Vitamin B_{12} model complex catalyzed methyl transfer reaction to alkylthiol under electrochemical conditions with sacrificial electrode†

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Catalytic methyl transfer reactions from methyl tosylate to 1-octanethiol catalyzed by heptamethyl cobyrinate perchlorate, [Cob(II)7C_1ester]ClO_4, were investigated under electrochemical conditions. As a model study for the cobalamin-dependent methyl transfer reaction from methyltetrahydrofolate to homocysteine, controlled-potential electrolyses were carried out at –1.0 V *vs*. Ag/AgCl using a zinc plate as the sacrificial anode at 50 °C in the dark. A turnover behaviour for the methyl transfer reaction was observed for the first time under non-enzymatic reaction conditions. Co(I) species, which is generated from the continuous electrolysis of [Cob(II)7C_1ester]ClO_4, and its methylated CH_3-Co complex were found to be important intermediates. The mechanism for such a methyl transfer reaction was investigated by product analysis, electronic spectroscopy and ESR spin-trapping experiments. A simple vitamin B_{12} model complex was also utilized as the catalyst for the methyl transfer reaction.

Introduction

Coenzyme B_{12} plays critical roles in several types of biological reactions.[1] Typically, adenosyl-cobalamin as shown in Fig. 1, catalyzed the enzymatic rearrangement of methylmalonyl-coenzyme A to succinyl-coenzyme A, while methylcobalamin acts as a cofactor in the enzyme catalyzed methylation at the sulfur of homocysteine using a methyl group from N^5-methyltetrahydrofolate, which leads to tetrahydrofolate and methionine as shown in Fig. 2. Moreover, B_{12}-dependent reductive dehalogenases play an important role in the dechlorination of aliphatic chlorinated organics.[2] Cyanocob(III)alamin is the most important commercially available form of the naturally occurring B_{12} derivatives.

Numerous model complexes and mechanistic studies have been investigated for the enzyme-mimic reactions of B_{12}.[3] In order to simulate the catalytic functions of B_{12}, we have been investigating hydrophobic vitamin B_{12} derivatives as shown in Fig. 3, which have ester groups in place of the peripheral amide moieties of the naturally occurring vitamin B_{12}.[4] Such complexes have proved to be excellent catalysts for the carbon-skeleton rearrangements leading to the intramolecular exchange of a functional group (X) and a hydrogen atom as shown in equation (1).[3a,5] Hydrophobic vitamin B_{12} derivatives were also found to act as excellent model compounds for the functional simulation of coenzymes B_{12} in the reductive dehalogenation.[6]

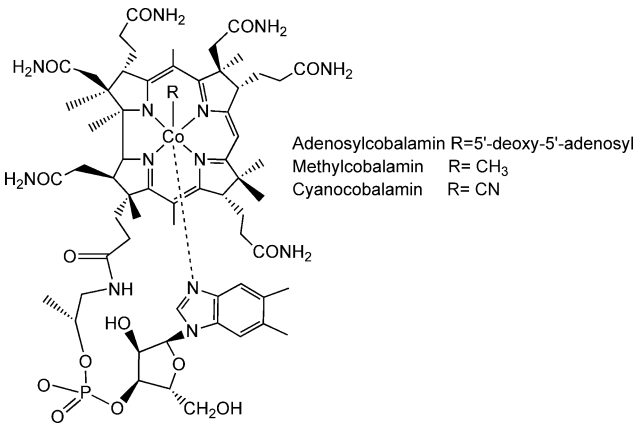


Fig. 1 Structure of vitamin B_{12} derivatives.

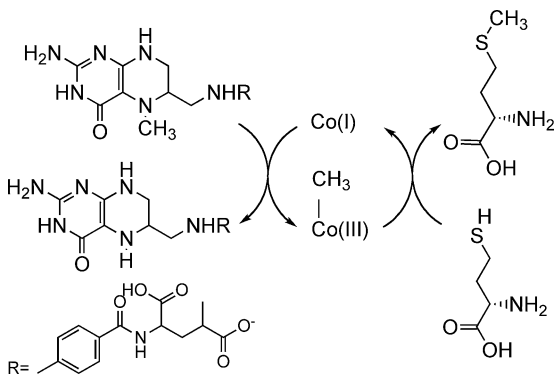
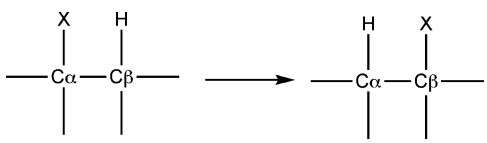


Fig. 2 Cobalamin-dependent methyl transfer from methyl tetrahydrofolate to homocysteine.



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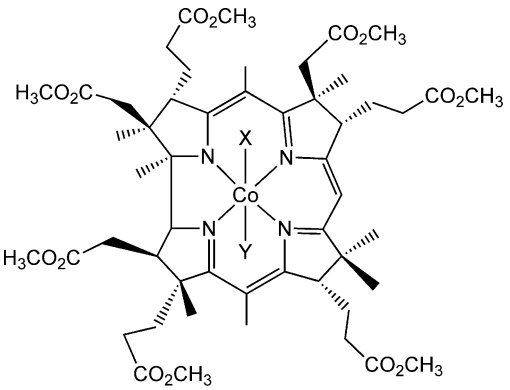
† Electronic supplementary information (ESI) available: ESI MS spectra for the interaction of [(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4 **2** and 1-octanethiol (Fig. S1). Electronic spectral change for the interaction of [(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4 **2** and 1-octanethiol (Fig. S2). The ESR spectra for the interaction of [(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4 **2** and 1-octanethiol in the presence of PBN (Fig. S3). See DOI: 10.1039/b909163g



1 [Cob(II)7C$_1$ester]$^+$, X= Y=None

2 [(CH$_3$)(H$_2$O)Cob(III)7C$_1$ester]$^+$, X=CH$_3$, Y=H$_2$O

3 [(CN)(H$_2$O)Cob(III)7C$_1$ester]$^+$, X=CN, Y=H$_2$O

Fig. 3 Hydrophobic vitamin B_{12} derivatives.

