the illumination a stream of cold air was blown over the tubes to prevent the temperature of the solutions rising above 35°. The time of irradiation was varied between minutes and days, depending on the compounds and their photolysis rate. In the case of methylcobalamin and methylcobaloxime a study of the time dependence of the methane–ethane production ratio on photolysis was undertaken, but no significant change was noted over a period of 24 hr of irradiation under these conditions. If the solubility of the samples was insufficient, suspensions of the finely powdered compounds were made. The sample tubes containing the suspensions were mechanically shaken during the photolysis.

Pyrolysis Experiments. Unless indicated otherwise, all samples were placed into test tubes, covered with serum caps, and made anaerobic as described above. The thermal decomposition was carried out by placing the sample tubes into a thermostatically controlled oil bath at temperatures between 215 and 225°.

Identification of Products. The photolysis and pyrolysis products were analyzed by gas chromatography utilizing a $^1/_8$ in. × 5 ft Poropak Q column at a helium flow rate of 25 cc/min, and a flame ionization detector. Excellent resolution was obtained by running isothermally (at 65°) for 2–5 min and then programming at a 15° temperature increase per minute to 170°. Under these conditions the following retention times were observed (in seconds): methane, 0; ethane, 70; propane, 280; n-butane, 495. The relative molar concentrations were obtained by comparing peak heights with a standard gas mixture. All results are given in relative mole per cent.

Joint Photolysis of Methylcobaloxime and Vitamin B_{12r}. Vitamin B_{12a} (10 mg, 5 ml of water) was treated with 15 mg of $NaBH_4$ under argon. Acetic acid (two drops) was added and the solution was allowed to stand until H_2 evolution ceased. Next there was added 10 mg of methyl(pyridine)cobaloxime. The solution was irradiated and shaken for 2 hr under argon. Paper chromatography of the reaction solution on tlc showed the presence of vitamin B_{12a} and methylcobalamin by comparison of the R_f values with authentic samples (solvent: butanol–2-propanol–water–acetic acid (100:100:100:3)).

Mass spectrographic analyses were performed at Shell Development Co., Emeryville, Calif., using a quadrupole mass spectrograph (EAI Quad 300). Prior to measurement the gases were absorbed on a Poropak column.

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Photochemical and Thermal Reduction of Cerium(IV) Carboxylates. Formation and Oxidation of Alkyl Radicals

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Abstract: The photochemical and thermal reduction of Ce^{IV} carboxylates to Ce^{III} proceed by decarboxylation and liberation of alkyl radicals. Alkanes are subsequently formed by hydrogen transfer, and alkenes, together with esters, result from oxidation of alkyl radicals by Ce^{IV}. n-Propyl and isopropyl radicals primarily afford propane, whereas t-butyl radicals are oxidized to isobutylene and t-butyl esters. The mechanism of the oxidation of alkyl radicals by Ce^{IV} is discussed. Quantum yield measurements show that photochemical homolysis of Ce^{IV} carboxylates is an efficient process. The thermal and photochemical reactions are otherwise equivalent. Alkyl radicals can be trapped with oxygen, chloroform, or Cu^{II}. If excess oxygen is employed a catalytic decarboxylation of pivalic acid occurs. Strong acids accelerate both the thermal and photochemical reduction of Ce^{IV}. Cationic carboxylatocerium(IV) species which are labile to homolysis and readily reduced by alkyl radicals are postulated as the reactive intermediates in the presence of acid.

Cerium(IV) salts have been widely employed as strong oxidants in aqueous solutions.[1] Cerimetry is a well-established analytical technique, since a variety of inorganic species as well as organic functional groups are readily oxidized.[2] The photochemical reduction of Ce^{IV} salts, particularly sulfate, perchlorate, and nitrate, in aqueous solutions has also

(1) For a pertinent review, see W. Richardson, "Oxidations in Organic Chemistry," K. Wiberg, Ed., Academic Press, New York, N. Y., 1965, Chapter 4.

(2) G. Smith, "Cerate Oxidimetry," G. F. Smith Chemical Co., 1942.