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Electrochemical Catalytic Carbon-skeleton Rearrangement Mediated by Imine/Oxime-type B_{12} Model Complex

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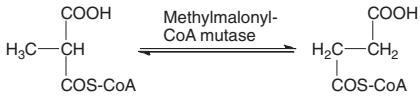
An electrochemical carbon-skeleton rearrangement of methylmalonate skeleton to succinate was successfully mediated by an imine/oxime-type cobalt complex using diethyl 2-bromomethyl-2-phenylmalonate as a model substrate of a coenzyme B_{12}-dependent enzymatic reaction. Cyclic voltammetric and mass spectrometric studies revealed that this electrocatalysis of the alkyl bromide with 1,2-migration of a carboxylic ester group was achieved by the duet redox process between the reduction of the monoalkylated complex and the oxidation of the dialkylated complex.

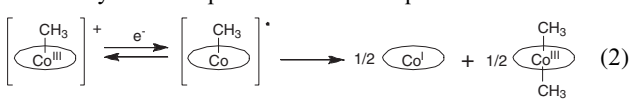
Among certain coenzyme B_{12}-dependent enzymes, methylmalonyl-CoA mutase (MMCM) catalyzes the carbon-skeleton rearrangement between *R*-methylmalonyl-CoA and succinyl-CoA utilizing coenzyme B_{12} as an organometallic cofactor (eq 1).[1] To be relevant for the enzymatic reaction, various B_{12} model complexes have been synthesized and their catalytic abilities investigated.[1,2] In particular, heptamethyl cobyrinate **1** has attracted interest because it has the same corrin framework as naturally occurring B_{12} as shown in Figure 1.[3] In addition, some imine/oxime-type cobalt complexes such as [Co^{III}{(DO)(DOH)-pn}Br_2] (**2**) (Figure 1) have also attracted interest due to their square-planar monoanionic ligands as suitable models for the corrin framework in B_{12}.[4] The monoanionic imine/oxime-type complexes were demonstrated to show the unique redox and coordination chemistry; the Co(III) monomethylated complex is active for electrochemical reduction resulting in the disproportionation to the Co(I) species and the Co(III) dimethylated complex, while the resulting Co(III) dimethylated complex is active for electrochemical oxidation resulting in fragmentation to the Co(III) monomethylated species.[4,5] The electrochemical technique is a conventional method for constructing the catalytic cycle, and we have succeeded in the functional simulation of B_{12}-dependent enzymatic reactions.[3,6] Interestingly, we demonstrated that the imine/oxime-type complexes successfully mediate the electrochemical carbon-skeleton rearrangements as model reactions of MMCM. A previous study implied that the oxidation of the Co(III) dialkylated intermediate is crucial for the carbon-skeleton rearrangements.[5] However, the reaction mechanism is still unclear because there is limited information on catalytic applications of the Co(III) dialkylated complexes, which is only from our previous report.



(1)

To probe the mechanism of the carbon-skeleton rearrangements mediated by the imine/oxime-type complexes, we here report the electrolysis of a new substrate, diethyl 2-bromomethyl-2-phenylmalonate (**3**), in the presence of [Co^{III}{(DO)(DOH)-pn}Br_2] (**2**). The substrate **3** was selected because it has two different functional groups (phenyl and carboxylic ester) migrating via different intermediates, which was confirmed by previous studies of **1**.[3,7] Thus, we expected the product contribution could provide a mechanistic insight into the migration reaction mediated by **2**. Furthermore, we demonstrated the first mass spectrometric study to detect the Co(III) dialkylated intermediate for investigating the reaction mechanism.

We first investigated the redox behavior of **2** in the presence of the substrate **3** by cyclic voltammetry. As shown in Figure 2 (solid line), the redox couples of Co(III)/Co(II) and Co(II)/Co(I) were observed at −0.16 and −0.72 V vs. Ag–AgCl, respectively, consistent with a previous study of a similar imine/oxime-type cobalt complex to **2**.[5] An irreversible reduction peak was also observed at −1.06 V vs. Ag–AgCl as shown in Figure 2. The potential of this reduction peak is comparable to that of the one-electron reduction of the Co(III) monomethylated complex reported in the previous work. It has been demonstrated that the Co(III) monomethylated complex is disproportionated into the Co(I) species and the Co(III) dimethylated complex by electrochemical reduction as shown in eq 2.[4,5] Thus, the irreversible peak at −1.06 V vs. Ag–AgCl in Figure 2 is ascribed to the one-electron reduction of the Co(III) monoalkylated complex species resulting from the oxidative addition of **3** to Co(I) species of **2**. The Co(III) monoalkylated complex species of **2** is disproportionated to the Co(I) species and the Co(III) dialkylated complex by the electrochemical reduction in a manner similar to the Co(III) monomethylated complex as shown in eq 3.



