Electrochemical Methyl-transfer Reaction to Alkylthiol Catalyzed by Hydrophobic Vitamin B_{12}

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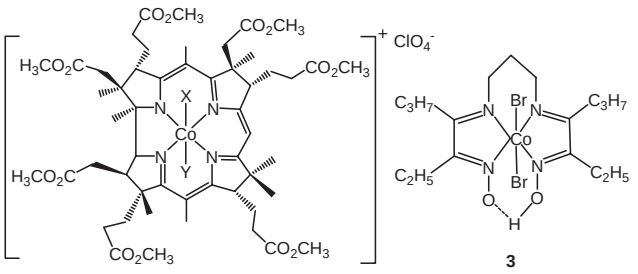
The catalytic methyl-transfer reaction from methyl tosylate to 1-octanethiol was carried out in the presence of heptamethyl cobyrinate perchlorate, hydrophobic vitamin B_{12}, under electrochemical conditions at -1.0 V vs. Ag/AgCl using a carbon-felt cathode and a zinc plate anode as the sacrificial electrode in an undivided cell. This catalytic reaction proceeded via the formation and dissociation of the cobalt–carbon bond in the hydrophobic vitamin B_{12}.

Cobalamin-dependent methionine synthase catalyzes the methyl-transfer reaction from methyltetrahydrofolate to homocysteine in most mammals and bacteria.[1] The methyl transfer from methyltetrahydrofolate to cob(I)alamin and the demethylation of the resulting methylcobalamin are generally considered to be a double-displacement mechanism similar to S_N2 reactions.[2] Although some model studies of the nonenzymatic methyl transfer have been reported,[3] the entire catalytic cycle with a reasonable yield has been difficult to achieve up to now.

On the other hand, hydrophobic vitamin B_{12}, heptamethyl cobyrinate perchlorate, [Cob(II)7C$_1$ester]ClO_4 (**1**) (Chart 1), which has ester groups in place of the peripheral amide moieties of the naturally occurring cobalamin,[4] was found to be an excellent model compound for the functional simulation of cobalamin-dependent enzymes.[5] Herein, the hydrophobic vitamin B_{12}-catalyzed the methyl-transfer reaction from methyl tosylate ($TsOCH_3$) to 1-octanethiol under electrochemical conditions is reported as shown in Figure 1. The controlled-potential electrolysis insured the continuous Co^I species, accepting the methyl group from $TsOCH_3$ and donating it to 1-octanethiol. The complex **1** was chosen as the initial catalyst for conveniently forming the supernucleophilic Co^I species. The turnover behavior was observed in this study for the first time under nonenzymatic conditions.

The formation and heterolytic cleavage of the Co–CH_3 bond in complex **2** is considered to be an indispensable process in this catalytic cycle. For the heterolytic cleavage of the Co–CH_3 bond under thermodynamic conditions, it was monitored by the direct



1: X = Y = None, [Cob(II)7C$_1$ester]ClO_4
2: X = CH_3, Y = H_2O, [(CH_3)(H_2O)Cob(III)7C$_1$ester]ClO_4

Chart 1.

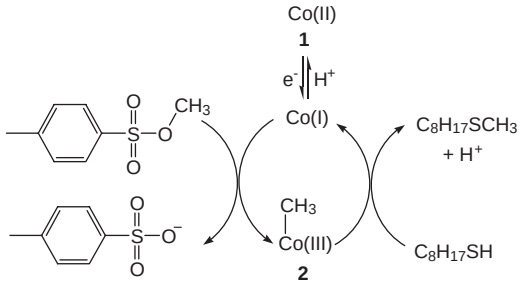


Figure 1. Methyl-transfer reaction catalyzed by **1**.

reaction of 1-octanethiol with the methylated hydrophobic vitamin B_{12} **2**, which was synthesized from **1** by a reported method.[6] It was reported that 1-hexanethiol was methylated by **2** in the presence of pyridine and $ZnCl_2$ in refluxing methanol.[3a] When we carried out the methylation of 1-octanethiol under similar reaction conditions, it could be methylated with a yield of 68% based on the complex **2**. Furthermore, the methylation proceeded at a yield more than 55% without pyridine.

As the next step, we applied the catalytic reaction using an electrochemical method. In order to examine the reactivity of the complex **1**, the redox behavior of **1** was investigated in DMF by cyclic voltammetry in the presence of $TsOCH_3$ as shown in Figure 2. The Co^{II}/Co^I couple was observed at -0.5 V vs. Ag/AgCl, and an irreversible reduction peak was observed at ca. -1.3 V vs. Ag/AgCl after the addition of $TsOCH_3$. This potential was consistent with that for the one-electron reduction of the complex **2**. This redox behavior indicates that the hydrophobic vitamin B_{12} is reduced to the Co^I species at -0.5 V vs. Ag/AgCl and then reacts with $TsOCH_3$ to form the methylated complex **2**. The cobalt–carbon bond in the complex **2** is cleaved to form the methyl radical and Co^I species at -1.3 V vs. Ag/AgCl.[5c]

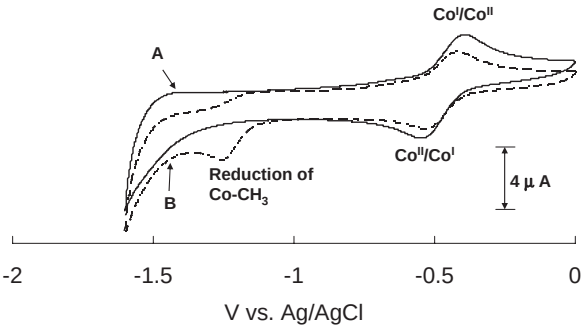


Figure 2. Cyclic voltammograms of [Cob(II)7C$_1$ester]ClO_4 (**1**) in DMF containing 0.1 M Bu_4NClO_4 at room temperature: A, **1** (1.0×10^{-3} M); B, after addition of $TsOCH_3$ (3.3×10^{-2} M) to the solution of **1**.

