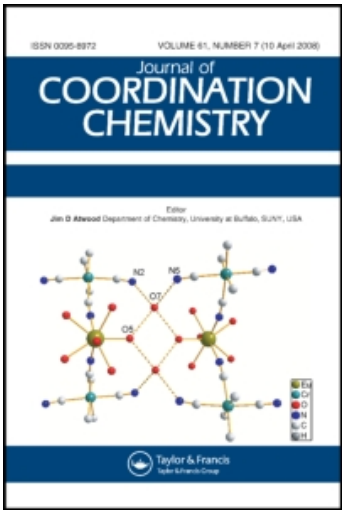

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Hydrophobic Vitamin B_{12}. X. Steric Effect in Electrochemical Carbon-Skeleton Rearrangement Catalyzed by Hydrophobic Vitamin B_{12} in Nonaqueous Media

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HYDROPHOBIC VITAMIN B_{12}. X.[†] STERIC EFFECT IN ELECTROCHEMICAL CARBON-SKELETON REARRANGEMENT CATALYZED BY HYDROPHOBIC VITAMIN B_{12} IN NONAQUEOUS MEDIA[††]

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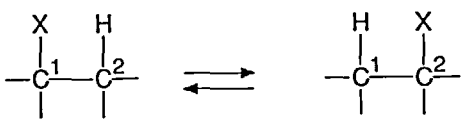
A steric effect in the carbon-skeleton rearrangement catalyzed by heptamethyl cobyrinate perchlorate, [Cob(II)7C_1ester]ClO_4, was investigated under electrochemical conditions. The controlled-potential electrolyses of alkyl halides having two carboxylic ester groups of different bulkiness on the same carbon atom, such as 2,2-bis(ethoxycarbonyl)-1-bromopropane, 1-bromo-2-*tert*-butoxycarbonyl-2-ethoxycarbonylpropane, 1-bromo-2-cyclohexyloxycarbonyl-2-ethoxycarbonylpropane, and 1-bromo-2-ethoxycarbonyl-2-phenoxycarbonylpropane, were carried out in *N,N*-dimethylformamide, as catalyzed by [Cob(II)7C_1ester]ClO_4, to give the corresponding ester-migrated products in the dark at -1.5 V *vs* SCE in the presence of acetic acid and at -2.0 V *vs* SCE without acetic acid. As regards a correlation between bulkiness of an ester group and a migration aptitude, a smaller ester group tends to migrate to the adjacent carbon atom more readily than a larger one. The origin of such a steric effect is discussed with attention to the rate-determining step.

Keywords: Hydrophobic vitamin B_{12}, rearrangement reaction, electrochemical reduction, controlled-potential electrolysis

INTRODUCTION

5'-Deoxyadenosylcobalamin (coenzyme B_{12}) serves as a cofactor in a variety of enzymatic processes which perform the intramolecular 1,2-interchange of a hydrogen atom with another substituent X on the adjacent carbon atom (equation 1).[1] Such 1,2-migration includes four carbon-skeleton rearrangements of reversible nature as follows:[2,3] methylmalonyl-CoA ⇌ succinyl-CoA, isobutyryl-CoA ⇌ *n*-butyryl-CoA, β-methylaspartate ⇌ glutamate, and methylitaconate ⇌ α-methyleneglutarate.



(1)

[†] Part IX of this series: Y. Murakami, Y. Hisaeda, and T. Ohno, *J. Chem. Soc., Perkin Trans. 2*, in press
[††] Dedicated to Professor Arthur E. Martell on the occasion of his 75th birthday.

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Recently, various organic reactions mediated by vitamin B_{12} derivatives or model complexes have been carried out rather extensively to aim at catalytic application of Co^{I} species (supernucleophiles) to organic syntheses, for example, stereoselective reduction of olefins and α,β-unsaturated carbonyl derivatives,[4,5] reductive elimination of oxazoline derivatives,[6] and reduction of alkyl halides and their addition to Michael olefins.[7] In addition, similar catalytic reactions have been examined under electrochemical conditions.[8] However, isomerization reactions accompanied by various carbon-skeleton rearrangements, which are granted to be typical enzymatic reactions catalyzed by coenzyme B_{12}, have been performed only to a limited extent under such conditions.[9,10]

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}.[11] These modified cobalt complexes are very soluble in a wide range of organic solvents and expected to be utilized as homogeneous catalysts in such media that reflect microenvironmental polarities of the active sites of enzymes. In this regard, we have previously demonstrated that carbon-skeleton rearrangement reactions catalyzed by a hydrophobic vitamin B_{12} under electrochemical conditions proceeded *via* formation of anionic intermediates, and the apparent migratory aptitude of electron-withdrawing groups was found to decrease in the order $COSR > COR > CO_2R > CN$.[9] We also pointed out that both the electronic character and steric bulkiness of the migrating groups must be responsible for this tendency. In this paper, we report in detail on the steric effect of the migrating groups in the electrochemical carbon-skeleton rearrangement of alkyl halides having two carboxylic ester groups of different steric bulkiness on the same carbon atom.