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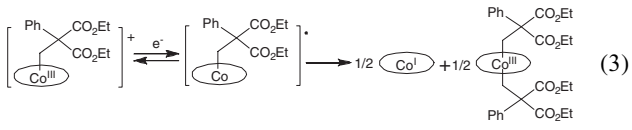

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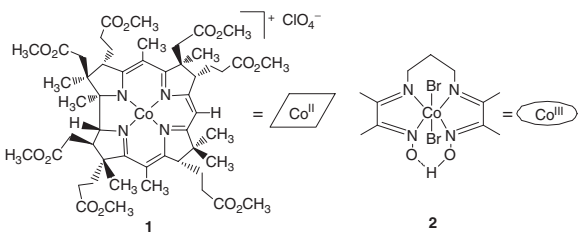


Figure 1. Structures of heptamethyl cobyrinate **1** and [Co^{III}{(DO)(DOH)pn}Br_2] (**2**).

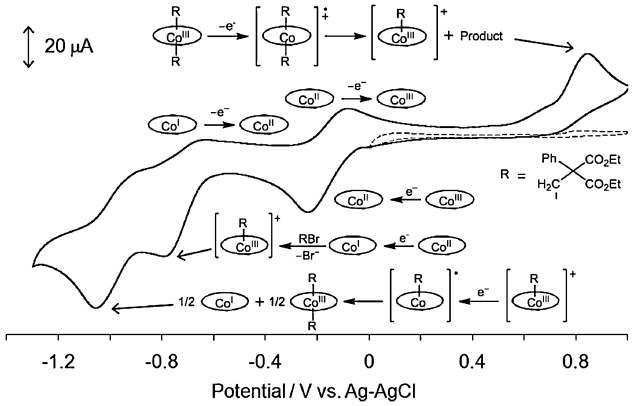
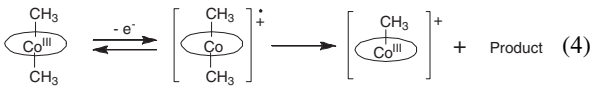


Figure 2. Cyclic voltammograms of **2** (4.5 mM) in the presence of an excess of **3** (10 mM) and in DMF containing *n*-Bu_4NPF_6 (5.0×10^{-2} M); sweep rate: 100 mV s^{-1}; scan ranges: (solid line) −1.2 to 1.0 V vs. Ag–AgCl, (broken line) 0 to 1.0 V vs. Ag–AgCl.

It has been demonstrated that the Co(III) dimethylated complex is inactive for the electrochemical reduction, but active for the electrochemical oxidation resulting in the fragmentation to the Co(III) monomethylated complex as shown in eq 4.[4,5] Thus, the irreversible oxidation peak at +0.86 V vs. Ag–AgCl in Figure 2 is ascribed to the one-electron oxidation of the Co(III) dialkylated complex, which results from the one-electron reduction of the Co(III) monoalkylated complex followed by disproportionation (eq 3). This assignment is consistent with the fact that the irreversible oxidation peak was not observed in the range of 0 to 1.0 V vs. Ag–AgCl as shown in Figure 2 (broken line), which suggests that the Co(III) dialkylated complex was not formed in this scan range. The anodic electrochemistry of the Co(III) dialkylated complex is a key process in the electrolysis of **3** as discussed below.

