

Methylation of Quinones by Methylcobalt Complexes in the Presence of Palladium Salt

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Methylation of 1,4-quinones by methylcobalt complexes has been studied in the presence or absence of some metal salts. Methylcobaloximes were found to afford mono-methylated quinones though the yield was very small in the absence of metal salts. The transmethylation was, however, remarkably promoted in the presence of transition metal salt such as Pd(II) and reached nearly 70% at the highest.

Methylcobalamins were also found to methylate 1,4-quinones to a slight extent but no promoting effect was recognized with Pd(II) probably due to complexing side reactions. Nevertheless, the observations may indicate that methylcobalt complexes act as methylating reagents not only for mercuric salts but also for organic compound such as 1,4-quinones. Reaction mechanisms are briefly discussed.

Much attention has been drawn to the similarity of the Co-C bond in the Co-alkyl derivatives of several model compounds of vitamin B₁₂ to that in alkylcorrinoids. Transalkylation, therefore, to some compounds such as Hg (II) by the complexes has been a subject of current interest in relation to the role of vitamin B₁₂ group in biological systems.²⁻⁴⁾

We were much concerned with the possible cleavage of the Co-C bond by organic compounds. Previously, only two kinds of chemical cleavage of the Co-C bonds in the methylcobalamin and in the model compounds by strong organic nucleophiles were studied: the cleavage by mercaptide anions as exemplified by the S-methylation of homocysteine to afford methionine, and that by an alkyl amide anion leading to N-methylation. Recently, however, the transmethylation to olefins by methylcobalamin as well as some corresponding model complexes in the presence of Pd (II) salt has been briefly reported.^{5,6)} Thus C-methylation of organic compounds has also become an object of interest.

After some preliminary survey, quinones were found to be C-methylated in the absence or presence of some additive such as Pd (II) by the Co-methyl derivatives of cobaloxime. Preliminary part of this work has been reported already,⁷⁾ and we wish to report in this paper the details of work.

Experimental

Materials—Methylbis(dimethylglyoximate)cobalt(III), methylbis(diacetylmonoxime-imino)-1,3-propanecobalt(III), and methylcobalamin were prepared respectively according to the reported methods.^{8,9)} *p*-

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Benzoquinone (supplied by Wako), 1,4-naphthoquinone (Tokyo Kasei) were employed as the substrates after sublimation in vacuum. PdCl_2 (Engelhard) was used as either $1.5 \times 10^{-1} \text{M}$ LiPdCl_3 solution in acetonitrile or $3 \times 10^{-1} \text{M}$ Li_2PdCl_4 solution in methanol after Heck's method.⁹⁾ Methyl substituted quinones were synthesized after Fieser¹⁰⁾ when required for the identification of products. All the other reagents were commercial.

Methylation of Quinones—Reactions were carried out usually in a mixture of equivalent volume of anhydrous acetonitrile and methanol (10 ml) in a tinted vessel equipped with a reflux condenser. A given methylcobalt complex (0.5 mmole) plus *p*-benzoquinone (BQ) (1 mmole) or 1,4-naphthoquinone (NQ) (1 mmole) were dissolved, and they were allowed to react under a nitrogen atmosphere at $40\text{--}50^\circ$ for 1–5 days in the dark. After the reactions, the solution was concentrated to ca. 1–2 ml and filtered. All the filtrates were subjected to gas-liquid chromatographic analysis (GLC).

Reactions were carried out also in the presence of some metal salts. To the mixed solution (10–25 ml) of LiPdCl_3 and Li_2PdCl_4 (total 1.5–4.5 mmole), the complex (0.5 mmole) plus either NQ (1–10 mmole) or BQ (1 mmole) were added, and the resultant solution was allowed to react under a nitrogen atmosphere or aerobically at $0\text{--}40^\circ$. Commercial Ni(II), Fe(III), Ag(I) and Cu(II) salts were also subjected to tests.

Reactions were carried out also under irradiation using a 200 W tungsten lamp from a distance of ca. 20 cm under a nitrogen atmosphere. The resultant mixtures were concentrated, filtered and analyzed as above.

With the use of methylcobalamin: Reactions were carried out in the dark under aerobic conditions.