However, few model studies and applications were reported for the cobalamin-dependent methyl transfer reaction from methyltetrahydrofolate to homocysteine as shown in Fig. 2 under non-enzymatic reactions.[7] Such a methyl transfer was reported to proceed with a net retention of stereochemistry at the transferred methyl group, as a double-displacement mechanism in which each transfer proceeds with an inversion of stereochemistry, similar to the S_N2 reactions. Cob(I)alamin has been shown to be a kinetically competent intermediate in the catalytic turnover.

We have reported an application of such a methyl transfer reaction for the methylation of arsenic trioxide by the methylated hydrophobic vitamin B_{12} derivatives in the presence of glutathione in order to develop a new detoxification method for arsenic.[8] Keese and co-workers reported the methylated hydrophobic vitamin B_{12} involved model methyl transfer reactions from methylamines to 1-hexanethiol in the presence of Zn and $ZnCl_2$ in refluxing ethanol as a pioneer study.[3c] The total yield of the hexyl methyl sulfide is 6%–15% based on the vitamin B_{12} model complexes. The low yield may be attributed to the conflict in activity between the methyl donor and methyl acceptor in the same environment, especially under neutral conditions.

Recently, we reported a new methyl transfer reaction from methyl tosylate to 1-octanethiol catalyzed by the hydrophobic vitamin B_{12}, [Cob(II)7C$_1$ester]ClO$_4$ **1**, under electrochemical conditions.[9] As a result, the turnover behaviour was observed for the first time under non-enzymatic conditions utilizing the electrochemical method because of its cleanliness. However, the total reaction mechanism for the electrochemical reaction was not clear.

Therefore, herein, such a methyl transfer reaction from methyl tosylate to 1-octanethiol catalyzed by the hydrophobic vitamin B_{12}, [Cob(II)7C$_1$ester]ClO$_4$ **1**, under electrochemical conditions as shown in Fig. 4 was further studied from the viewpoint of the reaction mechanism. The mechanism for such methyl transfer reactions was investigated by product analysis, electronic spectroscopy and ESR spin-trapping experiments. A simple vitamin B_{12} model complex was also utilized as the catalyst for such a methyl transfer reaction.

Table 1 Direct reaction of 1-octanethiol with methylated hydrophobic vitamin B_{12} **2**[a]

Entry	Complex **2** (M)	$ZnCl_2$ (M)	Pyridine (M)	Yield (%)[b]
1	3.2×10^{-4}	9.8×10^{-3}	3.2×10^{-3}	68 ± 4
2	3.2×10^{-4}	9.8×10^{-3}	None	63 ± 3
3	3.2×10^{-4}	None	3.2×10^{-3}	58 ± 1
4	3.2×10^{-4}	None	None	2 ± 1
5	None	9.8×10^{-3}	3.2×10^{-3}	0
6[c]	3.2×10^{-4}	9.8×10^{-3}	3.2×10^{-3}	55 ± 1

[a] The methylation of 1-octanethiol by complex **2** was carried out in methanol in the presence of additives at 65 °C in the dark for 24 h. Initial concentration: 1-octanethiol: 3.2×10^{-3} M; [b] The quantity of the products is the average of at least two repeated experiments from GC-MS results and the yield is based on the initial mol of hydrophobic vitamin B_{12}. [c] 3.2×10^{-3} M of N-tert-butyl-α-phenylnitron (PBN) was added.

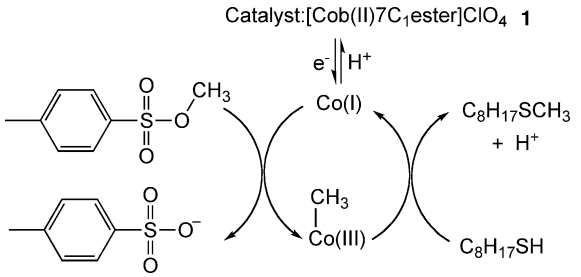


Fig. 4 Methyl transfer cycle from methyl tosylate to 1-octanethiol catalyzed by hydrophobic vitamin B_{12} [Cob(II)7C$_1$ester]ClO$_4$ **1**.

