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Hydrophobic Vitamin B_{12}. V. Electrochemical Carbon-Skeleton Rearrangement as Catalyzed by Hydrophobic Vitamin B_{12}: Reaction Mechanisms and Migratory Aptitude of Functional Groups†

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The carbon-skeleton rearrangements as catalyzed by heptamethyl cobyrinate perchlorate, [Cob(II)7C_1ester]ClO_4, were investigated under electrochemical conditions. The controlled-potential electrolysis of 2,2-bis(ethoxycarbonyl)-1-bromopropane, which is considered to be a model substrate for methylmalonyl-CoA mutase, was catalyzed by [Cob(II)7C_1ester]ClO_4 in *N,N*-dimethylformamide to give the rearrangement product, 1,2-bis(ethoxycarbonyl)propane, as a major one at −1.5 V vs. SCE in the presence of acetic acid and at potentials more cathodic than −1.8 V vs. SCE without acetic acid in the dark. The electrochemical carbon-skeleton rearrangement was postulated to proceed via formation of anionic intermediates. The electrolyses of 1-bromo-2-cyano-2-ethoxycarbonylpropane, 2-acetyl-1-bromo-2-ethoxycarbonylpropane, and 1-bromo-2-[(ethylthio)carbonyl]propane with [Cob(II)7C_1ester]ClO_4 also afforded the corresponding carbon-skeleton rearrangement products. The results indicated that substrates with two electron-withdrawing groups placed on the *β*-carbon atom with combinations of one carboxylic ester and one of carboxylic ester, acetyl, and cyano moieties readily gave the corresponding rearrangement products which were derived from individual migration of the substituent groups. Substrates with only one of the electron-withdrawing groups, carboxylic ester, acetyl, and cyano, did not give any rearrangement product, but a substrate with one thioester group afforded the corresponding rearrangement product. The migratory aptitude of electron-withdrawing groups was found to decrease in the order: COSR>COR>COOR>CN. Both electronic character and steric bulkiness of the migrating groups are apparently reflected on this tendency, even though relative contributions of these effects are much dependent on the nature of *β*-substituents.

We have previously prepared the cobalt complex of 1,19-dimethyl-A,D-didehydrocorrin (Hbdhc), having additional double bonds at peripheral positions and an additional angular methyl group as compared with the parent corrinoid, and investigated its structural properties in connection with vitamin B_{12} chemistry.[1,2] The bdhc complex is quite analogous to the corrinoid as far as electronic properties are concerned on the basis of its spectroscopic, electrochemical, and axial coordination behavior. On the other hand, the angular methyl groups in the complex exert an unusually large steric effect in the bimolecular reactions of Co^I(bdhc) with alkyl donors which result in the formation of an alkyl–cobalt bond. Even though the bdhc complex is considered to be a good B_{12} model, it does not catalyze the 1,2-migration reaction observed with vitamin B_{12}. This is indeed originated from the steric repulsion effect provided by the angular methyl group which prevents an alkyl fragment initially formed through the Co–C cleavage from staying close to the nuclear cobalt. In order to improve this stereochemical situation, it became necessary to develop another good vitamin B_{12} model.

Various cobalt complexes have been synthesized as model complexes,[3] but all of those complexes cannot be qualified as favorable model complexes in the light of the following aspects. (i) Redox behavior of the central cobalt, which is mainly controlled by basicity of an equatorial ligand, must be similar to that for the naturally occurring vitamin B_{12}. (ii) Electronic properties must be equivalent to those of the natural B_{12}, which are provided by the corrin ring with eight double bonds and the direct bond between A and D rings. (iii) The steric effects, which are caused by the methyl moiety and the hydrogen atom at C(1) and C(19) positions in the corrin ring, respectively, and by four propanamides and three acetamides placed at the *α*- and *β*-peripheral sites, respectively, must be retained by model complexes.

In order to simulate various functions of vitamin B_{12} as exerted in the hydrophobic active sites of enzymes concerned, we have been dealing with hydrophobic vitamin B_{12} derivatives which have ester groups in place of the peripheral amide moieties of the naturally occurring vitamin B_{12}.[4–12] These modified cobalt complexes satisfy all the above requirements and are readily soluble in a wide range of organic solvents.

Most of the vitamin B_{12} model reactions so far carried out are concerned merely with cleavage of the Co–C bond of the corresponding alkylated complexes[13] and cannot be regarded as catalytic ones.[14] Because the alkylated complexes in these reactions were prepared from cobalt complexes and alkyl halides in the presence of chemical reductants such as $NaBH_4$, it was difficult to establish the catalytic cycle and to eliminate an undesirable effect caused by reductants on the reaction. In order to overcome these

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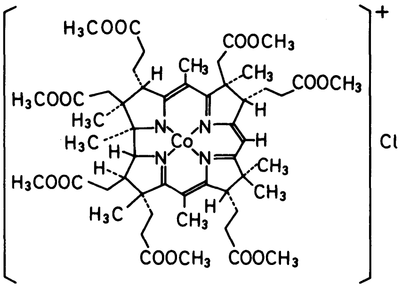
difficulties and set up clean reaction systems, we have adopted electrochemical means for reduction.[11] Recently, electrochemical reactions catalyzed by vitamin B_{12} derivatives or model complexes have been carried out rather extensively,[15-20] but catalytic isomerization reactions accompanied with the carbon-skeleton rearrangement, which are considered to be typical coenzyme B_{12}-dependent enzymatic reactions, have not been successfully performed yet.

In the present work, we have carried out the rearrangement reactions by electrochemical means for the first time as catalyzed by heptamethyl cobyrinate perchlorate, [Cob(II)7C_1ester]ClO_4, and reaction mechanisms involved in the electrolyses were clarified by means of various spectroscopic methods. Furthermore, we studied the migratory aptitude of functional groups in the carbon-skeleton rearrangement by employing several substrates having electron-withdrawing groups such as carboxylic ester, thioester, acetyl, and cyano moieties.



[Cob(II)7C_1ester]ClO_4

Results and Discussion

We have previously pointed out that [Cob(II)7C_1ester]ClO_4 is readily reduced to the univalent cobalt species of highly nucleophilic character by electrochemical means in nonaqueous media,[5] and catalytic reaction cycles shown in Scheme 1 were established. An alkylated complex, generated by the reaction between a univalent cobalt complex and an alkyl halide (RX), is generally decomposed by photolysis[10] or electrolysis to afford reduction and/or rearrangement products. First, we adopted 2,2-bis(ethoxycarbonyl)-1-bromopropane (**1**) which is considered to be a model substrate for methylmalonyl-CoA mutase. This bromide was originally used by Rêtey et al. as a model substrate,[21] but Tada et al. reported that the photochemical decomposition of the corresponding alkylated cobaloxime complex gave only the reduction product, 2,2-bis(ethoxycarbonyl)-propane, and the rearrangement product, 1,2-bis-(ethoxycarbonyl)propane, was not detected.[22] Furthermore, the ethoxycarbonyl group of this substrate does not migrate during the reaction with tributyltin hydride which acts to generate the corresponding free radical in the course of the reaction without a cobalt complex.[23]

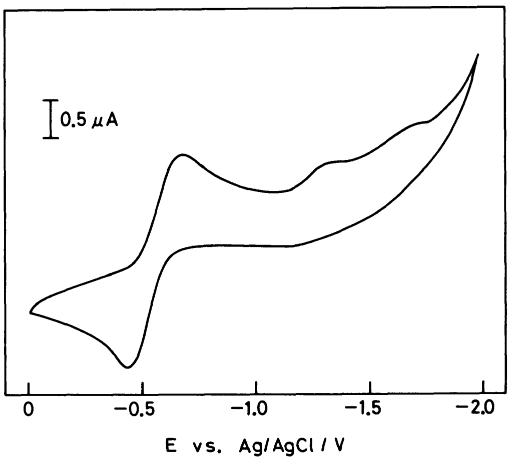
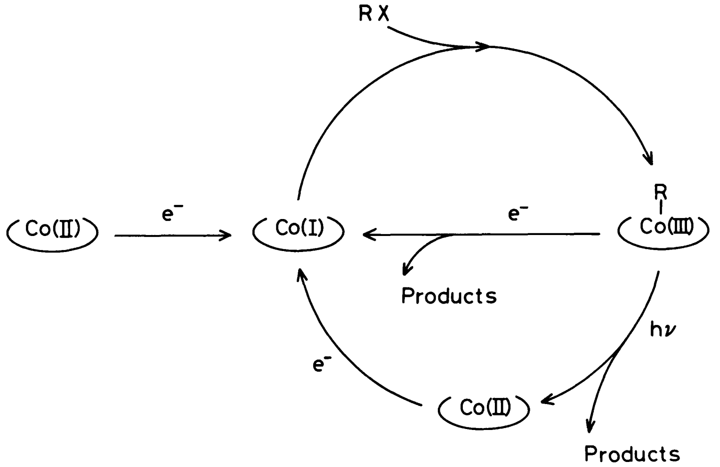


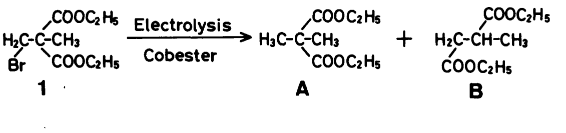
Fig. 1. Cyclic voltammogram of [Cob(II)7C_1ester]ClO_4 (7.2×10^{-4} mol dm^{-3}) in DMF containing 2,2-bis(ethoxycarbonyl)-1-bromopropane (0.10 mol dm^{-3}) and TBAF (0.10 mol dm^{-3}) at 20±2 °C in the dark; sweep rate, 100 mV s^{-1}.