EXPERIMENTAL

General Analyses and Measurements

Elemental analyses were performed at the Microanalysis Centre of Kyushu University. IR spectra were recorded on a JASCO IR-810 infrared spectrophotometer. ^1H NMR spectra were measured on a Hitachi R-24B and a Bruker AMX-500 spectrometer. An applied potential between working and reference electrodes in the electrolyses was maintained constant with a Hokuto Denko HA-305 potentiostat/galvanostat and electric charge was recorded on a Hokuto Denko HF-201 coulomb/amperehour meter. GLC analyses were carried out on a Shimadzu GC-9A apparatus equipped with a Shimadzu C-R3A-FFC chromatopac for data processing.

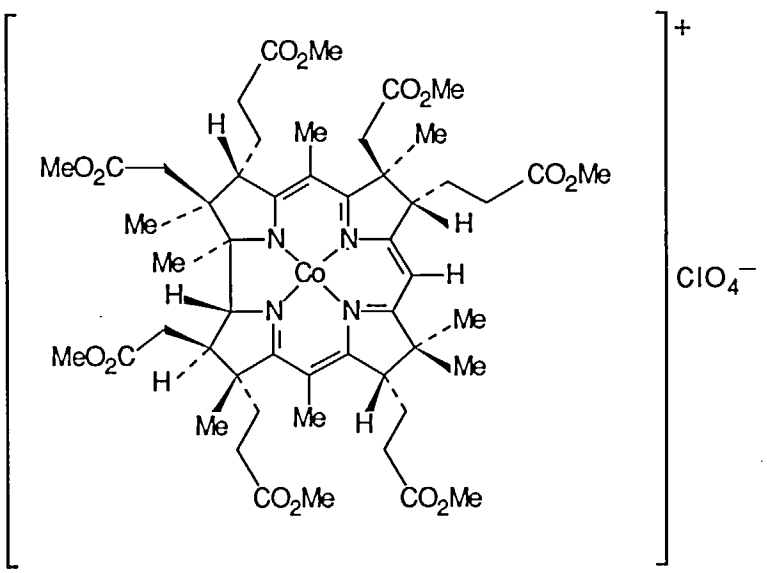
Catalytic Reactions

The electrolyses of various substrates were carried out upon addition of heptamethyl cobyrinate perchlorate, [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 working and auxiliary electrodes prepared with platinum meshes as reported previously.[9] A saturated calomel electrode (SCE) served as a reference which was separated from the bulk electrolyte solution by a salt bridge prepared with 1,2:4,5-*O*-dibenzylidene-D-glucitol[12] and

a *N,N*-dimethylformamide (DMF) solution of tetra-*n*-butylammonium tetrafluoroborate (TBAF; supporting electrolyte). A DMF solution containing [Cob(II)7C_1-ester]ClO_4, a substrate, an additive, and TBAF was subjected to electrolysis at an appropriate controlled potential under an 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 corresponding authentic samples into columns of Silicone DC-550, Thermon-3000, FON (Shimadzu Co., Japan), Silicone SE-30, Diocthyl Phthalate, and Dinonyl Phthalate (Gasukuro Kogyo Inc., Japan). A capillary column of Polyethylene Glycol-20M (Gasukuro Kogyo) was used for identification of isomers having similar structures. Quantitative analyses of the products were carried out by GLC on the basis of calibrations established independently by using authentic samples.

Materials

DMF was dried and purified just before use according to a standard procedure.[13] TBAF was prepared after the reported procedure.[14] [Cob(II)7C_1ester]ClO_4 was prepared from heptamethyl dicyanocobyrinate[15] as described previously.[16] 2,2-Bis(ethoxycarbonyl)-1-bromopropane (**1**) and 1,2-bis(ethoxycarbonyl)propane (**B**) were prepared according to methods described in the literature.[9] 2,2-Bis(ethoxycarbonyl)propane (**A**) was purchased from Nacalai Tesque, Inc., Japan, and purified by distillation before use. Other substrates and authentic samples were prepared according to the following procedures, and confirmed to be sufficiently pure by GLC.



[Cob(II)7C_1ester]ClO_4

1-Bromo-2-tert-butoxycarbonyl-2-ethoxycarbonylpropane (2)

Potassium hydroxide (20.8 g, 0.372 mol) dissolved in absolute ethanol (400 cm^3) was added dropwise over 1 h to an absolute ethanol solution (400 cm^3) of diethyl

methylmalonate (64.7 g, 0.371 mol) with stirring at room temperature. After the reaction mixture was refluxed for 10 h, the solvent was evaporated to dryness under reduced pressure. The resulting white powder was dissolved in water (300 cm^3), and hydrochloric acid (35% w/w) was added to it to adjust the final pH at 2.0. The product was extracted with diethyl ether (200 $cm^3 \times 3$), and the extract was washed with distilled water and dried over sodium sulfate. The product, methylmalonic acid monoethylester, was recovered by distillation under reduced pressure: bp 100°C/667 Pa; yield 24.4 g (42%); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.27(3H, t, $CH_2C\underline{H}_3$), 1.94(3H, d, $C\underline{H}_3CH$), 3.46(1H, q, $CH_3C\underline{H}$), 4.18(2H, q, $C\underline{H}_2CH_3$), 8.03 (1H, s, CO_2H).