Results and discussion

Direct reaction of 1-octanethiol with complex 2

The direct reaction of 1-octanethiol with complex **2** was carried out to examine the reactivity for the cleavage of the Co–CH_3 bond under thermodynamic conditions. As described in the introduction, 1-hexanethiol could be methylated by complex **2** in the presence of pyridine and $ZnCl_2$ in refluxing methanol.[3c] When we carried out the methylation of 1-octanethiol under similar reaction conditions, it could also be methylated with a yield of 68% based on complex **2** shown as entry 1 in Table 1. Almost no methylation product was observed without complex **2** or the additives as shown by entries 4 and 5 in Table 1. Furthermore, the methylation could also proceed with a yield greater than 63% without pyridine as shown by entry 2 in Table 1. The methylation efficiency was maintained when N-tert-butyl-α-phenylnitron (PBN) as the spin-trapping reagent was added as shown by entry 6 in Table 1. This experimental result indicates that such a methylation of 1-octanethiol does not proceed *via* a methyl radical route.

$$\text{n-}C_8H_{17}SH \xrightarrow[CH_3OH,\ \text{reflux}]{\text{Complex } \mathbf{2}} \text{n-}C_8H_{17}SCH_3 \qquad (2)$$

Redox behaviour of [Cob(II)7C$_1$ester]ClO$_4$ (1) in the presence of TsOCH$_3$

To examine the reactivity of complex **1**, the redox behaviour of complex **1** was investigated in the presence of $TsOCH_3$ in N,N-dimethylformamide (DMF) by cyclic voltammetry. The redox potential ($E_{1/2}$) for the Co(II)/Co(I) couple of complex **1** in the

dry DMF was observed at –0.49 V *vs.* Ag/AgCl, as shown in Fig. 5(b). An irreversible reduction peak (E_{red}) was observed at *ca.* –1.3V *vs.* Ag/AgCl after the addition of $TsOCH_3$, as shown in Fig. 5(c). This reduction potential was consistent with the reduction peak (E_{red}) at about –1.3 V *vs.* Ag/AgCl of complex **2** having a $Co–CH_3$ bond, as shown in Fig. 5(a). It was ascribed to the one-electron reduction intermediate of complex **2** leading to the reductive cleavage of the $Co–CH_3$ bond.[10] This redox behaviour indicates that the hydrophobic vitamin B_{12} is reduced to the Co(I) species at $E_{1/2}$ = –0.49 V *vs.* Ag/AgCl and reacts with $TsOCH_3$ to form the $Co–CH_3$ bond.

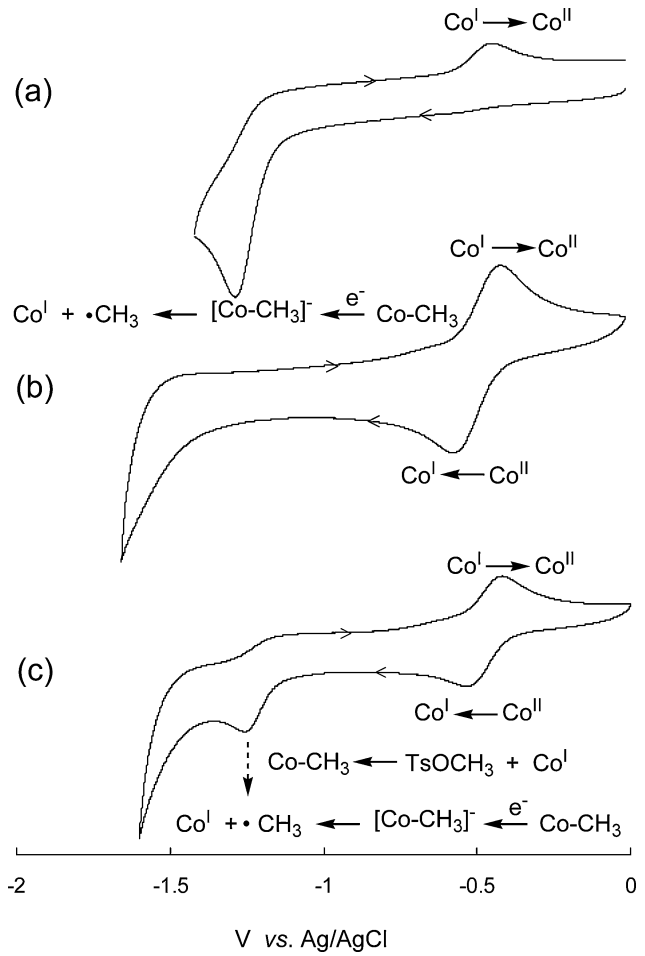


Fig. 5 Cyclic voltammograms of (a) DMF solution of $[(H_2O)(CH_3)Cob(II)7C_1ester]ClO_4$ **2** (1.0×10^{-3} M); (b) DMF solution of $[Cob(II)7C_1ester]ClO_4$ **1** (1.0×10^{-3} M); (c) $TsOCH_3$ (3.3×10^{-2} M) was added to (b). All solutions contained 0.1 M n-Bu_4NClO_4 and were carried out at room temperature under a nitrogen atmosphere; Sweep rate: 100 mV s^{-1}.

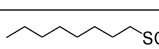
Catalytic cycle under electrochemical conditions

Based on the results described above, the catalytic methyl transfer reaction from $TsOCH_3$ to 1-octanethiol catalyzed by complex **1** was proposed to proceed by the scheme shown in Fig. 4, with the Co(I) and $Co–CH_3$ species as the important intermediates. We applied such a catalytic methylation to controlled-potential electrolyses at –1.0 V *vs.* Ag/AgCl in the presence of $TsOCH_3$, 1-octanethiol, and the catalyst of complex **1** in an undivided cell under various conditions as shown in Table 2. The continuous electrolysis ensured a continuous supply of Co(I) species, accepting the methyl group from $TsOCH_3$, donating it to 1-octanethiol. As a result, the methyl transfer reaction could be effectively achieved with a turnover number greater than 4 as shown by entries 1 and 2 in Table 2. The turnover behaviour was observed for the first time under non-enzymatic conditions. With the increase in the concentration of the substrate, the turnover behaviour was enhanced. On the other hand, the methyl transfer reaction did not effectively proceed under the conditions at room temperature or without the catalyst **1**, as shown by entries 3 and 7 in Table 2.