Scheme 1.

Redox Behavior. The redox behavior of [Cob(II)-7C_1ester]ClO_4 in *N*,*N*-dimethylformamide (DMF) containing 2,2-bis(ethoxycarbonyl)-1-bromopropane in a large excess and tetrabutylammonium tetrafluoroborate (TBAF) as a supporting electrolyte was examined by means of cyclic voltammetry as shown in Fig. 1.[12] The redox potential for the Co(II)/Co(I) couple on [Cob(II)7C_1ester]ClO_4 in DMF was observed at −0.56 V vs. Ag/AgCl in the presence of the alkyl bromide, while the corresponding potential in DMF was observed at −0.58 V vs. Ag/AgCl (−0.61 V vs. SCE) without the alkyl bromide.[5] An irreversible reduction peak was observed at ca. −1.3 V vs. Ag/AgCl and assigned to the formation of the one-electron reduction intermediate of the alkylated complex, which was generated by the reaction between the Co^I species and the alkyl halide. This value is in agreement with the one for heptamethyl methylaquacobyrinate perchlorate, [$(CH_3)(H_2O)$Cob(III)7C_1-ester]ClO_4, in DMF; −1.29 V vs. Ag/AgCl (−1.32 V vs. SCE). Its cathodic peak current was small in comparison with that for Co(II)/Co(I) due to the slow rate of reaction between the Co^I species and the substrate. In addition, the second irreversible reduction peak was observed at ca. −1.8 V vs. Ag/AgCl. This peak was assigned to the formation of the two-electron reduction intermediate of the alkylated complex as confirmed by coulometry and controlled-potential electrolysis described below. The first reduction peak for substrate **1** was observed at −2.7 V vs. Ag/AgCl by cyclic voltammetry in DMF without the hydrophobic vitamin B_{12}, so that the peaks observed in the range of −2.0—0 V vs. Ag/AgCl are not originated from the substrate itself. Consequently, the electrochemical behavior shown in Fig. 1 is consistent with the reduction processes shown in Scheme 5, indicating generation of mutually different intermediates by the electrolysis at −1.0, −1.5, and −2.0 V vs. SCE.[24]

Catalytic Reaction. The electrolysis of 2,2-bis(ethoxycarbonyl)-1-bromopropane was carried out upon addition of [Cob(II)7C_1ester]ClO_4 under various conditions. The following findings were obtained on the basis of the product analyses given in Table 1 (refer to Eq. 1). (i) At −1.0 V vs. SCE: products were obtained only when the reaction mixture was irradiated with the visible light, and the major product was the reduced one (**A** in Eq. 1). (ii) At −1.5 V vs. SCE in the dark: the rearrangement product (**B** in Eq. 1) was the major one when an efficient proton source such as acetic acid or propionic acid was added,[25] while the reduction product (**A**) was largely obtained when 2-propanol was added or without any additive. (iii) At −1.5 V vs. SCE under irradiation with the visible light: the major product was the reduced one even in the presence of acetic acid. (iv) At potentials more cathodic than −1.8 V vs. SCE in the dark: the rearrangement product (**B**) was largely obtained even in the absence of acetic acid. The catalysis was very efficient at −2.0 V vs. SCE, so that the rearrangement product was obtained in yields



$$\underset{\mathbf{1}}{BrH_2C\text{-}C(CH_3)(COOC_2H_5)_2} \xrightarrow[\text{Cobester}]{\text{Electrolysis}} \underset{\mathbf{A}}{H_3C\text{-}C(CH_3)(COOC_2H_5)_2} + \underset{\mathbf{B}}{H_3C\text{-}CH(COOC_2H_5)\text{-}CH_2\text{-}COOC_2H_5} \qquad (1)$$

Table 1. Product Analyses for Controlled-Potential Electrolysis of 2,2-Bis(ethoxycarbonyl)-1-bromopropane as Catalyzed by Hydrophobic Vitamin B_{12}[a)]

Entry	Electrolysis conditions					Yield/%[e)]	
	Potential V vs. SCE	Irradiation[b)]	Additive[c)]	Charge[d)] F mol^{-1}	Period h	A	B
1	−1.0	Irradiation	CH_3COOH	0.2	9	9—12	Trace
2	−1.5	Irradiation	CH_3COOH	3.0	12	36—41	3—10
3	−1.5	In the dark	CH_3COOH	3.0	6	16—18	40—46
4	−1.5	In the dark	C_2H_5COOH	3.0	9	15—17	25—28
5	−1.5	In the dark	$(CH_3)_2CHOH$	1.0	23	32—37	Trace
6	−1.5	In the dark	None	1.0	23	25—36	ca. 1
7	−1.8	In the dark	CH_3COOH	2.0	6	12—13	32—36
8	−1.8	In the dark	None	2.0	23	24—28	23—31
9	−2.0	In the dark	None	2.0	2	11—18	76—84

a) Electrolysis was carried out in a two-compartment cell equipped with Pt electrodes at 20±2 °C under argon atmosphere. Starting solutions composed of: [Cob(II)7C_1ester]ClO_4, 30 mg (2.6×10^{-5} mol): 2,2-bis(ethoxycarbonyl)-1-bromopropane, 1.0 g (3.8×10^{-3} mol); 30 mL of DMF containing 0.50 mol dm^{-3} TBAF. b) Irradiated with a 300-W tungsten lamp from a distance of 50 cm. c) CH_3COOH, 0.50 g (8.3×10^{-3} mol); C_2H_5COOH, 0.61 g (8.3×10^{-3} mol); $(CH_3)_2CHOH$, 0.50 g (8.3×10^{-3} mol). d) Electrical charge passed per mol of the substrate. e) Based on an initial amount of the substrate; the rest was the unreacted substrate (a small amount of $(CH_3CO_2)CH_2C(CH_3)(CO_2C_2H_5)_2$ was obtained when CH_3COOH was added); analyzed by GLC. Recovery of the catalyst: 80—90% at −1.0 V; 60—70% at −1.5 V; ca. 50% at −1.8 and −2.0 V vs. SCE.

equivalent to 100—110 times as much as a molar quantity of the hydrophobic vitamin B$_{12}$ after 2 h of the reaction.

Reaction Mechanisms. The reaction mechanisms for controlled-potential electrolyses were investigated by means of electronic spectroscopy, product analyses, and coulometry as well as by the spin-trapping ESR technique.

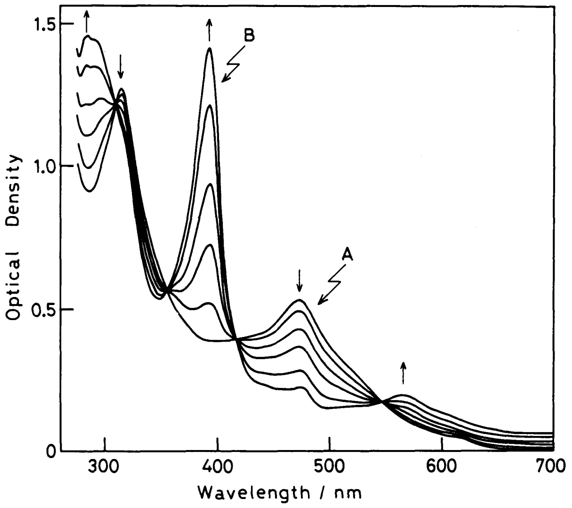


Fig. 2. Spectral change during electrochemical reduction of [Cob(II)7C$_1$ester]ClO$_4$ (5.2×10^{-5} mol dm^{-3}) in DMF containing 0.20 mol dm^{-3} TBAF at −1.0 V vs. SCE and 20.5±0.1 °C: A, [Cob(II)7C$_1$ester]ClO$_4$; B, Cob(I)7C$_1$ester. Trends of spectral change with time are shown by arrows.

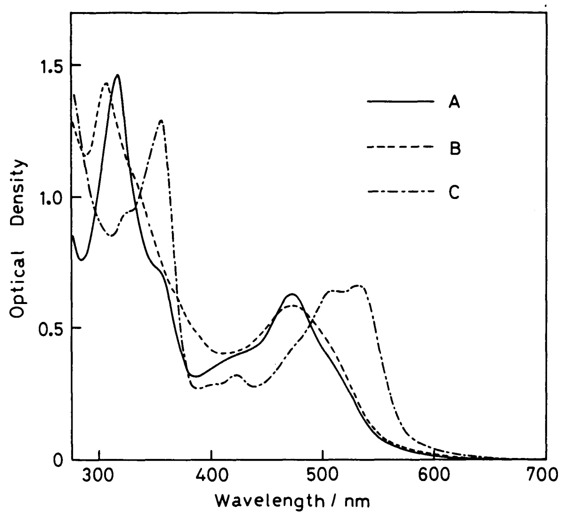


Fig. 3. Electronic spectra observed for a DMF solution containing [Cob(II)7C$_1$ester]ClO$_4$ (5.2×10^{-5} mol dm^{-3}), 2,2-bis(ethoxycarbonyl)-1-bromopropane (1.5×10^{-2} mol dm^{-3}), TBAF (0.20 mol dm^{-3}), and acetic acid (1.2×10^{-2} mol dm^{-3}) at 20.5±0.1 °C under the following conditions: A, before electrolysis under argon atmosphere; B, electrolysis at −1.0 V vs. SCE under argon atmosphere; C, sample B being irradiated with a 150-W tungsten lamp from a distance of 20 cm for 1 min under aerobic conditions.