A mixture of methylmalonic acid monoethylester (21.8 g, 0.14 mol) and thionyl chloride (50 cm^3, 0.25 mol) was refluxed for 8 h. After the excess thionyl chloride was evaporated under reduced pressure, a small amount of dry benzene was added to the residue with stirring. The mixture was evaporated under reduced pressure to give the acid chloride; IR (neat) 1800 cm^{-1} (acid chloride C=O). A benzene solution (100 cm^3) of the acid chloride was added dropwise over 1 h with stirring to a dry *tert*-butyl alcohol solution (200 cm^3) of triethylamine (17.0 g, 0.17 mol) placed in an ice bath, and the mixture was refluxed for 6 h. After addition of distilled water (300 cm^3), the resulting product was extracted with benzene (200 $cm^3 \times 2$), and the extract was washed with distilled water and dried over sodium sulfate. The product (1-*tert*-butoxycarbonyl-1-ethoxycarbonylethane) was recovered by distillation under reduced pressure: bp 70°C/400 Pa; yield 20.7 g (73%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.24 (3H, t, $CH_2C\underline{H}_3$), 1.27 (3H, d, $CHC\underline{H}_3$), 1.42 (9H, s, $C(CH_3)_3$), 3.28 (1H, q, $C\underline{H}CH_3$), 4.10 (2H, q, $C\underline{H}_2CH_3$).

A dry benzene solution (40 cm^3) of 1-*tert*-butoxycarbonyl-1-ethoxycarbonylethane (15.0 g, 7.4×10^{-2} mol) and subsequently a dry DMF solution (40 cm^3) of dibromomethane (17.4 g, 0.10 mol) were added dropwise to a suspension of sodium hydride (1.78 g, 7.4×10^{-2} mol) in dry benzene (20 cm^3) with vigorous stirring at room temperature under a nitrogen atmosphere. After the reaction mixture had been stirred for 2 h at room temperature, saturated aqueous ammonium chloride (100 cm^3) was added to it. The resulting product was extracted with diethyl ether (100 $cm^3 \times 2$), and the extract was washed with distilled water and dried over sodium sulfate. The product was recovered by distillation with a Kugelrohr apparatus under reduced pressure: bp 103°C/933 Pa; yield 12.9 g (59%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.24 (3H, t, $CH_2C\underline{H}_3$), 1.47 (12H, s, CCH_3 and $C(CH_3)_3$), 3.68 (2H, s, CH_2Br), 4.15 (2H, q, $C\underline{H}_2CH_3$). Anal.: Calcd for $C_{11}H_{19}BrO_4$: C, 44.76; H, 6.49%. Found: C, 44.84; H, 6.50%.

1-Bromo-2-cyclohexyloxycarbonyl-2-ethoxycarbonylpropane (3)

1-Cyclohexyloxycarbonyl-1-ethoxycarbonylethane was prepared from methylmalonic acid monoethylester (10.6 g, 6.8×10^{-2} mol) in a manner similar to that described above, bp 70–80°C/267–400 Pa: yield 9.0 g (58%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.26 (3H, t, $CH_2C\underline{H}_3$), 1.34 (3H, d, $CHC\underline{H}_3$), 1.52 (11H, s, cyclohexyl), 3.38 (1H, q, $C\underline{H}CH_3$), 4.15 (2H, q, $C\underline{H}_2CH_3$).

Then, bromomethylation of 1-cyclohexyloxycarbonyl-1-ethoxycarbonylethane (8.9 g, 3.9×10^{-2} mol) was carried out in a manner similar to that described above. The product was recovered by distillation under reduced pressure (bp 70–80°C/13–27 Pa) and further purified by chromatography on a column of Kieselgel 60H (E. Merck AG, West Germany) with ethylacetate–petroleum ether (10:1 v/v) as eluant:

yield 2.0 g (16%); IR (neat) 1730 cm^{-1} (ester C=O); 500 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.28 (3H, t, $CH_2C\underline{H}_3$), 1.46 (11H, s, cyclohexyl), 1.52 (3H, s, CCH_3), 3.73 (2H, s, CH_2Br), 4.22 (2H, dq, $C\underline{H}_2CH_3$). Anal.: Calcd for $C_{13}H_{21}BrO_4$: C, 48.74; H, 6.61%. Found: C, 48.61; H, 6.59%.

1-Bromo-2-ethoxycarbonyl-2-phenoxycarbonylpropane (4)

1-Ethoxycarbonyl-1-phenoxycarbonylethane was prepared from methylmalonic acid monoethylester (4.2 g, 2.7×10^{-2} mol) in a manner similar to that described above: bp 100°C/40 Pa; yield 2.6 g (43%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.24 (3H, t, $CH_2C\underline{H}_3$), 1.50 (3H, d, $CHC\underline{H}_3$), 3.60 (1H, q, $C\underline{H}CH_3$), 4.15 (2H, q, $C\underline{H}_2CH_3$), 6.8–7.6 (5H, m, phenyl).