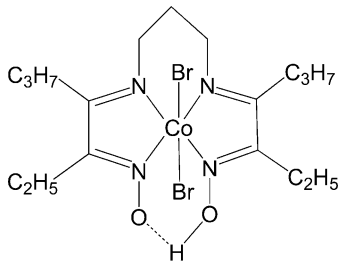
A simple vitamin B_{12} complex as shown in Fig. 6, the Costa-type model complex, $[Co(III)\{(C_2C_3)(DO)(DOH)\ pn\}Br_2]$,[5c] was also used as the catalyst as depicted by entry 8 in Table 2. A similar turnover behaviour was also observed under the reaction conditions similar to entry 1 in Table 2. However, the color of the solution was bleached after the electrolysis. Therefore, it seems that complex **4** is decomposed during the electrolysis. In comparison, complex **1** is a more stable and efficient catalyst under such electrochemical reaction conditions.

When pyridine was added to the controlled-potential electrolysis as depicted by entry 4 in Table 2, only 260% of the methylated product based on complex **1** was observed. Similarly, when complex **3**, having a cyanide ligand at the axial position, was

Table 2 Methyl transfer reaction from $TsOCH_3$ to 1-octanethiol in the presence of hydrophobic vitamin B_{12} under electrochemical conditions[a]

Entry	Catalyst	$TsOCH_3$ (mM)	$C_8H_{17}SH$ (mM)	Conditions	*V vs.* Ag/AgCl (V)	 μmol[b]	Yield (%)[c]
1	Complex **1**	13	12	Dark, 50 °C, 4 h	–1.0 V	104 ± 3	400
2	Complex **1**	130	120	Dark, 50 °C, 4 h	–1.0 V	150 ± 4	575
3	None	200	120	Dark, 50 °C, 4 h	–1.0 V	16 ± 2	—
4[d]	Complex **1**	13	12	Dark, 50 °C, 4 h	–1.0 V	56 ± 2	260
5	Complex **1**	13	12	*hv*, 50 °C, 4 h	–1.0 V	18 ± 2	70
6	Complex **1**	13	12	Dark, 50 °C, 4 h	–1.4 V	12 ± 1	46
7	Complex **1**	13	12	Dark, 25 °C, 4 h	–1.0 V	16 ± 1	62
8	Complex **4**	13	12	Dark, 50 °C, 4 h	–1.0 V	98 ± 5	375
9	Complex **3**	13	12	Dark, 50 °C, 4 h	–1.0 V	50 ± 2	190

[a] Controlled-potential electrolyses were carried out in DMF at –1.0 V *vs.* Ag/AgCl under a N_2 atmosphere at 50 °C in the dark. Initial concentration: [catalyst], 1.8×10^{-3} M; $TsOCH_3$, 1.3×10^{-2} M; thiol, 1.2×10^{-2} M; n-Bu_4NClO_4, 0.1 M; [b] The quantity of the product is the average of at least two repeated experiments from GC-MS results; [c] Yield is based on the initial mol of hydrophobic vitamin B_{12} **1**; [d] 13 mM of pyridine was added.



4 [Co(III){(C_2C_3)(DO)(DOH)pn}Br_2]

Fig. 6 Costa-type vitamin B_{12} model complex.

utilized as the catalyst as depicted by entry 9 in Table 2, only 188% of the methylated product based on complex **3** was observed under the same reaction conditions. The low conversion may be attributed to the shift in the redox potential of the Co^{II}/Co^{I} couple to the cathodic side in the presence of cyanide or pyridine, which was previously reported.[11] This makes the Co(II) complex more difficult to be reduced to the Co(I) species, thus leading to a slow reaction rate.

To investigate the reaction mechanism, we also carried out controlled-potential electrolyses under various conditions, including irradiation with visible light, utilizing a different potential, temperature, or using other counter electrodes. The difference in these reaction conditions is discussed in the next section.

Mechanistic aspects for cleavage of the Co–C bond

As described above, the Co(I) species and CH_3-Co complexes were considered as important intermediates in the catalytic methyl transfer reaction from $TsOCH_3$ to 1-octanethiol. In order to examine the reaction mechanism, the generation of the Co(I) and Co-CH_3 species, the formally heterolytic cleavage of the Co–CH_3 bond, and the interaction between complex **2** and 1-octanethiol were investigated as follows.

It has been previously reported that complex **1**, [Cob(II)7C_1ester]ClO_4, was readily reduced to the Co(I) species with a highly nucleophilic character by electrochemical means.[6,10] Such Co(I) species could react with the methyl donors, such as $TsOCH_3$, and become the Co-CH_3 complexes. When the controlled-potential electrolysis at −1.0 V *vs*. Ag/AgCl was followed by electronic spectroscopy, the electronic spectrum of the reaction solution containing **1** and 1-octanethiol (B in Fig. 7) has a similar absorption maxima at 307, 375, and 495 nm with complex **2**,[10,12] and is different from the DMF solution of the catalyst, complex **1** (A in Fig. 7). It also varied after irradiation with visible light under aerobic conditions (C in Fig. 7). Combined with the results discussed for the redox behaviour of complex **1** in the presence of $TsOCH_3$, this spectral change clearly indicates that complex **1** was reduced to the super-nucleophilic Co(I) species at this potential and reacted with $TsOCH_3$ to form complex **2** having a cobalt–carbon bond. Such CH_3-Co complexes could also be detected after 4 h of electrolysis, indicating the remaining catalytic ability of complex **1**.