(a) Electrolysis at −1.0 V vs. SCE. The controlled-potential electrolysis was followed by electronic spectroscopy. [Cob(II)7C$_1$ester]ClO$_4$ was reduced to Cob(I)7C$_1$ester, having an absorption maximum at 394 nm as shown in Fig. 2, when the electrolysis was carried out at −1.0 V vs. SCE in the absence of an alkyl halide. When the electrolysis with 2,2-bis(ethoxycarbonyl)-1-bromopropane was carried out at −1.0 V vs. SCE in the dark, [Cob(II)7C$_1$ester]ClO$_4$ was transformed into the corresponding alkylated complex with absorption maxima at 305 and 474 nm (curve B in Fig. 3). Upon irradiation of this complex with the visible light for a short period of time under aerobic conditions, the electronic spectrum indicated cleavage of the Co–C bond[10] (curve C in Fig. 3). These spectral changes apparently reflect the fact that the alkylated complex is formed at −1.0 V vs. SCE and subsequently decomposed under irradiation conditions.

The reaction was also examined by the spin-trapping technique with α-phenyl-*N*-(*t*-butyl)nitrone (PBN).[26] An ESR spectrum for the PBN spin adduct formed in the course of electrolysis at −1.0 V vs. SCE is shown in Fig. 4. An ESR signal was not observed in the dark (A in Fig. 4), but clear signals for the PBN spin adduct (A_N=14.9 G, A_H=2.7 G; 10^4G=1 T) were detected upon irradiation with the visible light under anaerobic conditions (B in Fig. 4). The identical signals were observed in the absence of acetic acid. The result indicates that the radical species is generated as the intermediate under irradiation conditions.

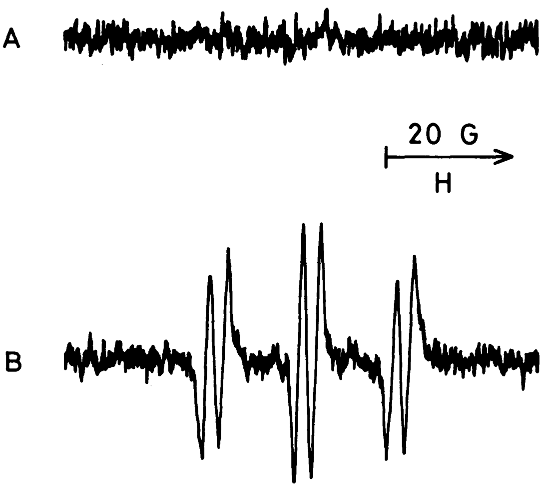
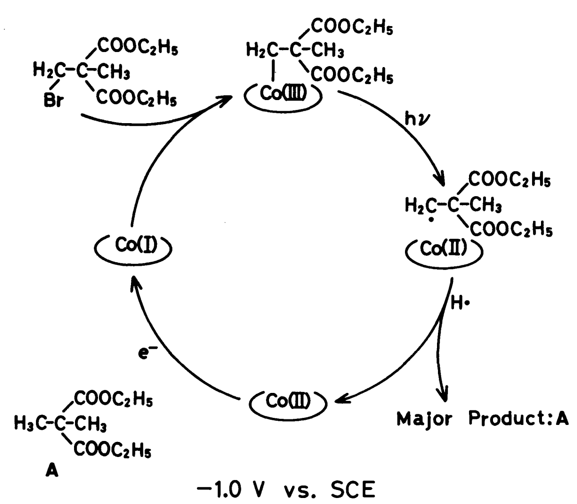


Fig. 4. ESR spectra observed during electrolysis (at −1.0 V vs. SCE) of a DMF solution containing [Cob(II)7C$_1$ester]ClO$_4$ (2.4×10^{-3} mol dm^{-3}), 2,2-bis(ethoxycarbonyl)-1-bromopropane(0.29 mol dm^{-3}),PBN (0.12 mol dm^{-3}), acetic acid (0.56 mol dm^{-3}), and TBAF (0.10 mol dm^{-3}) at room temperature: A, in the dark; B, irradiated with a 300-W tungsten lamp from a distance of 60 cm.

In the light of the spectral measurements and the product analyses for the electrolysis at −1.0 V vs. SCE, a reaction cycle takes place as shown in Scheme 2. The Co^{II} complex is first converted into the Co^{I} species by the electrochemical reduction. The alkylated complex is formed in the second place by the reaction of the super-nucleophilic Co^{I} species with 2,2-bis(ethoxycarbonyl)-1-bromopropane. The complex is then decomposed by the visible light to give the Co^{II} species and the alkyl radical. The radical species abstracts a hydrogen atom to afford the reduction product (**A**), and the Co^{II} complex repeatedly acts as a mediator.



Scheme 2.

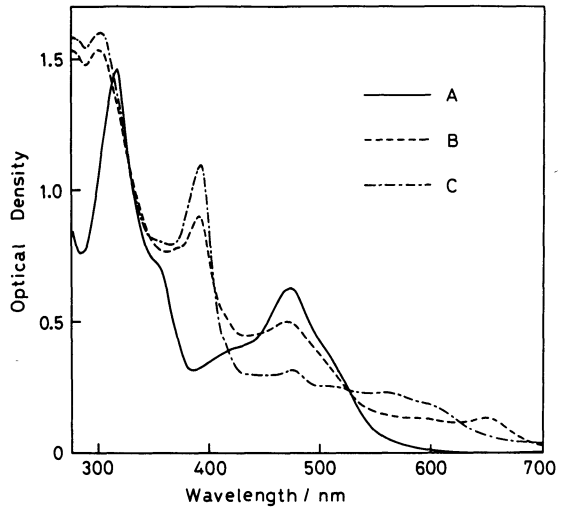


Fig. 5. Electronic spectra observed steadily during electrolysis of a DMF solution containing [Cob(II)7C$_1$-ester]ClO$_4$ (5.2×10^{-5} mol dm^{-3}), 2,2-bis(ethoxycarbonyl)-1-bromopropane (1.5×10^{-2} mol dm^{-3}), TBAF (0.20 mol dm^{-3}), and acetic acid (1.2×10^{-2} mol dm^{-3}) at 20.5±0.1 °C: A, before electrolysis; B, at −1.5 V vs. SCE; C, at −1.5 V vs. SCE without acetic acid.

(b) Electrolysis at −1.5 V vs. SCE. When the electrolysis was carried out at −1.5 V vs. SCE, absorption maxima were observed at 280, 302, 391, and 474 nm (curve B in Fig. 5). The spectrum indicates the formation of the alkylated complex and Cob(I)7C$_1$-ester. A similar spectral change was observed even in the absence of acetic acid (curve C in Fig. 5), but the absorbance intensity originated from Cob(I)7C$_1$ester was greater than that observed in the presence of acetic acid. These spectral features indicate that the alkylated complex is electrochemically decomposed at −1.5 V vs. SCE.

The electrolysis reaction without irradiation was also examined by the spin-trapping technique. ESR spectra for the PBN spin adducts formed in the course of electrolysis in the dark are shown in Fig. 6. ESR signals attributable to the PBN spin adducts were clearly observed (A in Fig. 6), while the signal intensities became much weaker upon addition of acetic acid (B in Fig. 6). Spin Hamiltonian parameters for the spin adducts are as follows: A_N=14.9 G, A_H=2.7 G; A_N=14.3 G, A_H=6.3 G. Only a single radical species with the former set of parameters was detected at the initial stage of the electrolysis. These values are identical with those observed for the electrolysis at −1.0 V vs. SCE under irradiation conditions. The latter set of parameters was assigned to another species formed in some secondary reactions. The result confirms that the radical species is generated as the electrolysis intermediate at −1.5 V vs. SCE without acetic acid while an efficient proton source such as acetic acid inhibits the formation of the radical species to a large extent.