1) To methanolic solutions (ca. 1 ml) of methylcobalamin (20 μmole), NQ or BQ (80 μmole each) were added and allowed to react at 50° . The samples for GLC were obtained by treating the reaction mixtures as already mentioned. 2) Reactions in the presence of Pd(II). To a methanolic solution (ca. 2.5 ml) of methylcobalamin (50 μmole), solutions (1.5 ml) of the two Pd(II) salts (total 300 μmole) and NQ (100, 200 and 400 μmole each; the latter two are cumulative amounts due to the addition in increment to the previous systems) were added, and allowed to react at room temperature. In the case of BQ, the molar ratio of methylcobalamin: BQ: Pd(II) were 1: 4: 6 based on 20 μmole of the methylcobalamin, and the reaction was carried out at 50° under otherwise identical conditions with above. The reaction mixture was considerably concentrated and subjected to GLC.

Analytical Procedure—Shimadzu gas chromatograph, Model GC-1B, equipped with flame ionization detector (FID) and a glass column (ϕ 4 mm \times 1.8 m) was used to analyze reaction products. Packings used for the identification of products were 20% Apiezon grease L on Celite 545 (30–60 mesh), 10% Silicone DC 550 on Flusin T6 (30–60 mesh), 2% Silicone XF 1105 on Gaschrom-Z (60–80 mesh) or 10% Silicone DC 11 on Unipor B (60–80 mesh).

Hitachi recording spectrophotometer, Model ESP-3T was employed to investigate the nature of interaction among methylcobalt complex, quinones and metal salts added.

Results and Discussion

As already mentioned, transmethylation reactions were investigated with respect to three kinds of methylcobalt complexes; these were methylbis(dimethylglyoximate)cobalt(III), methylbis(diacetylmonoxime-imino)-1,3-propanecobalt(III) and methylcobalamin. Because of no significant difference in the results obtained between the two former complexes, we shall describe our investigations for simplicity with "methylcobaloximes" and methylcobalamin, respectively.

Methylcobaloxime

Methylation reactions of 1,4-benzoquinone (BQ) and 1,4-naphthoquinone (NQ) were investigated in $\text{CH}_3\text{OH}\text{--}\text{CH}_3\text{CN}$ solution around 40° . Axial ligand such as imidazole, pyridine or triphenylphosphine was employed to investigate whether "*trans* effect" could be operative or not in this kind of transmethylation reaction.

No methylated products were detected, in the case of BQ, by FID gas chromatography whereas a very small amount ($\sim 1\%$) of 2-methyl-1,4-naphthoquinone, vitamin K_3 (designated as VK_3) was formed from NQ. When methylating agents such as CH_3I and $(\text{CH}_3)_2\text{SO}_4$ were substituted for methylcobaloxime, no methylated product was detected. The formation of VK_3 , even though its yield was very low, was confirmed also in another solvent such as $\text{CH}_3\text{CH}_2\text{OH}$.

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The rate of transmethylation seemed quite fast because the yield did not change from several minutes to days. In spite of the low yield, the formation of VK_3 would bear great significance with regard to the C-methylation of organic compound. Furthermore, when Pd (II) salts were added to the reaction system, VK_3 as well as the methylated product of BQ, namely, toluquinone (TQ) was found to yield to a remarkable extent. Some typical results are illustrated in Table I.

TABLE I. Reactions of Methylcobalt Complexes with Quinones in the Presence of Pd (II)

| Complex | Axial base | Molar ratio $CH_3(Co) : NQ : Pd (II)$ | Solvent MeCN: MeOH | Temp. (°C) | Time (hr) | Yield of VK_3 or TQ (mole %) ^{a)} |
|---------------------------|------------|--|-----------------------|---------------|--------------|---|
| I | H_2O | 1 : 2 : 3 | 1:1 | 0—40 | 24 | 28 |
| | Im | 1 : 2 : 3 | 1:1 | 0—40 | 24 | 30 |
| | Py | 1 : 2 : 3 | 1:1 | 0—40 | 24 | 30 |
| | $P\phi_3$ | 1 : 2 : 3 | 1:1 | 0—40 | 24 | 20 |
| | Im | 1 : 2 : 3 | 10:2 ^{b)} | 40 | 16 | 30 |
| | Im | 1 : 2 : 3 | 10:2 | 40 | 16 | 25 |
| | Im | 1 : 2 : 6 | 3:1 | R.T. | 24 | 40 |
| | Im | 1 : 2 : 6 | 3:1 | R.T. | 24 | 43 |
| $CH_3(Co) : BQ : Pd (II)$ | | | | | | |
| I | Im | 1 : 2 : 3 | 1:1 | 40 | 24—72 | 4 |
| II | Im | 1 : 2 : 3 | 1:1 | 40 | 48 | 3 |

complex I: methylbis(dimethylglyoximate) cobalt(III)

complex II: methylbis(diacetylmonoxime-imino)-1,3-propane cobalt(III)

a) counted per initial moles of $CH_3(Co)$

b) H_2O was present.