The cleavage of the Co–CH_3 bond in complex **2** was initially investigated by spectroscopic studies for the interaction between complex **2** and 1-octanethiol. Although the Co–CH_3 bond in methylcobalamin was considered to be relatively stable under thermodynamic conditions,[13] the Co–CH_3 bond in complex **2** was

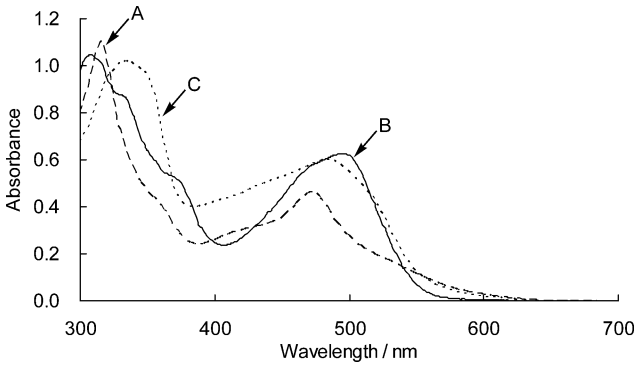


Fig. 7 Electronic spectra observed for (A): DMF solution of complex **1**; (B): Reaction solution after a 2 h controlled-potential electrolysis at −1.0 V *vs*. Ag/AgCl in DMF with complex **1** as the catalyst; (C): After the solution of (B) was irradiated with visible light under aerobic conditions.

rather active in the presence of an excess amount of 1-octanethiol. When an excess amount of 1-octanethiol was added to the DMF solution of complex **2** under aerobic conditions in the dark, the absorption maximum at 306 nm of complex **2** decreased while the absorption maximum at 336 nm increased along with a slight increase in the absorption between 550 and 680 nm as shown by (1) in Fig. 8. Such spectral changes indicate that a stronger axial ligand, such as thiols, coordinated to the central metal of the cobalt instead of water as shown in equation (3).

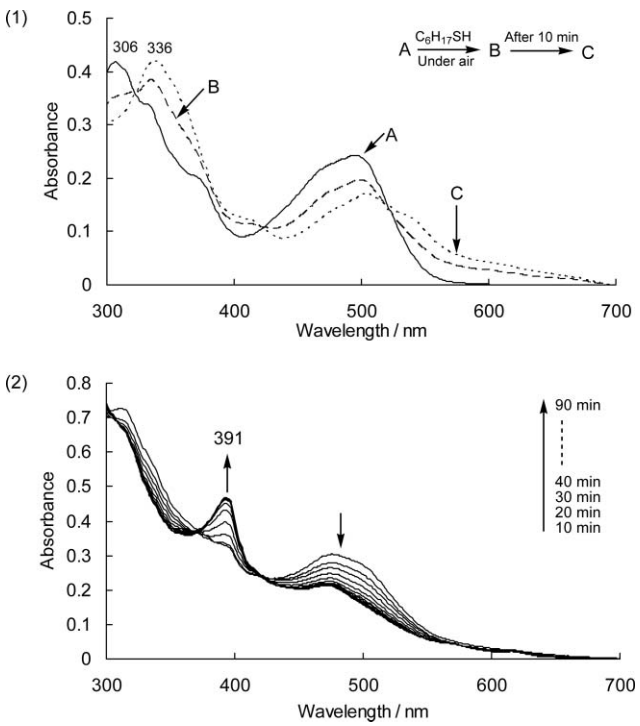
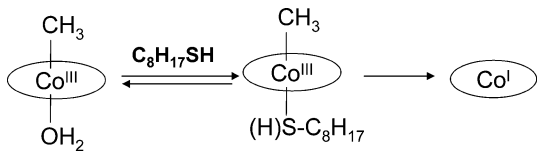


Fig. 8 Interaction of [(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4 **2** and 1-octanethiol observed from electronic spectra in DMF under aerobic conditions. (1), (A): complex **2** (15.0×10^{-5} M) in DMF; (B): after 1-octanethiol (8.7×10^{-3} M) added. (C): tracking spectrum after 1-octanethiol was added after 10 min; (2), tracking spectrum after (C) in (1) with an interval of 10 min for 1.5 h.

Such an interaction between complex **2** and 1-octanethiol was also observed from the ESI-MS analysis of complex **2** in the

presence of 1-octanethiol (see Fig. S1 in the ESI†). When 100 mol-equiv. of 1-octanethiol was added to the DMF solution of complex **2**, the peaks at 1198.34, 1182.28 and 1051.85 were observed to correspond to the CH_3-Co-$C_8H_{17}SH$, Co-$C_8H_{17}SH$, and CH_3-Co segments in the heptamethyl cobyrinate, such as complexes **1** and **2** as shown in Fig. S1.† The electronic spectroscopy was followed at intervals of 10 min after the addition of 1-octanethiol. The absorption maximum at 391 nm gradually increased which is characteristic of the Co(I) species as shown by (2) in Fig. 8. Furthermore, a color change in the solution from orange to dark green, indicating the formation of Co(I) species, could be observed when such an electronic spectrum was observed under anaerobic conditions (see Fig. S2 in the ESI†). These results indicate that the CH_3–Co bond in complex **2** has a strong interaction with 1-octanethiol and has a tendency to become a Co(I) species in the presence of 1-octanethiol.