A relationship between electrical quantity and

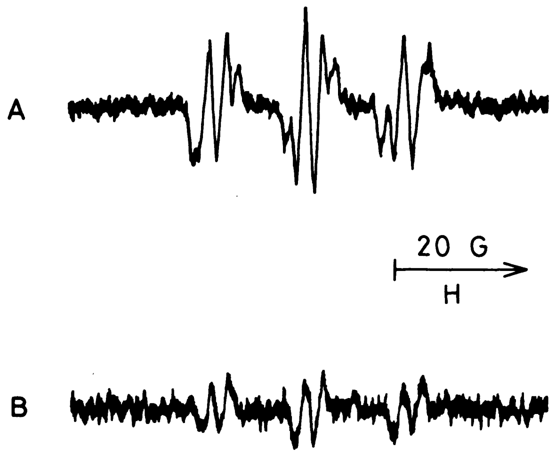
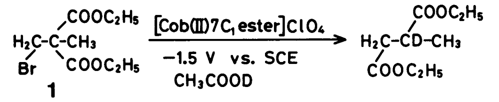


Fig. 6. ESR spectra observed during electrolysis (at −1.5 V vs. SCE) of a DMF solution containing [Cob(II)7C$_1$ester]ClO$_4$ (1.7×10^{-3} mol dm^{-3}), 2,2-bis(ethoxycarbonyl)-1-bromopropane (0.25 mol dm^{-3}), PBN (0.10 mol dm^{-3}), and TBAF (0.10 mol dm^{-3}) at room temperature in the dark: A, without acetic acid; B, in the presence of acetic acid (0.56 mol dm^{-3}).

product yield at the initial stage of electrolysis in the dark without acetic acid at −1.5 V vs. SCE is shown in Fig. 7. The reciprocal value (n) of the slope gives a number of electrons needed for the reaction; n=1.2 indicates one-electron reduction.

In order to identify the role of acetic acid, the electrolysis was carried out in the presence of the deuterated acetic acid (CH_3COOD) at −1.5 V vs. SCE in the dark. The product analysis by means of ^{1}H-NMR and mass spectral measurements clarified that the rearrangement product containing one deuterium, ($H_5C_2O_2C$)$CH_2CD(CH_3)(CO_2C_2H_5)$, was primarily obtained (refer to Eq. 2).[27] Its isotopic purity was estimated to be 55—60%D. Even when CD_3COOD was used, the isotopic purity remained the same. Reasons for the formation of the product without deuterium may be given as follows: (i) proton-exchange between the deuterated acetic acid and a trace amount of water involved in DMF takes place;[28,29] (ii) proton donation from formic acid formed by decomposition of DMF occurs;[28] (iii) a proton is abstracted from the quaternary ammonium salt, the supporting electrolyte (Hofmann elimination).[30] The electrochemical carbon-skeleton rearrangement is postulated here to proceed via formation of an anionic intermediate, and the proton from acetic acid attacks on the β-carbon of the substrate bound to the hydrophobic vitamin B_{12}.



$$\underset{\mathbf{1}}{\mathrm{H_2C(Br){-}C(CH_3)(COOC_2H_5)_2}} \xrightarrow[\substack{-1.5\ \mathrm{V\ vs.\ SCE} \\ \mathrm{CH_3COOD}}]{[\mathrm{Cob(II)7C_1ester}]\mathrm{ClO_4}} \mathrm{H_2C(COOC_2H_5){-}CD(CH_3){-}COOC_2H_5} \qquad (2)$$

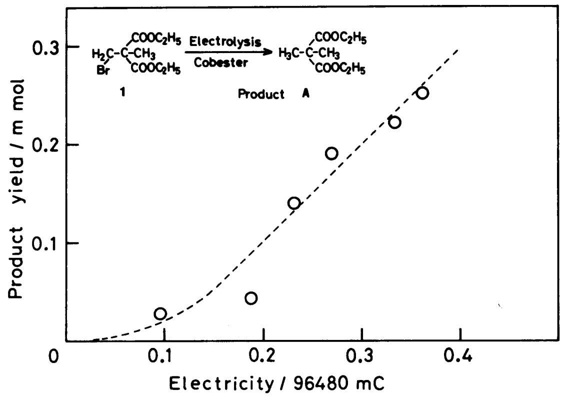
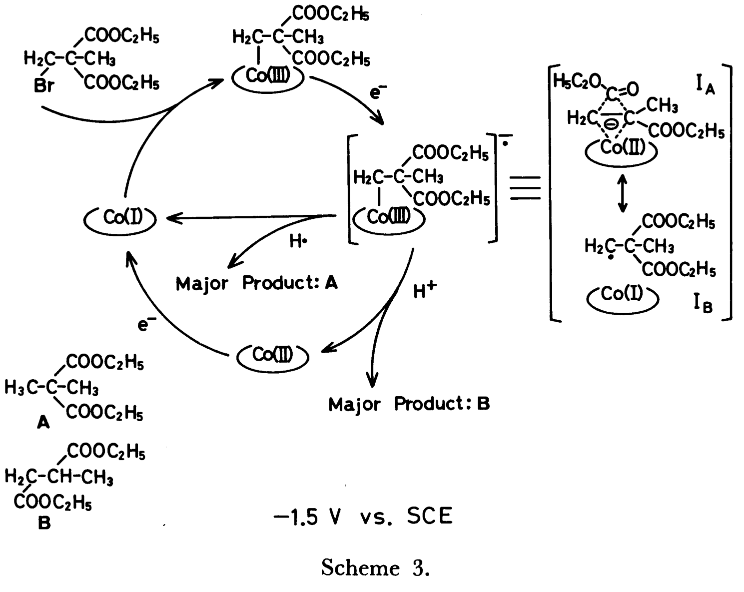


Fig. 7. Relationship between quantity of electricity and yield of the reduction product, 2,2-bis(ethoxycarbonyl)-propane, for electrolysis at −1.5 V vs. SCE and 20± 2 °C in the dark. Initial solution: [Cob(II)7C$_1$ester]-ClO_4, 30 mg (2.6×10^{-5} mol); 2,2-bis(ethoxycarbonyl)-1-bromopropane, 1.0 g (3.8×10^{-3} mol); 30 mL of DMF containing 0.50 mol dm^{-3} TBAF.

In the light of the above results, the electrolysis at −1.5 V vs. SCE proceeds via reaction cycles shown in Scheme 3. The mechanism for alkylation of the hydrophobic vitamin B_{12} is identical with that at −1.0 V vs. SCE (vide supra). The alkylated complex is then reduced to the one-electron reduction intermediate at −1.5 V vs. SCE in the dark. The electronic structure for the intermediate seems to be represented by two canonical forms I$_A$ and I$_B$ (Scheme 3). The proton attack on the β-carbon of the substrate induces the carbon-skeleton rearrangement, followed by the cobalt–carbon bond cleavage. On the other hand, the one-electron reduction intermediate is spontaneously decomposed to afford the Co^I chelate and the alkyl radical in the absence of an efficient proton source. The reduction product (**A**) is mainly produced from the alkyl radical by rapid abstraction of the hydrogen atom.

(c) Electrolysis at −2.0 V vs. SCE. When the electrolysis was carried out at −1.8 V vs. SCE, the absorbance originated from Cob(I)7C$_1$ester was more intense than that observed during the electrolysis at −1.5 V vs. SCE (Fig. 8). The alkylated complex was



Scheme 3.

decomposed to the Co^I complex at potentials more cathodic than −1.8 V vs. SCE in the dark, since the Co^I species was steadily observed by electronic spectroscopy during the electrolysis. The spin-trapping technique was not applicable to the electrolysis at −2.0 V vs. SCE, because spin adducts were formed to a limited extent by electrolysis of the substrate itself even in the case without the hydrophobic vitamin B_{12}.

A relationship between electrical quantity and product yield for the electrolysis at −2.0 V vs. SCE in the dark is shown in Fig. 9; the *n* value of 2.3 indicates the electrolysis takes place via two-electron reduction (line C). Thus, the reaction at −2.0 V vs. SCE must proceed through a cycle shown in Scheme 4. The alkylated complex, which is generated in a manner as observed at −1.0 V vs. SCE, is converted into the two-electron reduction intermediate in the dark. This intermediate is decomposed to the Co^I chelate and the anionic species, and rearrangement product is obtained from the latter.

(d) Overall feature of electrolysis mechanisms. The formation conditions for the reduction and rearrangement products in the electrolysis of 2,2-bis(ethoxycarbonyl)-1-bromopropane as catalyzed by the hydrophobic vitamin B_{12} are summarized in Scheme 5. The rearrangement product is obtained primarily from the anionic intermediates, I_A and I_C, while the simple reduction product is mainly

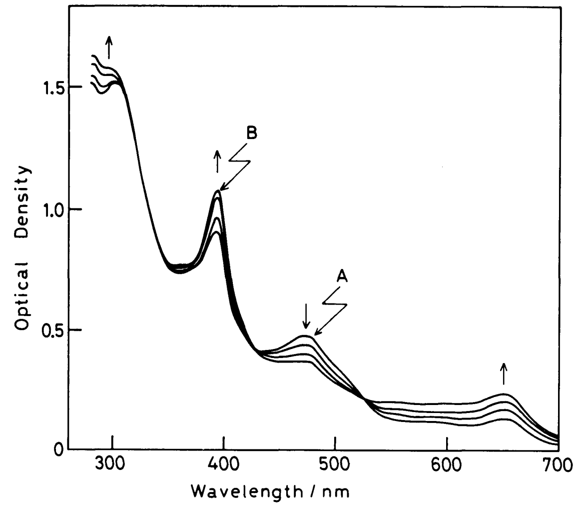


Fig. 8. Electronic spectra observed during electrolysis of a DMF solution containing $[Cob(II)7C_1ester]ClO_4$ (5.2×10^{-5} mol dm^{-3}), 2,2-bis(ethoxycarbonyl)-1-bromopropane (1.5×10^{-2} mol dm^{-3}), TBAF (0.20 mol dm^{-3}), and acetic acid (1.2×10^{-2} mol dm^{-3}) at 20.5 ±0.1 °C: A, steady state at −1.5 V vs. SCE; B, steady state at −1.8 V vs. SCE (electrolysis potential was reset at −1.8 V vs. SCE after state A was attained; trends of spectral change are shown by arrows).