Because of the drastic effect of Pd(II) salts on the transmethylation reactions, we have further investigated the reaction characteristics in the presence of Pd(II).

(1) **Effect of the Axial Bases**—As shown in Table I, the cobaloximes with aquo, imidazole, and pyridine bases gave VK_3 in much the same yield, while that with triphenylphosphine base in lower yield. Apart from the probable replacement of the aquo base by acetonitrile in the mixed solvent used, the cause of no reactivity difference among the methylcobaloximes with the nitrogenous bases and an aquo base was studied by electronic absorption spectroscopy, the imidazole complex being taken as an example.

The imidazole complex exhibited a weak broad band around 440 nm attributed to the charge-transfer absorption characteristic of the Co- CH_3 group, while the tetrachloropalladate showed a band at 436 nm. When the two were mixed, new and rather strong bands at 443 nm and 384 nm were observed. On the other hand, the aquo complex showed the identical band at 443 nm with that of the imidazole complex-Pd(II) system. Thus, displacement of the imidazole from the Co atom by Pd(II) could be postulated. This postulation is supported by the observation of the identical band at 443 nm shown by the imidazole complex-hydrochloric acid system in which the imidazole is no doubt displaced from the coordination as the protonated form.

Now, the band at 384 nm exhibited by the imidazole complex-Pd(II) system is, as was expected, attributed to the absorption by the displaced imidazole-Pd(II) complex, as evidenced by the identical band shown by imidazole-Pd(II) system.

In the case of the pyridine complex, similar phenomena were observed except the 443 nm band was observed in CH_3OH , whereas in the case of the triphenylphosphine complex, no such phenomena were observed.

Consequently, it is concluded that the methylcobalt complexes with the nitrogenous bases change primarily into the aquo complex-like species on interaction with the Pd(II) as a result of the displacement of the bases from the coordination. "Trans effect" therefore was not clear in the presence of Pd(II).

(2) **Effect of Pd(II) Concentration**—The higher Pd(II) concentrations were the more VK₃ was formed. Such effect is shown for NQ in Fig. 1 where R denotes the molar ratios of varying amounts of Pd(II) to a fixed amount of methylcobaloxime.

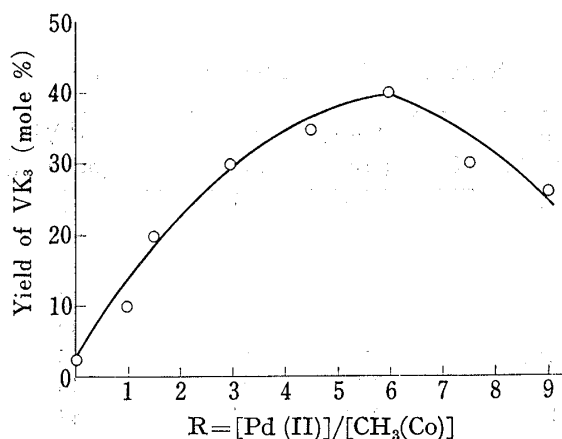


Fig. 1. Effect of Pd(II) Concentration on the Yield of VK₃

NQ: CH₃(Co)=2:1 reaction time: ca. 5 min

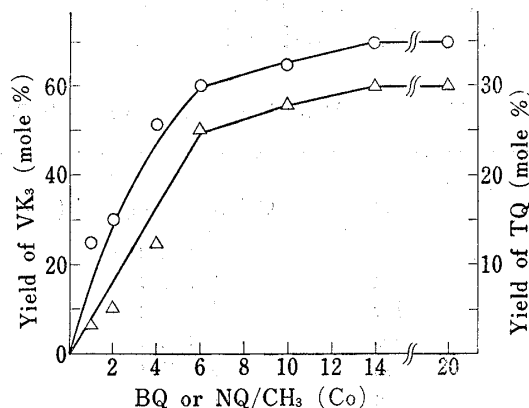


Fig. 2. Effect of Quinone Concentration on the Yield of VK₃ or TQ

reaction time: ca. 5 min
 —○—: VK₃, —△—: TQ
 Each yield was obtained from a competitive run using NQ plus BQ simultaneously.

As shown in Fig. 1, the yield of VK₃ increased with increasing R's, reaching the maximum of ca. 40% at R=6; on the contrary, however, higher R's than 6 unexpectedly depressed the yield.

(3) **Effect of Quinone Concentration**—The effect of quinone concentration was studied primarily in expectation of catalysis with respect to Pd(II) like in certain other reactions.¹¹⁾ When Pd(II) was used in very small amounts, no meaningful effect of quinone concentration was found. Thus, the effect of varying concentration of quinone was studied at R=6, and the results are shown in Fig. 2.