(3)

Such a formal heterolytic cleavage of the CH_3–Co bond could also be supported by the experimental results from the controlled-potential electrolysis under the conditions which facilitated the generation of methyl radicals. When the electrolysis was carried out under irradiation by visible light to form methyl radicals,[10] almost no catalytic cycles could be observed as in entry 5 in Table 2. When the reaction was carried out at –1.4 V *vs*. Ag/AgCl, which also facilitates the generation of methyl radicals by electrolysis of the cobalt–carbon bond as shown in Fig. 5(c),[14] the methylation still did not carry through with a good result, as shown by entry 6 in Table 2. The results suggest that the methyl radical is not utilized for the methylation of 1-octanethiol. Therefore, the catalytic methyl-transfer reactions effectively proceed at –1.0 V *vs*. Ag/AgCl in the dark to avoid generation of the methyl radical.

To further confirm the formal heterolysis of the Co–CH_3 bond in complex **2**, an ESR spin-trapping experiment using PBN was performed in the presence of complex **2** and 1-octanethiol (see Fig. S3 in the ESI†). This experiment helped us understand if methyl radicals were generated when the methyl group transferred from the CH_3-Co intermediate to 1-octanethiol. No generation of methyl radicals was observed in the DMF solution of complex **2** when 1-octanthiol was added to the DMF solution of complex **2** and PBN in the dark. Moreover, no more methyl radicals were trapped when this solution containing complex **2**, 1-octanethiol and PBN was irradiated with visible light for 1 min. In comparison, when the same DMF solution containing PBN and complex **2** was fully irradiated with visible light for 1 min, a strong PBN spin adduct of the methyl radicals was observed. This experimental result clearly indicated that most of the CH_3–Co bonds in complex **2** cleaved to the formally $^+CH_3$ and Co^I species *via* heterolysis in the presence of 1-octanethiol in the dark. Therefore, this catalytic methyl transfer reaction from methyl tosylate to 1-octanethiol mainly proceeds *via* the formally $^+CH_3$ species which comes from the formal heterolytic cleavage of the Co–CH_3 bonds.

Table 3 Effect of various anodes on the catalytic methyl transfer cycle to 1-octanethiol[a]

Entry	Complex **1** (μmol)	Working electrode	Counter electrode	SCH3 (μmol)[b]	SCH3 Yield (%)[c]
1	26.1	Carbon-felt	Zn	104 ± 3	400
2	26.1	Carbon-felt	Mg	68 ± 4	261
3	26.1	Carbon-felt	Pt	6 ± 1	23

[a] Controlled-potential electrolyses were carried out in DMF at –1.0 V *vs*. Ag/AgCl under N_2 atmosphere at 50 °C in the dark. Initial concentration: Complex **1**, 1.8×10^{-3} M; $TsOCH_3$, 1.3×10^{-2} M; thiol, 1.2×10^{-2} M; n-Bu_4NClO_4, 0.1 M; [b] The quantity of the product is the average of at least two repeated experiments from GC-MS results; [c] Yield is based on the initial mol of hydrophobic vitamin B_{12}.

Effect of sacrificial zinc electrode

The zinc ion plays important roles for the binding and activation of the cobalamin-dependent methyl transfer reaction *in vivo*.[15] In this electrochemical catalytic system, the Zn^{2+}, which comes from the sacrificial zinc plate anode during the electrolysis, is also considered an important activating factor, like a Lewis acid, to activate the SH group in 1-octanethiol to a stronger nucleophile, *i.e.*, the S^- ion. Such activation could be easily understood when Mg or Pt was used instead of the Zn plate anode as shown in Table 3. Nearly no catalytic cycles could be observed when a Pt-mesh was utilized as the counter electrode, and the catalytic methylation could not proceed well with Mg as the anode.

Proposed total reaction mechanism

To further confirm that such a reduction system of controlled-potential electrolysis is necessary, we also examined the feasibility of a methyl transfer reaction without controlled-potential electrolysis under anaerobic conditions using complex **2**, $[(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4$, as the initial catalyst. In consideration of the sensitivity of the Co(I) species to oxygen, the freeze-pump-thaw cycles were utilized to fully remove the atmospheric oxygen. But, nearly no catalytic cycles could be observed when the reactions were carried out at 50 °C for 20 h. This may attributed to the fact that the Co(I) species reacts with a proton to form an inactive Co(II) species. Such protons may come from the deprotonation of 1-octanethiol. Therefore, to regenerate the Co-CH_3 intermediate, the reduction such as the controlled-potential electrolysis is an indispensable step for the catalytic methyl transfer cycle to maintain the high concentration of the Co(I) species.