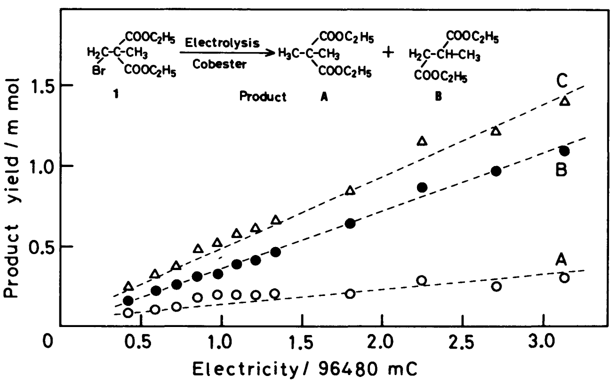
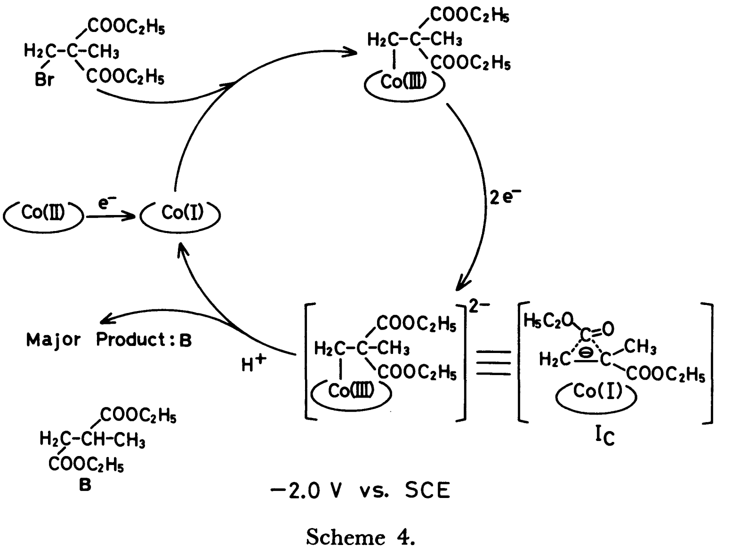


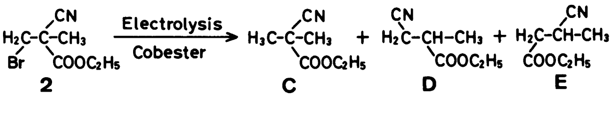
Fig. 9. Relationships between quantity of electricity and product yield for electrolysis at −2.0 V vs. SCE and 20±2 °C in the dark: A, yield of the reduction product, 2,2-bis(ethoxycarbonyl)propane; B, yield of the rearrangement product, 1,2-bis(ethoxycarbonyl)propane; C, total yield. Initial solution: $[Cob(II)7C_1ester]ClO_4$, 30 mg (2.6×10^{-5} mol); 2,2-bis(ethoxycarbonyl)-1-bromopropane, 1.0 g (3.8×10^{-3} mol); 30 mL of DMF containing 0.50 mol dm^{-3} TBAF.



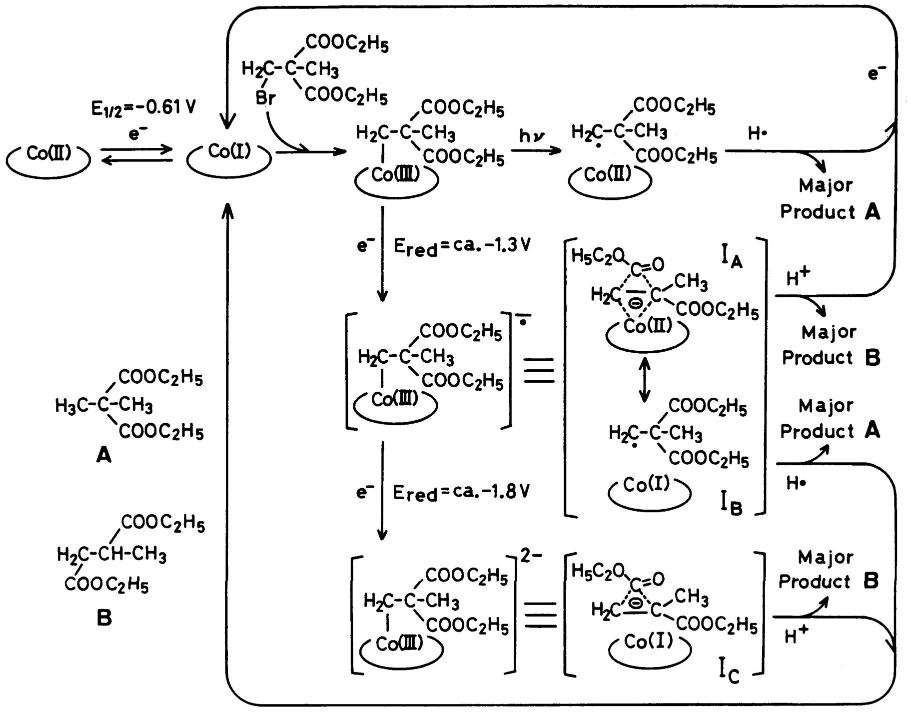
Scheme 4.

produced from the radical species. In particular, the two-electron reduction intermediate (Ic) is more effective in affording the rearrangement product. Since the identical radical species, which is produced by the reaction of the present substrate with tributyltin hydride[23] or by the photolysis of the present substrate bound to cobaloxime,[22] does not give the rearrangement product, the anionic reaction intermediates are the primary source for the rearrangement product. The present study demonstrates the first example of the rearrangement as catalyzed by a vitamin B_{12} model under electrochemical conditions.

Electrolyses of Various Substrates. In order to make further characterization of the catalytic proficiency of the hydrophobic vitamin B_{12} and clarify the migratory aptitude of functional groups in the electrochemical rearrangement reaction, other substrates were also used here. These substrates and the corresponding products are shown in Eqs. 3—8. All the substrates showed their first reduction peaks at −2.7±0.1 V vs. Ag/AgCl as confirmed by cyclic voltammetry.



$$\underset{\mathbf{2}}{BrH_2C\text{-}C(CN)(COOC_2H_5)\text{-}CH_3} \xrightarrow[\text{Cobester}]{\text{Electrolysis}} \underset{\mathbf{C}}{H_3C\text{-}C(CN)(COOC_2H_5)\text{-}CH_3} + \underset{\mathbf{D}}{(CN)H_2C\text{-}CH(COOC_2H_5)\text{-}CH_3} + \underset{\mathbf{E}}{(C_2H_5OOC)H_2C\text{-}CH(CN)\text{-}CH_3} \qquad (3)$$

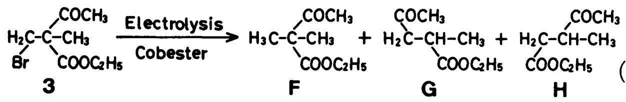


Scheme 5.

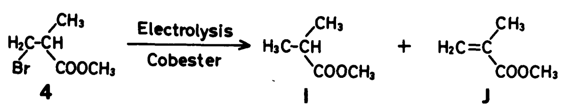
Table 2. Product Analyses for Controlled-Potential Electrolysis of 1-Bromo-2-cyano-2-ethoxycarbonylpropane as Catalyzed by Hydrophobic Vitamin B_{12}[a)]

Entry	Electrolysis conditions					Yield/%[e)]		
	Potential V vs. SCE	Irradiation[b)]	Additive[c)]	Charge[d)] F mol^{-1}	Period h	**C**	**D**	**E**
1	−1.0	Irradiation	None	0.3	8	5	Trace	Trace
2	−1.5	In the dark	None	1.0	21	32—34	Trace	ca. 1
3	−1.5	In the dark	CH_3COOH	3.0	6	31—32	2—3	56—63
4	−2.0	In the dark	None	2.0	8	28—32	2—3	60—64

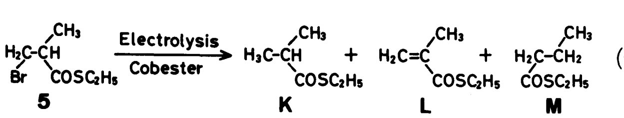
a) Electrolysis was carried out in a two-compartment cell equipped with Pt electrodes at 20±2 °C under argon atmosphere. Starting solutions composed of: $[Cob(II)7C_1ester]ClO_4$, 30 mg (2.6×10^{-5} mol); 1-bromo-2-cyano-2-ethoxycarbonylpropane, 1.0 g (4.5×10^{-3} mol); 30 mL of DMF containing 0.50 mol dm^{-3} TBAF. b) Irradiated with a 300-W tungsten lamp from a distance of 50 cm. c) CH_3COOH, 0.50 g (8.3×10^{-3} mol). d) Electrical charge passed per mol of the substrate. e) Based on an initial amount of the substrate; the rest was the unreacted substrate (a small amount of $(CH_3CO_2)CH_2C(CH_3)(CO_2C_2H_5)(CN)$ was obtained when CH_3COOH was added); analyzed by GLC. Recovery of the catalyst: 80—90% at −1.0 V; 60—70% at −1.5 V; ca. 50% at −2.0 V vs. SCE.