Then, bromomethylation of 1-ethoxycarbonyl-1-phenoxycarbonylethane (2.5 g, 1.1×10^{-2} mol) was carried out in a manner similar to that described above. The product was recovered by distillation with a Kugelrohr apparatus under reduced pressure: bp 105–110°C/27 Pa; yield 1.0 g (29%); IR (neat) 1730 cm^{-1} (ester C=O); 500 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.33 (3H, t, $CH_2C\underline{H}_3$), 1.70 (3H, s, CCH_3), 3.82 (1H, d, CH_2Br), 3.97 (1H, d, CH_2Br), 4.31 (2H, dq, $C\underline{H}_2CH_3$), 7.09 (2H, d, *o*-H in phenyl), 7.26 (1H, t, *p*-H in phenyl), 7.39 (2H, t, *m*-H in phenyl). Anal.: Calcd for $C_{13}H_{15}BrO_4$: C, 49.68; H, 4.81%. Found: C, 49.81; H, 4.70%.

2-tert-Butoxycarbonyl-2-ethoxycarbonylpropane (C)

This compound was obtained by the reaction of 1-*tert*-butoxycarbonyl-1-ethoxycarbonylethane (4.0 g, 2.0×10^{-2} mol) with methyl iodide in a manner similar to that adopted for the preparation of **2**: bp 85–90°C/400 Pa; yield 1.2 g (28%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.24 (3H, t, $CH_2C\underline{H}_3$), 1.48 (15H, s, $C(CH_3)_3$ and $C(CH_3)_2$), 4.15 (2H, q, $C\underline{H}_2CH_3$).

1-tert-Butoxycarbonyl-2-ethoxycarbonylpropane (D)

A dry benzene solution (30 cm^3) of 3-ethoxycarbonylbutyryl chloride[17] (2.2 g, 1.2×10^{-2} mol) was added dropwise over 30 min to a dry *tert*-butyl alcohol solution (100 cm^3) containing dry triethylamine (1.8 g, 1.8×10^{-2} mol) placed in an ice bath, and the reaction mixture was refluxed for 5 h. After distilled water (50 cm^3) was added to the reaction mixture, the resulting product was extracted with benzene (50 $cm^3 \times 2$) and dried over sodium sulfate. The product was recovered by distillation with a Kugelrohr apparatus under reduced pressure: bp 65–70°C/27–40 Pa; yield 0.80 g (31%); IR (neat) 1730 cm^{-1} (ester C=O); 500 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.20 (3H, d, $CHC\underline{H}_3$), 1.26 (3H, t, $CH_2C\underline{H}_3$), 1.44 (9H, s, $C(CH_3)_3$), 2.32 (1H, dd, $CHC\underline{H}_2$), 2.64 (1H, dd, $CHC\underline{H}_2$), 2.85 (1H, m, $C\underline{H}CH_2$), 4.14 (2H, q, $C\underline{H}_2CH_3$).

2-tert-Butoxycarbonyl-1-ethoxycarbonylpropane (E)

This compound was derived from ethyl 3-chloroformylbutyrate[17] (1.4 g, 7.8×10^{-3} mol) in a manner similar to that adopted for the preparation of **D**: bp 65–70°C/27–40 Pa; yield 0.80 g (47%); IR (neat) 1730 cm^{-1} (ester C=O); 500 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.18 (3H, d, $CHC\underline{H}_3$), 1.26 (3H, t, $CH_2C\underline{H}_3$), 1.44 (9H, s, $C(CH_3)_3$), 2.34 (IH, dd, $CHC\underline{H}_2$), 2.67 (1H, dd, $CHC\underline{H}_2$), 2.80 (1H, m, $C\underline{H}CH_2$), 4.14 (2H, q, $C\underline{H}_2CH_3$).

2-Cyclohexyloxycarbonyl-2-ethoxycarbonylpropane (F)

This was obtained by the reaction of 1-cyclohexyloxycarbonyl-1-ethoxycarbonylethane (5.0 g, 2.2×10^{-2} mol) with methyl iodide in a manner similar to that adopted for the preparation of **2**: bp 95°C/400 Pa; yield 2.0 g (38%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.25 (3H, t, $CH_2C\underline{H}_3$), 1.44 (11H, s, cyclohexyl), 1.52 (6H, s, $C(CH_3)_2$), 4.20 (2H, q, $C\underline{H}_2CH_3$).

1-Cyclohexyloxycarbonyl-2-ethoxycarbonylpropane (G)

This compound was obtained by the reaction of 3-ethoxycarbonylbutyryl chloride (1.0 g, 5.6×10^{-3} mol) with cyclohexyl alcohol in a manner similar to that for the preparation of **D**: bp 70°C/27 Pa; yield 0.40 g (30%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.22 (3H, d, $CHC\underline{H}_3$), 1.25 (3H, t, $CH_2C\underline{H}_3$), 1.43 (11H, s, cyclohexyl), 2.60 (2H, m, $CHC\underline{H}_2$), 3.00 (1H, m, $C\underline{H}CH_2$), 4.21 (2H, q, $C\underline{H}_2CH_3$).