In light of these results, we propose the mechanism for the catalytic methyl transfer reaction from methyl tosylate to 1-octanethiol catalyzed by complex **1** under electrochemical conditions as shown in Fig. 9. The controlled-potential electrolysis at –1.0 V *vs*. Ag/AgCl efficiently generated the supernucleophilic Co(I) species from complex **1**. The Co(I) species facilitate the formation of the Co-CH_3 intermediate by reaction with methyl tosylate. Under thermodynamic conditions, with the help of Zn^{2+} and the interaction between the Co–CH_3 bond and the activated 1-octanethiol, the Co–CH_3 bond cleaved with the result that the methyl group was transferred to the 1-octanethiol to form the methylated product. The forming Co(I) species may react with

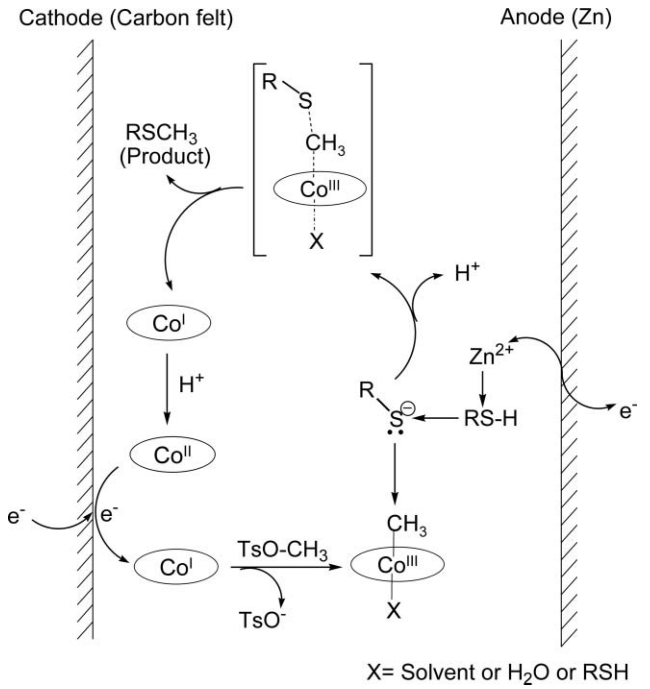


Fig. 9 Proposed mechanism for methyl transfer cycle from methyl tosylate to 1-octanethiol catalyzed by [Cob(II)7C_1ester]ClO_4 **1** under electrochemical conditions.

the proton from 1-octanethiol to form the Co(II) species. And then, the catalyst will be activated to the Co(I) species under electrochemical conditions.

Conclusions

In conclusion, a methyl transfer cycle from $TsOCH_3$ to 1-octanethiol catalyzed by the hydrophobic vitamin B_{12} was developed under electrochemical conditions. Complex **1**, [Cob(II)7C_1ester]ClO_4, proved to be one of the best catalysts for use under these electrochemical reaction conditions. The catalytic methyl transfer reaction proceeded well under continuous controlled-potential electrolysis at −1.0 V *vs.* Ag/AgCl at 50 °C in the dark with a carbon-felt cathode and a sacrificial Zn-plate anode. The turnover behaviour was observed for the first time under non-enzymatic conditions. The formation and the formal heterolytic cleavage of the Co–CH_3 bond are important for the catalytic methyl transfer reaction. The total reaction mechanism for such an electrochemical methyl transfer reaction catalyzed by hydrophobic vitamin B_{12} was determined by various spectroscopic techniques. This is also a valuable model study for the biological cobalamin-dependent methyl transfer reactions. A higher turnover number for the methyl transfer reaction and an application for the useful organic synthesis can be expected based on this findings.

Experimental

Materials

All solvents and chemicals were of reagent grade and used without further purification. Dry N,N-dimethylformamide (DMF) was purchased from Nakalai Chemicals and stored under an N_2 atmosphere. Methanol was dried and purified just before use according to the standard procedure. Tetra-n-butylammonium perchlorate (n-Bu_4NClO_4) was purchased from Nakalai Chemicals (Special grade) and dried at room temperature under vacuum before use. Heptamethyl cobyrinate perchlorate **1**, and aquomethyl heptamethyl cobyrinate perchlorate **2** were synthesized by the reported method with cyanocobalamin as the starting material.[16] The Costa-type vitamin B_{12} model complex **4**, [Co(III){(C_2C_3)(DO)(DOH)pn}Br_2] was synthesized as already reported by our laboratory.[5c]

General analysis and measurements

The electronic absorption spectra were measured using a Hitachi U-3310 or U-3000 spectrophotometer and a 10-mm cell. The ^{1}H NMR spectra were recorded by a Bruker Avance 500 spectrometer at the Centre of Advanced Instrumental Analysis, Kyushu University, and the chemical shifts (in ppm) were referenced relative to the residual protic solvent peak. Cyclic voltammograms were obtained using a BAS ALS-630C electrochemical analyzer. The gas chromatography-mass spectra (GC-MS) were obtained using a Shimadzu GCMS-QP5050A equipped with a J&W Scientific DB-1 column (length: 30 m; ID: 0.25 mm, film: 0.25 mm) and helium as the carrier gas. For the measurement, the injector and detector temperatures were 250 °C, the oven temperature was initially held at 100 °C for 2 min, then increased to 240 °C at the rate of 10 °C/min. A 500-W tungsten lamp was used for the visible light irradiation experiment. The CSI-MS was measured by an AccuTOF CS JMS-T100cs from JEOL. The controlled-potential electrolyses were carried out using a Hokuto Denko HA 301 potentiostat/galvanostat and the electrical quantity was recorded by a Hokuto Denko HF 201 coulomb/ampere-hour meter. Thin layer chromatography was carried out with silica gel 60 N (spherical, neutral) as the solid phase purchased from Kanto Chemical, Co., Inc. The ESR spectra were measured by a Bruker EMX Plus 8/2.7 spectrometer at room temperature.