(4)



(5)



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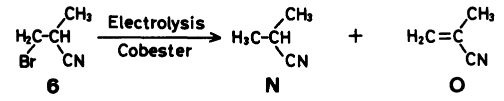

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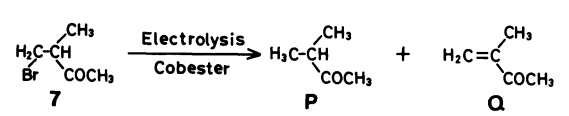


(8)

(a) Substrates with two electron-withdrawing groups. The product analyses for the electrolyses of 1-bromo-2-cyano-2-ethoxycarbonylpropane (**2**) and 2-acetyl-1-bromo-2-ethoxycarbonylpropane (**3**) are respectively shown in Tables 2 and 3. The following findings are based on the product analyses for the reaction with substrate **2** (Table 2; refer to Eq. 3). (i) At −1.0 V vs. SCE: products were obtained only when the reaction mixture was irradiated with the visible light, and the major product was the reduced one, 2-cyano-2-ethoxycarbonylpropane (**C**). (ii) At −1.5 V vs. SCE in the dark: the ester-migrated product, 2-cyano-1-ethoxycarbonylpropane (**E**), was the major one when acetic acid was added, while the reduction product (**C**) was largely obtained without any proton source. (iii) At −2.0 V vs. SCE in the dark: the rearrangement product (**E**) was the major one even in the absence of a proton source. (iv) The ester-migrated product (**E**) was produced more readily than the cyano-migrated one, 1-cyano-2-ethoxycarbonylpropane (**D**), under all the conditions; **E**:**D**=96:4.

The following results provide the basis for clarification of the reaction mechanisms concerned. (i) As for cyclic voltammetry performed in DMF on the alkylated complex[31] derived from the hydrophobic vitamin B12 and **2**, the first reduction wave was observed at −1.25 V vs. Ag/AgCl and the second one at −1.80 V vs. Ag/AgCl. (ii) On the basis of the relation between electrical quantity and product yield, one-electron reduction (n=1.1) and two-electron reduction (n=2.0) took place at −1.5 and −2.0 V vs. SCE, respectively. (iii) When CH_3COOD was used as a proton source at −1.5 V vs. SCE in the dark, the rearrangement product containing one deuterium, $(H_5C_2O_2C)CH_2CD(CH_3)(CN)$, was obtained as the major product. Its isotopic purity was estimated to be 50—60%D. These results are comparable to those obtained for the reaction with **1**. It may be concluded that the electrolyses of **2** catalyzed by the hydrophobic vitamin B12 proceed via formation of intermediates identical in electronic nature with those given in Scheme 5. It became apparent that the ester group has a higher tendency to migrate than the cyano group. This is in contrast with a previous result reported by Rêtey et al.,[32] showing that the cyano-migrated product was obtained as a major one by photolysis of the alkylated complex derived from cobalamin and **2**. They concluded that the cyano group has a somewhat higher tendency to migrate than the ethoxycarbonyl group. Since their experimental conditions allow to generate primarily the radical species, the migratory aptitude of cyano and ester groups seems to become reversed under the present conditions which allow to give the anionic intermediates.

The electrolysis of substrate **3** gave the following

Table 3. Product Analyses for Controlled-Potential Electrolysis of 2-Acetyl-1-bromo-2-ethoxycarbonylpropane as Catalyzed by Hydrophobic Vitamin B_{12}[a)]

Entry	Electrolysis conditions					Yield/%[e)]		
	Potential V vs. SCE	Irradiation[b)]	Additive[c)]	Charge[d)] F mol^{-1}	Period h	F	G	H
1	−1.0	Irradiation	None	1.0	20	2—3	7—10	Trace
2	−1.5	In the dark	None	1.0	20	10—13	53—60	ca. 1
3	−1.5	In the dark	CH_3COOH	3.0	10	15—20	73—83	ca. 1
4	−2.0	In the dark	None	2.0	12	2—5	90—93	3—4

a) Electrolysis was carried out in a two-compartment cell equipped with Pt electrodes at 20±2 °C under argon atmosphere. Starting solutions composed of: $[Cob(II)7C_1ester]ClO_4$, 30 mg (2.6×10^{-5} mol); 2-acetyl-1-bromo-2-ethoxycarbonylpropane, 1.0 g (4.2×10^{-3} mol); 30 mL of DMF containing 0.50 mol dm^{-3} TBAF. b) Irradiated with a 300-W tungsten lamp from a distance of 50 cm. c) CH_3COOH, 0.50 g (8.3×10^{-3} mol). d) Electrical charge passed per mol of the substrate. e) Based on an initial amount of the substrate; the rest was the unreacted substrate (a small amount of $(CH_3CO_2)CH_2C(CH_3)(COCH_3)(CO_2C_2H_5)$ was obtained when CH_3COOH was added); analyzed by GLC. The catalyst was recovered to the same extents as given in Table 2.

results on the basis of product analyses (Table 3; refer to Eq. 4). (i) The major product was the acetyl-migrated one, 1-acetyl-2-ethoxycarbonylpropane (**G**) under all the electrolysis conditions such as at −1.0 V vs. SCE under irradiation with the visible light, at −1.5 V vs. SCE in the dark with or without acetic acid, and at −2.0 V vs. SCE in the dark. (ii) A proportion of the rearrangement products was the highest under the electrolysis conditions at −2.0 V vs. SCE. (iii) The acetyl-migrated product (**G**) was much more favorably obtained than the ester-migrated one, 2-acetyl-1-ethoxycarbonylpropane (**H**), under all the conditions. These results are different from those for the electrolysis of **1** and indicate that the acetyl group can also migrate via a radical mechanism. This concept is in agreement with previous results which demonstrate that the acetyl group very readily undergoes the 1,2-migration via formation of radical intermediates.[22,33)]

The following results may give some insight into the reaction mechanism. (i) The second reduction wave for the alkylated complex was scarcely detected by cyclic voltammetry carried out on [Cob(II)7C$_1$-ester]ClO$_4$ in DMF containing **3** in a large excess. The corresponding alkylated complex was quite labile and could not be isolated by ordinary procedures.[9,34)] (ii) Numbers (*n*) of electrons consumed during the electrolysis was 1.3 and 1.6 at −1.5 and −2.0 V vs. SCE, respectively. (iii) When CH_3COOD was used as a proton source at −1.5 V vs. SCE in the dark, the rearrangement product containing one deuterium on the β-carbon was obtained as the major product.[35)]

It is not apparent from the above results if the electrolysis at −2.0 V vs. SCE proceeds along with two-electron reduction or not so. The reaction mechanism for the electrolysis of **3** catalyzed by the hydrophobic vitamin B$_{12}$ may be different from that given in Scheme 5, but the detail is not clear at present. The acetyl group may also migrate via a radical mechanism, but the acetyl-migrated rearrangement reaction proceeds much favorably as the electrolysis potential becomes more cathodic.

(b) Substrates with only one electron-withdrawing group. The electrolyses of 1-bromo-2-methoxycarbonylpropane (**4**), 1-bromo-2-[(ethylthio)carbonyl]propane (**5**), 1-bromo-2-cyanopropane (**6**), and 1-bromo-2-acetylpropane (**7**), each with only one electron-withdrawing group, were carried out in the same manner. The β-elimination products were obtained primarily; 2-methoxycarbonylpropene (**J**), 2-cyanopropene (**O**), and 2-acetylpropene (**Q**) from substrates **4**, **6**, and **7**, respectively (refer to Eqs. 5, 7, and 8). Only the electrolysis of substrate **5**, having one thioester group on the β-carbon, afforded the corresponding rearrangement product, 1-[(ethylthio)carbonyl]propane (**M**) as shown in Table 4 (refer to Eq. 6). (i) At −1.5 V vs. SCE in the dark: the reduction product, 2-[(ethylthio)carbonyl]propane (**K**) was the major one without any additive, while the rearrangement one (**M**) was obtained when acetic acid was added. (ii) At −2.0 V vs. SCE in the drak: the rearrangement product (**M**) was dominantly obtained even in the absence of acetic acid. (iii) The β-elimination product, 2-[(ethylthio)carbonyl]-1-propene (**L**), was also largely obtained under the conditions that allow the formation of **M**. Thus, the rearrangement reaction during the electrolysis of **5** must proceed via reaction mechanisms similar to those given in Scheme 5.