2-Cyclohexyloxycarbonyl-1-ethoxycarbonylpropane (H)

This compound was obtained by the reaction of ethyl 3-chloroformylbutyrate (1.0 g, 5.5×10^{-3} mol) with cyclohexyl alcohol in a manner similar to that for the preparation of **D**: bp 75°C/40 Pa; yield 0.40 g (30%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.20 (3H, d, $CHC\underline{H}_3$), 1.24 (3H, t, $CH_2C\underline{H}_3$), 1.42 (11H, s, cyclohexyl), 2.60 (2H, m, $CHC\underline{H}_2$), 3.00 (1H, m, $C\underline{H}CH_2$), 4.20 (2H, q, $C\underline{H}_2CH_3$).

2-Ethoxycarbonyl-2-phenoxycarbonylpropane (I)

This compound was obtained by the reaction of 1-ethoxycarbonyl-1-phenoxycarbonylethane (6.0 g, 2.7×10^{-2} mol) with methyl iodide in a manner similar to that for the preparation of **2**: bp 105–110°C/400 Pa; yield 2.0 g (31%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.26 (3H, t, $CH_2C\underline{H}_3$), 1.52 (6H, s, $C(CH_3)_2$), 4.16 (2H, q, $C\underline{H}_2CH_3$), 6.8–7.6 (5H, m, phenyl).

2-Ethoxycarbonyl-1-phenoxycarbonylpropane (J)

This compound was obtained by the reaction of 3-ethoxycarbonylbutyryl chloride (1.0 g, 5.6×10^{-3} mol) with phenol in a manner similar to that for the preparation of **D**: bp 90°C/40 Pa; yield 0.60 g (44%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.20 (3H, d, $CHC\underline{H}_3$), 1.24 (3H, t, $CH_2C\underline{H}_3$), 2.65 (2H, m, $CHC\underline{H}_2$), 3.00 (1H, m, $C\underline{H}CH_2$), 4.20 (2H, q, $C\underline{H}_2CH_3$), 6.8–7.6 (5H, m, phenyl).

1-Ethoxycarbonyl-2-phenoxycarbonylpropane (K)

This compound was obtained by the reaction of ethyl 3-chloroformylbutyrate (1.0 g, 5.5×10^{-3} mol) with phenol in a manner similar to that for the preparation of **D**: bp 90–95°C/40 Pa; yield 0.40 g (31%); IR (neat) 1730 cm^{-1} (ester C=O); 60 MHz ^1H NMR ($CDCl_3$, TMS) δ 1.22 (3H, d, $CHC\underline{H}_3$), 1.25 (3H, t, $CH_2C\underline{H}_3$), 2.60 (2H, m, $CHC\underline{H}_2$), 3.00 (1H, m, $C\underline{H}CH_2$), 4.22 (2H, q, $C\underline{H}_2CH_3$), 6.8–7.6 (5H, m, phenyl).

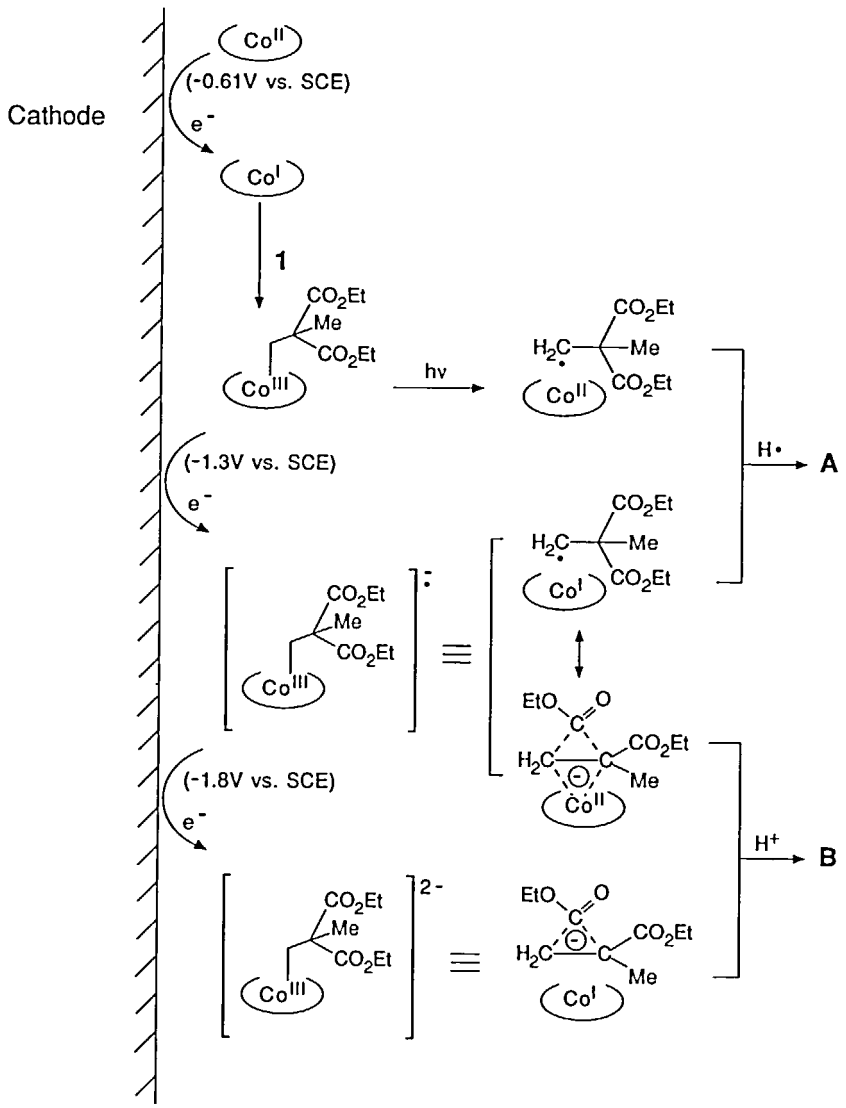
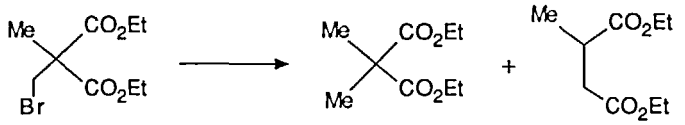