Cyclic voltammetry

A cylindrical three-electrode cell was used that was equipped with a 1.6 mm diameter platinum wire as the working electrode, a 25 mm platinum wire as the counter electrode and an Ag/AgCl (3.0 M NaCl) electrode as the reference electrode. The scan rate was up to 100 mV s^{-1} and the half-wave potential ($E_{1/2}$) was calculated to be 0.56 V *vs.* Ag/AgCl as the $E_{1/2}$ value of ferrocene–ferrocenium (Fc/Fc^+). The dry DMF solution of the vitamin B_{12} derivatives (1.0×10^{-3} M) and n-Bu_4NClO_4 (1.0×10^{-1} M) were deaerated by N_2 gas bubbling before the measurements, and the cyclic voltammetry was carried out under an N_2 gas atmosphere at room temperature. The redox behaviours of [(H_2O)(CH_3)Cob(III)7C_1ester]ClO_4 **2** and [Cob(II)7C_1ester]ClO_4 **1** in the presence of $TsOCH_3$ were investigated in the dark.

Methylation of 1-octanethiol by methylated hydrophobic vitamin B_{12} (2)

The direct reaction of 1-octanethiol (3.2×10^{-3} M) with the methylated hydrophobic vitamin B_{12} **2** (3.2×10^{-4} M) was investigated in the presence of additives (3.2×10^{-3} M of pyridine or 9.8×10^{-3} M of $ZnCl_2$) in refluxing methanol in the dark for 24 h. The

reaction solution was passed through a short silica gel column and analyzed by GC-MS with biphenyl as the internal standard.

Catalytic methyl transfer reaction under electrochemical conditions

Controlled-potential electrolyses were carried out in dry DMF at –1.0 V *vs.* Ag/AgCl under an N_2 atmosphere in an undivided electrolysis cell using a mini three-neck flask. The undivided electrolysis cell was equipped with a condenser and three electrodes; *i.e.*, a carbon felt working cathode, a sacrificial Zn-plate anode, and an Ag/AgCl reference electrode as shown in Fig. 10. For a typical reaction, a DMF solution of the vitamin B_{12} derivatives (1.8×10^{-3} M), $TsOCH_3$ (1.3×10^{-2} M), 1-octanethiol (1.2×10^{-2} M), an additive (if necessary) and n-Bu_4NClO_4 (1.0×10^{-1} M) were subjected to electrolysis for 4 h in the dark at 50 °C. After allowing the reaction to cool to ambient temperature, the reaction solution was diluted with 80 ml of water and extracted with 80 ml of CH_2Cl_2. The CH_2Cl_2 layer was washed with water (3×50 ml) to completely remove the DMF and then dried with Na_2SO_4. The filtrate was concentrated and passed through a silica gel column eluting with CH_2Cl_2 to remove the n-Bu_4NClO_4 and vitamin B_{12} derivative. The products were then analyzed by GC-MS with biphenyl as the internal standard.

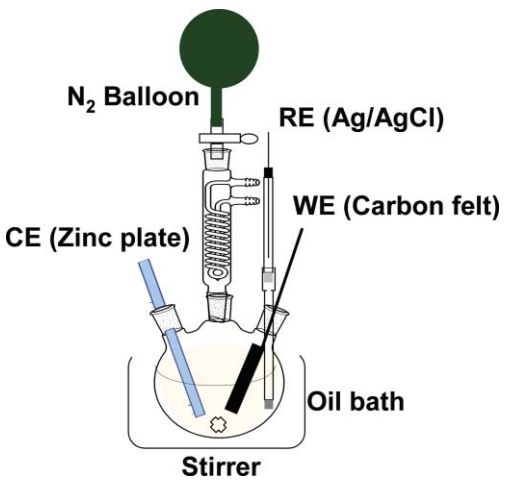


Fig. 10 Condenser equipped with a three-electrode undivided electrolysis cell under a nitrogen atmosphere.

ESR spin-trapping studies

The ESR spin-trapping experiment was conducted using the methylated hydrophobic vitamin B_{12} in the presence of an excess amount of 1-octanethiol with N-tert-butyl-α-phenylnitron (PBN) as the spin-trapping reagent. A 5.6 mg (2.4×10^{-3} M) sample of $[(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4$ **2** was dissolved in 2 ml of dry DMF and deaerated by N_2 gas bubbling for 15 min. 1 ml of the DMF solution was added to the bottle containing 40 mg (2.3×10^{-1} M) of PBN and the final solution was transferred to the ESR tube immediately before measurement in the dark. Ten μl (5.5×10^{-2} M) of 1-octanethiol was added to the remaining 1 ml of the DMF solution, and then transferred to a new ESR tube immediately before measurement in the dark. Both of these ESR tubes were irradiated with visible light for 1 min and measured again. As a comparison, the ESR spin-trapping experiment was also carried out for (1) the DMF solution of PBN (2.3×10^{-1} M) and $[(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4$ (2.4×10^{-3} M); (2) the DMF solution of PBN (2.3×10^{-1} M); and (3) the DMF solution of PBN (2.3×10^{-1} M) and 1-octanethiol (5.5×10^{-2} M).

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