(c) Migratory aptitude. The following aspects became apparent for the electrolyses of substrates **1**—**7**. (i) Substrates with two electron-withdrawing groups on the β-carbon atom tend to give the corresponding rearrangement products which are derived from individual migration of the groups (refer to Eqs. 1, 3, and 4). (ii) Substrates with only one of the electron-withdrawing groups do not give the rearrangement products (refer to Eqs. 5, 7, and 8), except for the substrate with one thioester group (refer to Eq. 6). The sulfur atom with d-orbitals seems to stabilize the anionic intermediates which subsequently afford the rearrangement product. (iii) The rearrangement reaction readily proceeds under the electrolysis

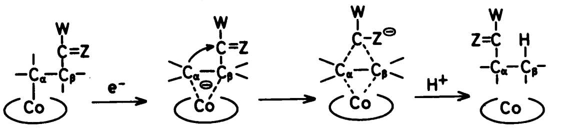
Table 4. Product Analyses for Controlled-Potential Electrolysis of 1-Bromo-2-[(ethylthio)carbonyl]-propane as Catalyzed by Hydrophobic Vitamin B$_{12}$[a)]

Entry	Electrolysis conditions				Yield/%[d)]		
	Potential V vs. SCE	Additive[b)]	Charge[c)] F mol^{-1}	Period h	**K**	**L**	**M**
1	−1.5	None	1.0	5	37—41	ca. 1	ca. 1
2	−1.5	CH_3COOH	1.0	3	8—16	7—13	15—21
3	−2.0	None	2.0	3	18—22	22—28	33—41

a) Electrolysis was carried out in a two-compartment cell equipped with Pt electrodes at 20±2 °C under argon atmosphere in the dark. Starting solutions composed of: [Cob(II)7C$_1$ester]ClO$_4$, 6 mg (4.4×10^{-6} mol); 1-bromo-2-[(ethylthio)carbonyl]propane, 200 mg (9.0×10^{-4} mol); 7 mL of DMF containing 0.50 mol dm^{-3} TBAF. b) CH_3COOH, 0.10 g (1.7×10^{-3} mol). c) Electrical charge passed per mol of the substrate. d) Based on an initial amount of the substrate; the rest was the unreacted substrate; analyzed by GLC. The catalyst was recovered to the same extents as given in Table 2.

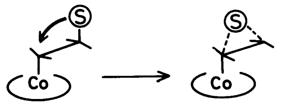
conditions which allow the formation of anionic intermediates.

In the light of the above results, the migratory aptitude of electron-withdrawing groups decreases in the following sequence: COSR>COR>COOR>CN. Both electronic character and steric bulkiness of the migrating groups must be responsible for this tendency. For the formation of the *quasi*-cyclopropane ring in the intermediate stage shown in Scheme 5, attack of the α-carbanion on the β-substituent group is progressively enhanced as the substituent becomes more electron-withdrawing (refer to Eq. 9).



(9)

Stabilization of the anionic intermediates may be achieved through delocalization of negative charge within the *quasi*-cyclopropane ring, and its extent controls the migratory aptitude. On the other hand, a more bulky substituent on the β-carbon atom must be placed at the *anti*-position to the cobalt atom when the alkylated complex is formed (refer to Eq. 10) so



(10)

that such a bulky group readily migrates via formation of the *quasi*-cyclopropane ring. Relative contributions of both electronic and steric effects are much dependent on the nature of β-substituents.

Conclusion. The present study demonstrates for the first time the carbon-skeleton rearrangements catalyzed by a vitamin B_{12} model under electrochemical conditions. The carbon-skeleton rearrangement was postulated to proceed via formation of the anionic intermediates. In the light of the reactions with various substrates, the migratory aptitude of functional groups was clarified. However, it is not relevant to apply these mechanisms directly to the corresponding vitamin B_{12}-dependent enzymatic reactions, since the reduction potential as high as −2.0 V vs. SCE would not be expected in vivo. The rearrangement reaction is generally considered to proceed via radical mechanisms in vivo, but the nature of such radical species must be different from those in homogeneous solution. The reactivity of radical species may be subjected to change by the microenvironmental properties provided by apoenzymes at the reaction sites. In this regard, we have studied the catalytic behavior of the hydrophobic vitamin B_{12} in apoenzyme models such as hydrophobic cyclophanes and bilayer membranes.[34,36]

In the light of the present study, it became apparent that the rearrangement reactions of model substrates readily proceed under stronger reduction conditions. Hydrophobic vitamin B_{12}'s are expected to be widely utilized as specific catalysts for fine organic syntheses via the 1,2-migration process of various functional groups.

Experimental

General Analyses and Measurements. Elemental analyses were performed at the Microanalysis Center of Kyushu University. IR spectra were taken on a JASCO IR-810 infrared spectrophotometer, while electronic absorption spectra were recorded on a Hitachi 340 spectrophotometer. ESR spectra were obtained on a JEOL JES-ME3 X-band spectrometer equipped with a 100 kHz field modulation unit; a standard MgO/Mn^{II} sample calibrated with a NMR magnetometer was employed for calibration of the magnetic field. ^1H-NMR spectra were taken on a Hitachi R-24B or a JEOL JNM-FX100 spectrometer, and mass spectroscopic analyses were performed on a JEOL JMS-01SG-2 spectrometer.[37] Cyclic voltammograms were obtained on a Yanaco P-8 polarograph or an apparatus composed of a Hokuto Denko HA-501 potentiostat/galvanostat and a Hokuto Denko HB-104 function generator. An applied potential between the working and reference electrodes in the electrolysis was maintained constant with a Hokuto Denko HA-305 potentiostat/galvanostat and the electrical quantity was recorded on a Hokuto Denko HF-201 coulomb/ampere-hour meter. GLC analyses were carried out on a Shimadzu GC-4C or a Shimadzu GC-9A apparatus equipped with a Shimadzu C-R3A-FFC chromatopac.

Cyclic Voltammetry. An elecrtochemical cell similar to that reported in literature[38] was used and equipped with platinum wire of 0.5-mm diameter as working and auxiliary electrodes. A saturated calomel electrode (SCE) or an Ag/AgCl electrode was served as a reference which was separated from a bulk electrolyte solution by a salt bridge prepared with benzylidene-D-sorbitol[39] and a DMF solution of tetrabutylammonium tetrafluoroborate (TBAF; supporting electrolyte) (5.0×10^{-2} mol dm^{-3}). DMF solutions containing the cobalt complex, TBAF, and the inside of the cell were maintained under argon atmosphere throughout each measurement. All measurements were carried out at 20±2 °C, and the scan rate was varied in a range from 10 through 200 mV s^{-1}. Half-wave potentials ($E_{1/2}$) and anodic and cathodic currents were evaluated according to the method described previously.[40]

Catalytic Reactions. The electrolyses of various substrates were carried out upon addition of [Cob(II)7C_1ester]ClO_4 in a cylindrical three-electrode cell which was divided into two internal compartments with a single sheet of microporous polypropylene membrane and equipped with platinum mesh as working and auxiliary electrodes (Fig. 10). A DMF solution of [Cob(II)7C_1ester]ClO_4, a substrate, an additive, and TBAF was subjected to electrolysis at an appropriate controlled-potential under argon atmosphere. Then, the reaction mixture was distilled in vacuo and analyzed for products by means of GLC. Identification of the reaction products was performed by coinjection of the distilled sample and the corresponding authentic samples into columns of Silicone DC-550, Silicone SE-30, and Dioctyl phthalate. A capillary column of Polyethylene

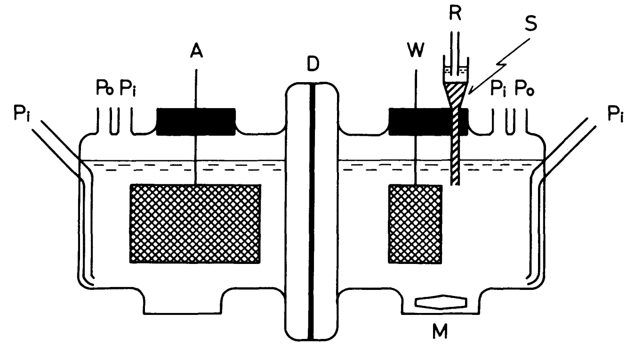


Fig. 10. Three-electrode cell for controlled-potential electrolysis: A, auxiliary electrode (Pt mesh); D, diaphram (Duragard: microporous polypropylene membrane); M, magnetic stirrer; P_i, inert gas inlet; P_o, inert gas outlet; R, reference electrode (SCE); S, salt bridge (prepared with benzylidene-D-sorbitol and a nonaqueous solution of TBAF); W, working electrode (Pt mesh).

Glycol-20M was used for identification of isomers having similar structures such as **D** and **E** or **G** and **H**. Each product separated by preparative GLC on Silicone DC-550 was identified by means of ^{1}H-NMR and mass spectroscopy.

Spectroscopic Measurements. Controlled-potential electrolyses under various conditions were carried out in a three-electrode cell modified for electronic and ESR spectral measurements, as described previously.[40] An applied potential between the working and reference electrodes was maintained constant with a conventional potentiostat and monitored with a Takeda Riken TR-6656 digital multimeter.