FIGURE 1 Proposed mechanism for the electrolysis of **1** as catalyzed by hydrophobic vitamin B_{12}.

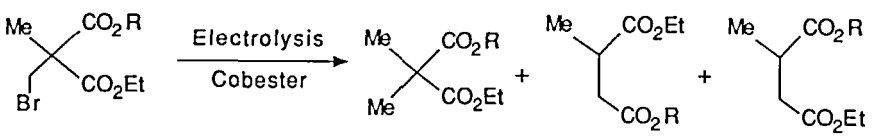
RESULTS AND DISCUSSION

We have already clarified that the electrochemical carbon-skeleton rearrangement of an alkyl halide with two electron-withdrawing groups on the same carbon atom proceeded effectively in the presence of [Cob(II)7C_1ester]ClO_4.[9] We reached a conclusion that the 1,2-migration of an electron-withdrawing group takes place *via* formation of anionic intermediates as shown in Figure 1 for the reaction of **1** (refer to equation 2) on the basis of investigations by electronic spectroscopy, coulometry,



1 A B (2)

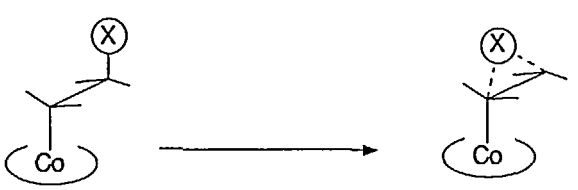
and spin-trapping ESR techniques as well as by product analyses obtained by utilization of relevant deuterium compounds. The bivalent cobalt complex is first converted into the univalent cobalt species by the electrochemical reduction at −0.61 V *vs* SCE ($E_{1/2}$ in DMF). The alkylated complex is formed in the second place by the reaction of the supernucleophilic Co^{I} species with **1**. The complex is decomposed upon irradiation with visible light to give the bivalent cobalt species and the alkyl radical, which subsequently abstracts a hydrogen atom to afford the reduction product (**A**). On the other hand, the alkylated complex is reduced to the one-electron reduction intermediate at −1.3 V *vs* SCE in the dark. The electronic structure for the intermediate seems to be represented by two canonical forms (refer to Figure 1). The proton attack on the β-carbon atom of the substrate induces the carbon-skeleton rearrangement, followed by the cobalt–carbon bond cleavage to afford the rearrangement product (**B**). However, the one-electron reduction intermediate is spontaneously decomposed to afford the Co^{I} species and the alkyl radical in the absence of an efficient proton source. The reduction product (**A**) is mainly derived from the alkyl radical by rapid abstraction of a hydrogen atom. The alkylated complex is converted into the two-electron reduction intermediate at −1.8 V *vs* SCE in the dark (refer to Figure 1). This intermediate is then decomposed to the Co^{I} chelate and the anionic species, and rearrangement product **B** is obtained from the latter. In addition, we have described in a previous paper that both electronic character and steric bulkiness of migrating groups must be responsible for the migratory aptitude.[18] In order to clarify the steric effect originating from a migrating group in the 1,2-migration, we carried out the electrolyses of alkyl halides having two ester groups of different bulkiness on the same carbon atom as shown in equation 3. We expected initially that



(3)

R = Et, Bu^{t},  , Ph

a more bulky substituent on the β-carbon atom is placed at the conformational position *anti* to the cobalt atom when the alkylated complex is formed, so that such a bulky group readily migrates *via* formation of the *quasi*-cyclopropane ring as shown in equation 4.