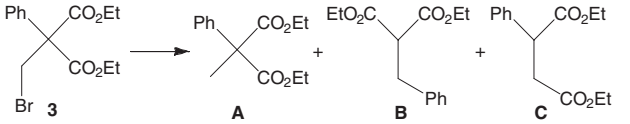


(4)

Based on the investigation by cyclic voltammetry, the controlled-potential electrolysis of **3** in the presence of a catalytic amount of **2** was carried out in DMF under various conditions.[8] The products were analyzed by GC-MS as summarized in Table 1. The electrolysis did not efficiently proceed at −0.90 V vs. Ag–AgCl, and the simple reduced product **A** was almost exclusively obtained as shown in Entry 1. This product probably results from the relatively slow thermolysis of the Co–C bond of the monoalkylated complex, which is formed by the reaction between the Co(I) species and **3**. On the other hand, the electrolysis more efficiently proceeded at −1.20 V than at −0.90 V vs. Ag–AgCl due to the effective electrochemical reduction of the Co(III) monoalkylated complex as shown in Entry 2. Interestingly, under the present conditions, the carboxylic ester migrated product **C** was obtained as the major product. It should be noted that this electrochemical 1,2-migration of the carboxylic ester group serves as an analogy for the carbon-skeleton rearrangement of methylmalonate to succinate mediated by MMCM (eq 1).

The participation of an oxidizable intermediate during the 1,2-migration of the carboxylic ester group was confirmed by the following experiments. When the electrolysis cell was divided into two internal compartments with a polypropylene membrane at the same employed potential, **A** and **B** were mainly obtained as shown in Entry 3. This indicates that the membrane prevents the diffusion of the Co(III) dialkylated complex formed at the cathode to the anode, resulting in the decreased selectivity for **C**. The comparison of the product ratios of **C** between Entries 2 and 3 suggests that the coupled redox processes are necessary for the 1,2-migration of the carboxylic ester group. In addition, the use of a zinc plate anode instead of a Pt mesh anode also reduced the selectivity for **C** as shown in Entry 4. This suggests that the oxidation of the zinc plate as a sacrificial anode is superior to that of the Co(III) dialkylated complex, resulting in the decreased selectivity for **C** and the higher conversion. Therefore, the oxidation of the Co(III) dialkylated complex is crucial for the 1,2-migration of the carboxylic ester group.

Table 1. Electrolysis of **3** mediated by B_{12} model complex **2**[a]



Entry	Potential /V[b]	Charge /F mol^{-1} [c]	Conversion /%[d]	Product ratio/%[e]		
				A	B	C
1	−0.90	0.4	3	98	2	trace
2	−1.20	1.5	10	36	1	62
3[f]	−1.20	0.3	10	83	11	6
4[g]	−1.20	1.7	36	86	8	6

[a]Controlled-potential electrolyses were carried out in DMF using a three-electrode cell with a Pt mesh cathode and a Pt mesh anode under a N_2 atmosphere. Initial concentration: $[\mathbf{2}] = 5.0 \times 10^{-4}$ M, $[\mathbf{3}] = 5.0 \times 10^{-2}$ M, $[n\text{-}Bu_4NPF_6] = 0.25$ M. [b]Employed potential (V) vs. Ag–AgCl. [c]Electrical charge passed per mol of **3**. [d]Conversion was estimated by the recovery of **3**. [e]Products were analyzed by GC-MS. [f]The cell was divided into two internal compartments with a single sheet of a microporous polypropylene membrane. [g]Use of a Zn anode instead of a Pt mesh anode.

To confirm the participation of the Co(III) dialkylated complex as an oxidizable intermediate during the 1,2-migration of the carboxylic ester group, ESI-MS was performed under the same conditions as Entry 2 in Table 1. The Co(III) monoalkylated and dialkylated complexes were detected as shown in Figure 3, consistent with the former voltammetric study. It should be emphasized that this mass spectrometric data are the first evidence to directly detect the Co(III) dialkylated intermediate during the 1,2-migration of the carboxylic ester group. On the other hand, the participation of the Co(III) monoalkylated complex in the 1,2-migration of the carboxylic ester group is ruled out because the Co(III) monoalkylated complex is inactive for the electrochemical oxidation.[4]

The phenyl-migrated product **B** was also obtained as a carbon-skeleton rearrangement product under all the conditions as shown in Table 1. We reported the catalysis of **3** mediated by heptamethyl cobyrinate **1** under electrochemical and photochemical conditions.[3,7] These studies demonstrated that the phenyl-migrated product **B** is formed via a radical intermediate, which results from the one-electron reduction of the Co(III) monoalkylated complex (eq 5.1).[3,7] Thus, in the present study of the imine/oxime-type complex **2**, it is reasonable to expect that the product **B** is also formed via a radical intermediate. The