Materials. Heptamethyl dicyanocobyrinate, $(CN)_2$Cob(III)7C$_1$ester, was derived from cyanocobalamin after the method of Werthemann et al.[41] Preparation of [Cob(II)7C$_1$ester]ClO$_4$ from $(CN)_2$Cob(III)7C$_1$ester has been described previously.[4] Tetrabutylammonium tetrafluoroborate (TBAF) was prepared after the reported procedure.[42] α-Phenyl-*N*-(*t*-butyl)nitrone (PBN) as a spin-trapping agent, CH_3COOD (98 atom %D) (both from Aldrich Chemical Co., U.S.A.), and CD_3COOD (99.6 atom %D) of Commissariat á l'Enerqie Atomique, France were used as supplied. *N,N*-Dimethylformamide (DMF) was dried and purified just before use according to the standard procedure.[28] The substrates were prepared by the following procedures.

2,2-Bis(ethoxycarbonyl)-1-bromopropane (1). A solution of diethyl methylmalonate (11.2 g, 0.064 mol) in dry benzene (40 mL) and subsequently a solution of dibromomethane (16.0 g, 0.092 mol) in dry DMF (40 mL) were added dropwise to a suspension of sodium hydride (1.54 g, 0.064 mol) in dry benzene (20 mL) with vigorous stirring at room temperature under nitrogen atmosphere. After the reaction mixture being stirred for 2 h at room temperature, a saturated aqueous ammonium chloride (100 mL) was added to it. The resulting product was extracted with diethyl ether (100 mL×2), and the extract was washed with distilled water and dried over sodium sulfate. The product was recovered by distillation under reduced pressure (75—76 °C/5.3 Pa), and its purity was confirmed by GLC: Yield 12.0 g (70%); IR (neat) 1735 cm^{-1} (ester C=O); ^{1}H-NMR ($CDCl_3$, TMS) δ=1.30 (6H, t, $CH_2C\underline{H}_3$), 1.50 (3H, s, CH_3), 3.80 (2H, s, CH_2Br), and 4.20 (4H, q, $C\underline{H}_2CH_3$).

Found: C, 40.60; H, 5.68%. Calcd for $C_9H_{15}BrO_4$: C, 40.47; H, 5.66%.

1-Bromo-2-cyano-2-ethoxycarbonylpropane (2). This compound was derived from 1-cyano-1-ethoxycarbonylethane[43] (16.2 g, 0.128 mol) in a manner similar to that described above. The product was recovered by distillation under reduced pressure (80—90 °C/40—66 Pa) and further purified by preparative GLC on Silicone DC-550: Yield 16.2 g (68%); IR (neat) 2240 (C≡N) and 1740 cm^{-1} (ester C=O); ^{1}H-NMR ($CDCl_3$, TMS) δ=1.16 (3H, t, $CH_2C\underline{H}_3$), 1.54 (3H, s, CH_3), 3.46 (2H, m, CH_2Br), and 4.12 (2H, q, $C\underline{H}_2CH_3$).

Found: C, 38.42; H, 4.54; N, 6.52%. Calcd for $C_7H_{10}BrNO_2$: C, 38.20; H, 4.58; N, 6.36%.

2-Acetyl-1-bromo-2-ethoxycarbonylpropane (3). This substrate was prepared from ethyl 2-methylacetoacetate[44] (20 g, 0.14 mol) in a manner similar to that described above. The product was recovered by distillation under reduced pressure (70—72 °C/102 Pa) and purified further by preparative GLC on Silicone DC-550: Yield 12 g (36%); IR (neat) 1740 (ester C=O) and 1720 cm^{-1} (ketone C=O); ^{1}H-NMR ($CDCl_3$, TMS) δ=1.18 (3H, t, $CH_2C\underline{H}_3$), 1.41 (3H, s, CH_3), 2.10 (3H, s, $COCH_3$), 3.61 (2H, s, CH_2Br), and 4.13 (2H, q, $C\underline{H}_2CH_3$).

Found: C, 40.41; H, 5.36%. Calcd for $C_8H_{13}BrO_3$: C, 40.53; H, 5.53%.

1-Bromo-2-methoxycarbonylpropane (4). 3-Bromo-2-methylpropionic acid (51.3 g, 0.31 mol), which was obtained by the reaction of methacrylic acid with hydrogen bromide in acetic acid,[45] was esterified with methanol (100 mL) containing sulfuric acid (1 mL). The product was extracted with diethyl ether and recovered from the extract by distillation under reduced pressure (72.5—73.0 °C/2530 Pa): Yield 50.0 g (90%); IR (neat) 1750 cm^{-1} (ester C=O); ^{1}H-NMR ($CDCl_3$, TMS) δ=1.28 (3H, d, CH_3), 2.84 (1H, m, CH), 3.47 (2H, m, CH_2Br), and 3.66 (3H, s, CO_2CH_3).

Found: C, 33.27; H, 4.98%. Calcd for $C_5H_9BrO_2$: C, 33.17; H, 5.01%.

1-Bromo-2-[(ethylthio)carbonyl]propane (5). This was prepared according to a reported procedure.[1]

1-Bromo-2-cyanopropane (6). This compound was prepared by the reaction of 2-cyanopropene (15.0 g, 0.22 mol) with 30%(w/w) hydrogen bromide in acetic acid (100 mL) in a usual manner,[45] bp 35—40 °C/107 Pa: Yield 17.0 g (51%); IR (neat) 2240 cm^{-1} (C≡N); ^{1}H-NMR ($CDCl_3$, TMS) δ=1.44 (3H, d, CH_3), 3.10 (1H, m, CH), and 3.45 (2H, d, CH_2Br).

Found: C, 32.46; H, 4.11; N, 9.38%. Calcd for C_4H_6BrN: C, 32.46; H, 4.09; N, 9.46%.

1-Bromo-2-acetylpropane (7). This substrate was prepared by the reaction of 2-acetylpropene (5.0 g, 0.059 mol) with hydrogen bromide in methanol,[45] bp 60 °C/2670 Pa: Yield 1.0 g (10%); IR (neat) 1705 cm^{-1} (ketone C=O); ^{1}H-NMR ($CDCl_3$, TMS) δ=1.18 (3H, d, CH_3), 2.20 (3H, s, $COCH_3$) 2.29 (1H, m, CH), and 3.51 (2H, m, CH_2Br). This compound was so labile that its elemental analysis was not possible.

Authentic Samples. 2,2-Bis(ethoxycarbonyl)propane (**A**), 2-methoxycarbonylpropane (**I**), 2-methoxycarbonylpropene (**J**), 2-cyanopropane (**N**), 2-cyanopropene (**O**), 2-acetylpropane (**P**), and 2-acetylpropene (**Q**) were purchased from Nakarai Chemicals and purified by distillation before use; confirmed to be sufficiently pure by ^{1}H-NMR and GLC.

2-Cyano-1-ethoxycarbonylpropane (**E**),[46] 2-acetyl-2-ethoxycarbonylpropane (**F**),[44] 1-acetyl-2-ethoxycarbonylpropane (**G**),[47,48] 2-acetyl-1-ethoxycarbonylpropane (**H**),[47] 2-[(ethylthio)carbonyl]propane (**K**),[1] 2-[(ethylthio)carbonyl]-1-propene (**L**),[1] and 1-[(ethylthio)carbonyl]propane (**M**),[1] were prepared according to the methods described in literatures and confirmed to be sufficiently pure by ^{1}H-NMR and GLC.

1,2-Bis(ethoxycarbonyl)propane (B). This compound was derived from the corresponding carboxylic acid (10 g, 0.08 mol) by refluxing it in ethanol containing sulfuric acid, bp 74—75 °C/670 Pa: Yield 7.8 g (54%); IR (neat) 1735 cm^{-1} (ester C=O); ^{1}H-NMR ($CDCl_3$, TMS) δ=1.25 (6H, t, $CH_2C\underline{H}_3$), 1.30 (3H, d, CH_3), 2.60 (2H, m, CH_2), 2.90 (1H, m, CH), and 4.20 (4H, q, $C\underline{H}_2CH_3$).

2-Cyano-2-ethoxycarbonylpropane (C). This was obtained by the reaction of 1-cyano-1-ethoxycarbonylethane (5.0 g, 0.039 mol) with methyl iodide in a manner similar to that adopted for the preparation of **1**, bp 95 °C/4000 Pa: Yield 3.0 g (54%); IR (neat) 2240 (C≡N) and 1740 cm^{-1} (ester C=O); ^{1}H-NMR ($CDCl_3$, TMS) δ=1.30 (3H, t, $CH_2C\underline{H}_3$), 1.58 (6H, s, CH_3), and 4.18 (2H, q, $C\underline{H}_2CH_3$).

2-Cyano-1-ethoxycarbonylpropane (D). This compound was prepared by the reaction of 1-bromo-2-ethoxycarbonylpropane (5.0 g, 0.026 mol) with potassium cyanide (2.5 g, 0.038 mol) in a manner similar to that reported previously,[43] bp 85 °C/4000 Pa: Yield 0.30 g (10%); IR (neat) 2240 (C≡N) and 1735 cm^{-1} (ester C=O); ^{1}H-NMR ($CDCl_3$, TMS) δ=1.28 (3H, t, $CH_2C\underline{H}_3$), 1.32 (3H, d, CH_3), 2.62 (2H, br s, CH_2), 2.70 (1H, m, CH), and 4.12 (2H, q, $C\underline{H}_2CH_3$).

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