(4)

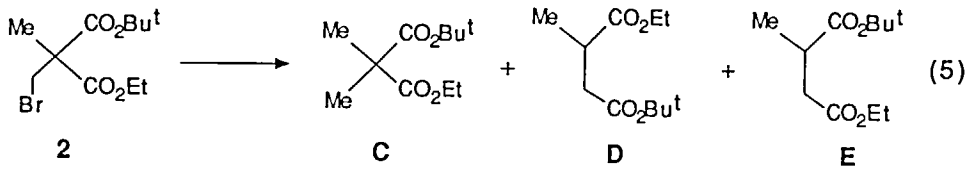
TABLE I

Product analyses for controlled-potential electrolyses of alkyl bromides **1** and **2** catalyzed by hydrophobic vitamin B_{12} in the dark.[a]

	Electrolysis conditions				Yield/%[e]		
	Potential		Charge[d]	Period			
Substrate[b]	V *vs* SCE	Additive[c]	F mol^{-1}	h	Unrearranged product[f]	CO_2R-migrated product[g]	CO_2Et-migrated product[h]
1	−1.5	CH_3CO_2H	3.0	8	16–18		40–46
1	−2.0	None	2.0	6	18–20		70–72
2	−1.5	CH_3CO_2H	3.0	10	22–25	9–12	15–18
2	−2.0	None	2.0	5	28–30	23–25	43–45

[a] Electrolysis was carried out in a two-compartment cell equipped with Pt-mesh electrodes at 20 ± 2°C under an argon atmosphere. Starting solutions were composed of: [Cob(II)7C_1ester]ClO_4, 30 mg (2.6×10^{-5} mol); **1**, 694 mg (2.6×10^{-3} mol); **2**, 767 mg (2.6×10^{-3} mol); 30 cm^3 of DMF containing 5.0×10^{-2} mol dm^{-3} TBAF. [b] Refer to equations 2 and 5. [c] CH_3CO_2H, 500 mg (8.3×10^{-3} mol dm^{-3}). [d] Electrical charge passed per mol of the substrate. [e] Based on an initial amount of the substrate; the rest was unreacted substrate; analyzed by GLC; refer to equations 2 and 5. [f] Unrearranged products were **A** and **C** for substrates **1** and **2**, respectively. [g] Bulky ester-migrated product **D** for substrate **2**. [h] Ethoxycarbonyl-migrated products **B** and **E** for substrates **1** and **2**, respectively.

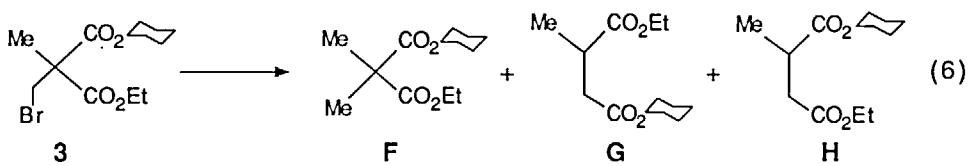
The electrolysis of **2**, which has a *tert*-butoxycarbonyl group and an ethoxycarbonyl group, was carried out upon addition of [Cob(II)7C_1ester]ClO_4. The product analyses for its controlled-potential electrolyses are shown in Table I along with those for **1** under identical experimental conditions (refer to equations 2 and 5). The



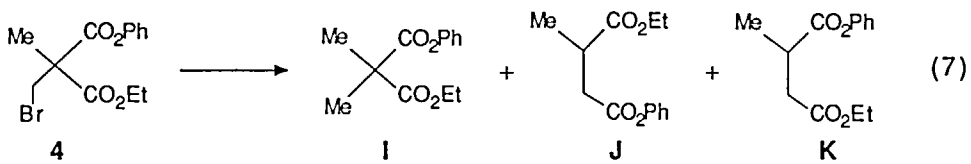
(5)

data reveal the following: (i) at −1.5 V *vs* SCE, the rearrangement products (**B**, **D**, and **E** in equations 2 and 5) were the major ones when an efficient proton source such as acetic acid was present; (ii) at −2.0 *vs* SCE, the rearrangement products were largely obtained even in the absence of acetic acid; (iii) the ethoxycarbonyl-migrated product (**E**) was obtained more readily than the *tert*-butoxycarbonyl-migrated one (**D**); **E**:**D** = 3:2 regardless of applied potentials. This result indicates that a bulky substituent migrates less readily to the adjacent carbon atom, being contrary to our expectation.

The electrolyses of the substrates having other bulky esters were examined as shown in equations 6 and 7. The product analyses for the electrolyses of **3** and **4**



(6)



(7)

catalyzed by [Cob(II)7C_1ester]ClO_4 are summarized in Table II. The steric effect on the migratory aptitude of electron-withdrawing groups in **3** and **4** was similar to that observed for **2**. The ethoxycarbonyl-migrated products (**H** for **3** and **K** for **4**) were produced more readily than the cyclohexyloxycarbonyl-migrated (**G**) and the phenoxycarbonyl-migrated species (**J**); **H**:**G** = 2:1, **K**:**J** = 2:1. It is concluded on these grounds that a carboxylic ester with a less bulky alcohol group migrates more readily than one with a larger alcohol group.