The yields of VK₃ and TQ increased remarkably with increasing quinones; amounting respectively to the maxima of ca. 70% and ca. 30% at NQ or BQ/CH₃(Co)=14, over which they maintained plateau.

Effect of some other metal salts was also studied on the yield of VK₃, and the results are shown in Fig. 3.

Among them, only Ni (II) exhibited a little promoting effect on the reaction, whereas CuCl₂ decreased the yield almost to none contrary to expectation. Consequently, Pd (II) was the most effective agent and promoted the transmethylation considerably, while Ni (II) was much inferior to Pd (II), and others were ineffective at all. Thus, the application of Pd (II) salt as a very effective additive has been shown to be extensible at least to the methylation of quinones, leading to a novel and convenient route to the synthesis of methyl substituents of quinones.

Previously, the formation of VK₃ by the reaction of methylcobalamin with NQ under photoirradiation was briefly reported, other conditions being unspecified.¹²⁾ Also the formation of TQ by the reaction of the methylcobalamin with BQ under anaerobic irradiation was merely suggested in another report.¹³⁾

Therefore, the transmethylation reactions were investigated under photoirradiation with methylcobaloximes. The results are shown in Table II.

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

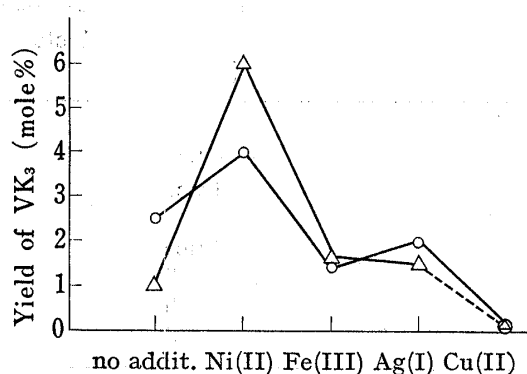


Fig. 3. Effect of Metal Salt added on the VK₃ Yield

CH₃(Co): NQ: metal salt=1: 2: 6

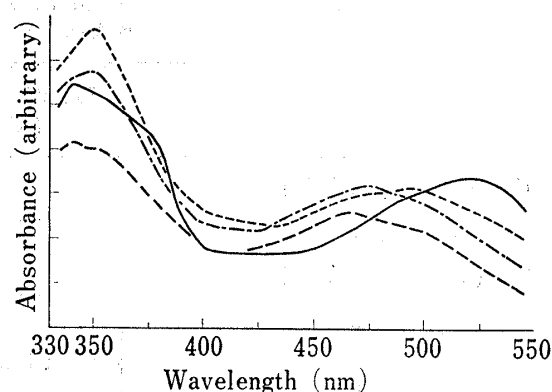


Fig. 4. Spectral Changes of Methylcobalamin upon interacting with Pd(II) in Methanol

—: methylcobalamin
 ---: soon after mixing with Pd(II)
: after 1 hr
 - · - · -: after 24 hr

TABLE II. Photochemical Reactions of Complex I (Py) with Quinones under N₂

| Molar ratio | Solvent | Light source | Temp. (°C) | Time (hr) | Yield (mole %) |
|-------------------------------------|---------|-------------------|------------|-----------|-----------------------|
| CH ₃ (Co)Py: NQ 1 : 1 | benzene | W lamp (200 W) | 50 | 8 | VK ₃ ca. 1 |
| CH ₃ (Co)Py: BQ 1 : 1 | | | | | TQ ca. 4 |

The reactions respectively afforded VK₃ and TQ as was expected though the yields were very small.

Methylcobalamin

To compare the reactivity of methylcobalamin with that of methylcobaloxime, trans-methylation reactions were investigated with respect to methylcobalamin under nearly identical conditions with the methylcobaloxime case. The results are summarized in Table III.

In the absence of any additive, the reactions afforded only a trace amount of VK₃ instantaneously from NQ under aerobic conditions, while no TQ was perceptible from BQ. On the other hand, in the presence of Pd (II) salt, there was a certain trend as to the formation of TQ and VK₃ although their yields were still very poor.

To examine the cause, the electronic absorption spectra were studied on the methylcobalamin-Pd (II) system.

As shown in Fig. 4, when a mixture of each solution of them was recorded soon after the mixing in the dark, new absorption bands appeared at 351 and 468 nm while the bands at 340 and 522 nm, attributed to the cobalamin, disappeared to a certain extent. As time elapses, the former absorption became strong, while the latter band shifted to 472 and finally to 496 nm. On standing the solution further, precipitates were formed.