Table 1. Methyl-transfer reaction from $TsOCH_3$ to 1-octanethiol[a]

Entry	Catalyst	C[b] /F mol^{-1}	Product ($C_8H_{17}SCH_3$) /μmol[c]	Yield/%[d]
1	**1**	12.8	104 ± 3	400
2[e]	**1**	5.3	16 ± 2	62
3[f]	**1**	18.6	18 ± 2	70
4	None	2.2	22 ± 2	—
5	**3**	16.7	98 ± 5	375
6[g]	**1**	158.9	12 ± 2	46

[a]Controlled-potential electrolyses were carried out in DMF at −1.0 V vs. Ag/AgCl at 50 °C under N_2 atmosphere in the dark with a carbon-felt cathode and a zinc plate anode in the undivided cell. Initial concentration: [catalyst], 1.8×10^{-3} M; $TsOCH_3$, 1.3×10^{-2} M; 1-octanethiol: 1.2×10^{-2} M; Bu_4NClO_4, 0.1 M. [b]Electrical charge passed per mol of the catalyst. [c]The quantity of the product is the average of at least two repeated experiments. [d]Yield is based on the initial mole of hydrophobic vitamin B_{12} used. [e]At room temperature. [f]Under irradiation of 500-W visible light. [g]At the potential of −1.4 V vs. Ag/AgCl.

We applied the catalytic methylation by electrochemical means. The controlled-potential electrolyses were carried out in DMF in the presence of 1-octanethiol, $TsOCH_3$, and the complex **1** in an undivided cell under various reaction conditions. The following results were obtained on the basis of the product analyses listed in Table 1. (i) The methyl-transfer reaction could be effectively achieved with a turnover number of 4 at 50 °C and −1.0 V vs. Ag/AgCl in the dark as shown in Entry 1. On the other hand, the methyl-transfer reaction did not effectively proceed at room temperature or without complex **1** (Entries 2 and 4). (ii) When the electrolysis was carried out under irradiation by visible light as shown in Entry 3, which facilitated the formation of the CH_3 radicals, the catalytic cycle was scarcely observed. (iii) The reaction at −1.4 V vs. Ag/AgCl also did not proceed with good results as shown in Entry 6. This suggests that the CH_3 radical generated at this potential is not utilized for the methylation of 1-octanethiol. (iv) When we used a simple model complex **3** as a catalyst,[7] the methyl-transfer reaction proceeded as shown in Entry 5. However, complex **3** decomposed during the electrolysis.

In order to examine the reaction mechanism, the reaction was followed by electronic spectroscopy. The electronic spectrum observed during the electrolysis is shown in Figure 3A. This spectrum had absorption maxima at 307, 375, and 495 nm, and the spectrum was changed to Figure 3B after irradiation by visible light. These absorption spectra and the photochemical behavior were similar to those for the complex **2**.[8] This result indicates that the complex **1** was reduced to form the Co^I species at this potential and reacted with $TsOCH_3$ to form complex **2** with a cobalt–carbon bond.

The formally heterolytic cleavage of CH_3–Co in the complex **2** to Co^I species and CH_3^+ species was confirmed by a spectroscopic experiment. When an excess amount of 1-octanethiol was added to the DMF solution of complex **2** under anaerobic conditions, the electronic spectrum dramatically changed to that with an absorption maximum at 393 nm, which is characteristic of the Co^I species. The electrolysis results suggest that the methyl-transfer reaction did not proceed under methyl radical forming conditions as shown in Entries 3 and 6 in Table 1, which are also supported by the heterolytic cleavage in this methyl-transfer reaction.

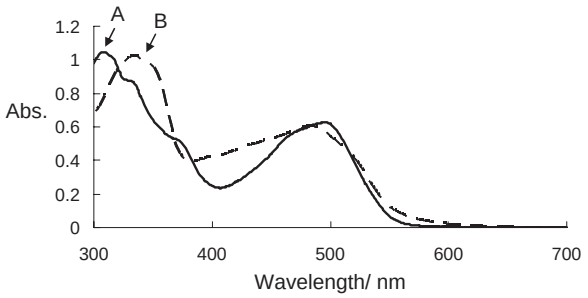


Figure 3. Electronic spectra observed during electrolysis with **1** as the catalyst: A, Controlled potential at −1.0 V vs. Ag/AgCl for 2 h in DMF; B: After irradiation with visible light under aerobic conditions.

Zn^{2+} coming from the sacrificial zinc plate anode is important for this methyl-transfer reaction and is expected to work as a Lewis acid to activate the SH group to become a better nucleophile, i.e., the S^- anion.[9] When Pt mesh was used as the anode, no methylated product could be detected. The catalytic reaction can proceed by the scheme shown in Figure 1 using electronic spectroscopy and product analyses under various conditions.

In conclusion, a methyl-transfer cycle from $TsOCH_3$ to 1-octanethiol catalyzed by the hydrophobic vitamin B_{12} (**1**) was developed under specific electrochemical conditions. The turnover behavior was observed for the first time in a nonenzymatic model system.

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