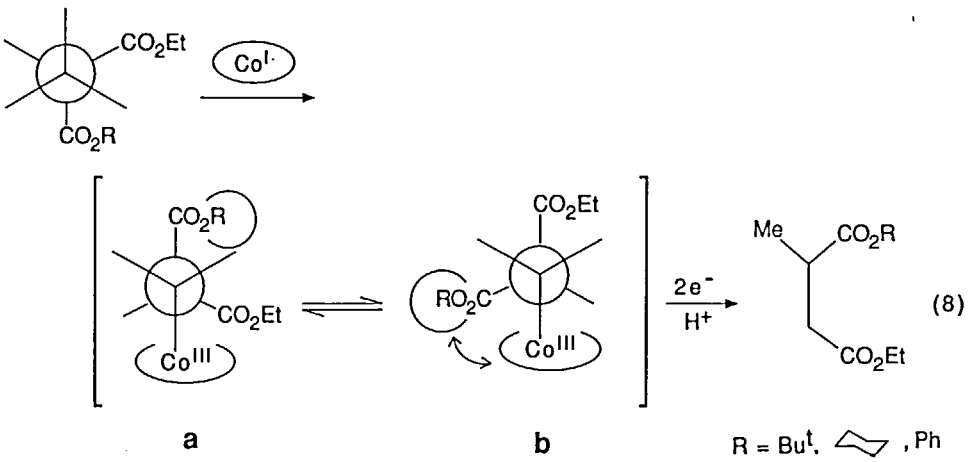
The above steric effect is understood on the basis of the following concept. When the 1,2-migration proceeds plausibly *via* formation of the *quasi*-cyclopropane ring as shown in equation 4, the substituent placed at the conformational position *anti* to the cobalt atom may migrate to the adjacent carbon. The alkylated complex, derived from the reaction between the univalent cobalt complex and an alkyl halide, may exist in two conformational isomers (**a** and **b** in equation 8). If the steric stability of **a** is compared with that of **b**, **b** is less stable than **a** because larger steric repulsion is

TABLE II

Product analyses for controlled-potential electrolyses of alkyl bromides **3** and **4** catalyzed by hydrophobic vitamin B_{12} in the dark.[a]

	Electrolysis conditions				Yield/%[e]		
	Potential		Charge[d]	Period			
Substrate[b]	V *vs* SCE	Additive[c]	F mol^{-1}	h	Unrearranged product[f]	CO_2R-migrated product[g]	CO_2Et-migrated product[h]
3	−1.5	CH_3CO_2H	3.0	8	19–20	8–10	16–18
3	−2.0	None	2.0	5	22–25	20–23	45–49
4	−1.5	CH_3CO_2H	3.0	9	24–27	8–12	16–19
4	−2.0	None	2.0	5	27–31	18–20	42–44

[a] Electrolysis was carried out by the same procedure as given in Table I. Starting solutions were composed of: [Cob(II)7C_1ester]ClO_4, 30 mg (2.6×10^{-5} mol); **3**, 834 mg (2.6×10^{-3} mol); **4**, 819 mg (2.6×10^{-3} mol); 30 cm^3 of DMF containing 5.0×10^{-2} mol dm^{-3} TBAF. [b] Refer to equations 6 and 7. [c] CH_3CO_2H, 500 mg (8.3×10^{-3} mol dm^{-3}). [d] Electrical charge passed per mol of the substrate. [e] Based on an initial amount of the substrate; the rest was unreacted substrate; analyzed by GLC; refer to equations 6 and 7. [f] Unrearranged products were **F** and **I** for substrates **3** and **4**, respectively. [g] Bulky ester-migrated products **G** and **J** for substrates **3** and **4**, respectively. [h] Ethoxycarbonyl-migrated products **H** and **K** for substrates **3** and **4**, respectively.



expected between the corrin ring of the hydrophobic vitamin B_{12} and the substituent (R) for the former. Since the 1,2-migration reaction proceeds *via* cleavage of the cobalt–carbon bond, the rate-determining step must involve cleavage of the cobalt–carbon bond. Under such circumstances, conformer **b** readily undergoes decomposition relative to conformer **a** as mediated by the steric repulsion. Consequently, the migration of the ethoxycarbonyl group as a small substituent prevails over the migration of the larger ester groups.

In conclusion, it became apparent from the present investigation of the steric effect in the electrochemical 1,2-migration catalyzed by the hydrophobic vitamin B_{12} that a more bulky substituent migrates less readily to the adjacent carbon atom. This steric effect indicates that the rate-determining step of the electrolysis does not refer to the formation of the cobalt–carbon bond but to its cleavage. The electronic effect in the 1,2-migration is quite important as clarified in our previous paper,[9] but the steric effect is not unimportant. It is not relevant to apply these mechanisms directly to the corresponding vitamin B_{12}-dependent enzymatic reactions, since a reduction potential as high as -1.8 or -2.0 V *vs* SCE would not be attained *in vivo*. Our studies are directed toward the development of catalytic systems capable of performing effective 1,2-migrations accompanied with asymmetric selectivity.

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