In the cobalamin, apart from the Co-bound methyl group, there are three possible complexing moieties, namely, the benzimidazole, amides in the side chains, and the orthophosphate. In the presence of Pd (II), the benzimidazole would be displaced from the coordination as a result of complexing with Pd (II) and the amides might also complex with Pd (II), whereas

TABLE III. Reactions of Methylcobalamin with Quinones in the Absence or Presence of Pd(II) in MeOH

| Reactants (molar ratio) | Reaction temp. (°C) | Monomethylated products (mole %) |
|---|------------------------|-------------------------------------|
| CH ₃ (Co) : BQ : Pd (II) 1 : 4 : 0 1 : 4 : 6 | 50 | not detected trace |
| CH ₃ (Co) : NQ : Pd (II) 1 : 4 : 0 1 : 2 : 6 1 : 4 : 6 1 : 8 : 6 | 50 } room temp. | trace 5 5 8 |

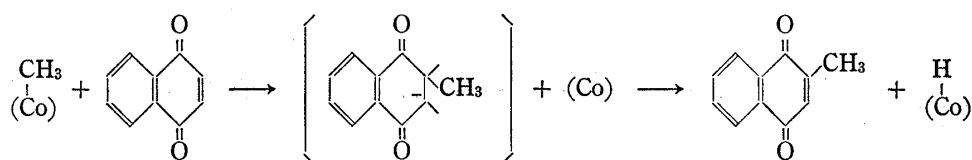
reaction time: ca. 5 min

such behavior by the orthophosphate is the least considered. Such speculation is supported by similar observations in cyanocobalamin-Pd (II) system.¹⁴⁾

Therefore, although the cause of the very low reactivity cannot be elucidated, an explanation for it would be that the complexations might take place before the Co-C bond was cleaved, which might bring about the increased stability of the Co-C bond.

Possible Mechanisms. Studying the demethylation of methylcobalamin in the presence of Hg (II) salts, we have proposed that HgL⁺ attacks the cobalt-carbon bond¹⁵⁾ leading to the cleavage of the bond. In other words, the methyl acceptor was considered to act as a Lewis acid. Since quinones are known also to be soft Lewis acids, it seems likely that quinones may attack the Co-C bond as electrophile, leaving the Co moiety in the trivalent oxidation state. On elimination of the hydride from the intermediate adduct, the product will be formed. This kind of reaction scheme is illustrated in the Chart 1.

no additive :



with Pd(II) :

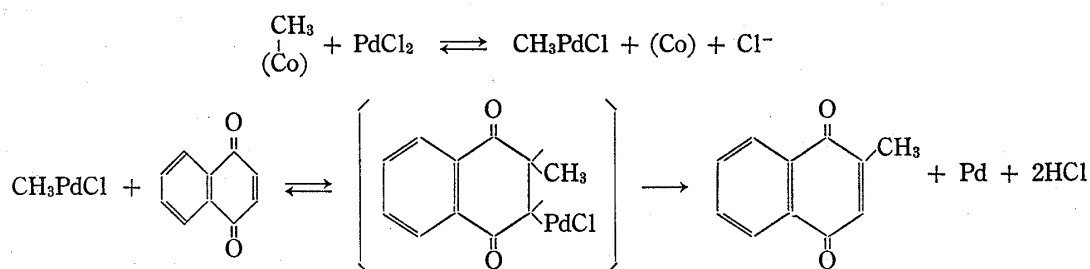


Chart 1. Possible Reaction Pathways for Transmethylation

As to the promoting effect exerted by Pd (II), methylpalladium intermediate could be postulated. Studying the demethylation reactions of methylcobalamin spectrophotometrically, Yamamoto has actually found that the reactions were promoted in the presence of Pd (II).¹⁶⁾ The finding may strongly support the postulation that the overall transmethylation proceeds

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via methylpalladium intermediate. The methylation of quinones in the presence of Pd (II) is also schematically illustrated. When methyl radicals are generated from the complex upon photoirradiation, part of them may add to quinone, because the latter is well-known to be radical acceptor.

The results of the reaction in the absence of any additive might give a biochemical implication on the possible direct C-methylation unknown thus far of some substrates leading to the methylated products such as mitomycin, an antibiotic having quinone ring and produced in certain bacteria which have B₁₂-dependent methionine biosynthesis system, by methylcorrinoids *in vivo*.

On the other hand, those in the presence of Pd (II) might give another biochemical implication of the probable transmethylation to some substrates *via* biocatalyst.

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