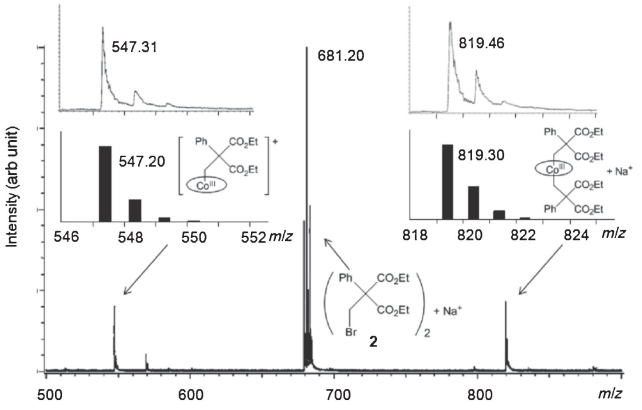
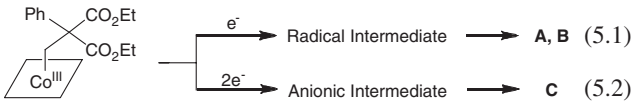


Figure 3. ESI mass spectrum for the electrolysis solution (Entry 2 in Table 1). Inset: experimental (top) and theoretical (bottom) isotopic distributions for the intermediates.

radical intermediate is probably formed during the disproportionation which is induced by the one-electron reduction of the Co(III) monoalkylated complex. The simple reduced product **A** is also formed via the radical intermediate (eq 5.1). The dimerized products were not detected because the concentrations of the generated radical intermediates would be low with the small catalytic amount of **2**. On the other hand, previous studies of **1** demonstrated that the carboxylic ester-migrated product **C** is formed via not a radical, but anionic intermediate, which results from the two-electron reduction of the Co(III) monoalkylated complex (eq 5.2).[3] In the present study of **2**, it is reasonable to expect that the carboxylic ester-migrated product **C** forms via not a radical, but cationic intermediate. This probably results from the oxidation of the Co(III) dialkylated complex via a highly labile Co(IV) intermediate, which was previously reported for other organocobalt(III) complex systems.[9]



Based on the previous and present results, a proposed mechanism at −1.20 V vs. Ag–AgCl in the undivided cell is shown Figure 4. The electrochemically generated Co(I) species of **2** induces the oxidative addition of the alkyl bromide **3** to the cobalt center with debromination. The resulting Co(III) monoalkylated complex is reduced to the one-electron-reduction intermediate, resulting in the disproportionation to the Co(I) species and the Co(III) dialkylated complex. The dialkylated complex is oxidized on the anode to afford the monoalkylated complex and the 1,2-migration product **C** via a cationic intermediate. The simply reduced product **A** and the phenyl-migrated product **B** are formed via a radical intermediate resulting from the one-electron reduction of the monoalkylated complex.

In conclusion, the complementary reactivities of the imine/oxime-type Co(III) mono- and dialkylated complexes were successfully applied to the duet electrosynthesis which combines the cathodic and anodic reactions in a single cell.[10] The present study demonstrated that the dialkylated complex facilitated the 1,2-migration of a carboxylic ester group of **2** as the oxidizable intermediate, which was detected by ESI-MS.

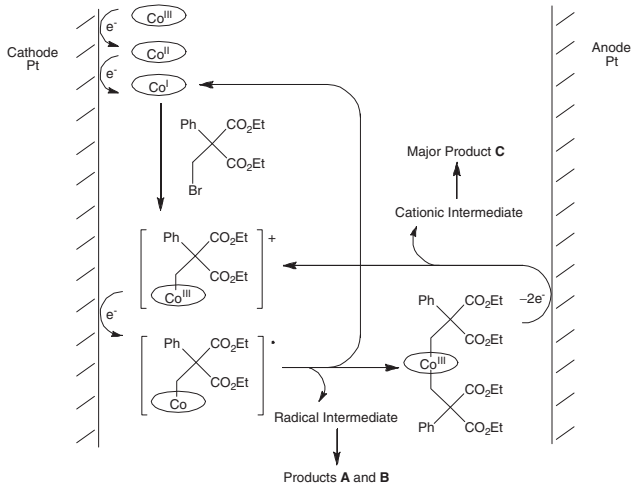


Figure 4. Proposed mechanism of electrolysis of **3** at −1.20 V vs. Ag–AgCl in the undivided cell.

This finding stands in contrast to the reactivity of the heptamethyl cobyrinate **1** which does not form a dialkylated complex due to the steric hindrance of the corrin to the cobalt center during alkylation.

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