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Electrochemical reactions mediated by vitamin B_{12} derivatives in organic solvents

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Contents

Abstract

Vitamin B_{12} enzymes, involving the cobalt species as a catalytic center, mediate various isomerization reactions accompanied by carbon-skeleton rearrangements. In order to simulate the catalytic 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

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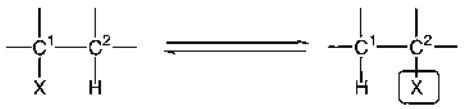
B_{12}. In this work, the carbon-skeleton rearrangements as mediated by hydrophobic vitamin B_{12} derivatives were investigated under electrochemical conditions. The controlled-potential electrolyses of alkyl halides with various electron-withdrawing groups were carried out, and the electrochemical carbon-skeleton rearrangements proceeded effectively via formation of anionic intermediates. These reactions can also be applied to the ring-expansion reactions. We have prepared a novel vitamin B_{12} derivative, [Cob(II)7Phe(OBzl)]ClO_4, having phenylalanine residues on the peripheral side chains. [Cob(II)7Phe(OBzl)]ClO_4 effectively catalyzed 1,2-migration of the carboxylic ester in 1-bromo-2,2-bis(ethoxycarbonyl)propane at -1.0 V vs. SCE under irradiation conditions. A strapped hydrophobic vitamin B_{12} was prepared in order to change the enantioselectivity, and the controlled-potential electrolysis of a racemic alkyl halide was carried out in the presence of vitamin B_{12} derivatives. Product analyses and computational calculations suggested that the stability of alkylated complexes dominated the enantioselectivity of reduction products.

Keywords: Vitamin B_{12} derivative; Electroorganic synthesis; Redox chemistry; 1,2-Migration; Ring-expansion; Enantioselective reaction

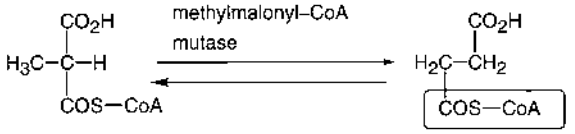
1. Introduction

Vitamin B_{12}-dependent enzymes, involving the cobalt species as a reaction site, catalyze various isomerization reactions leading to the intramolecular exchange of a functional group (X) and a hydrogen atom between neighboring carbon atoms (refer to Eq. (1)) [1,2].



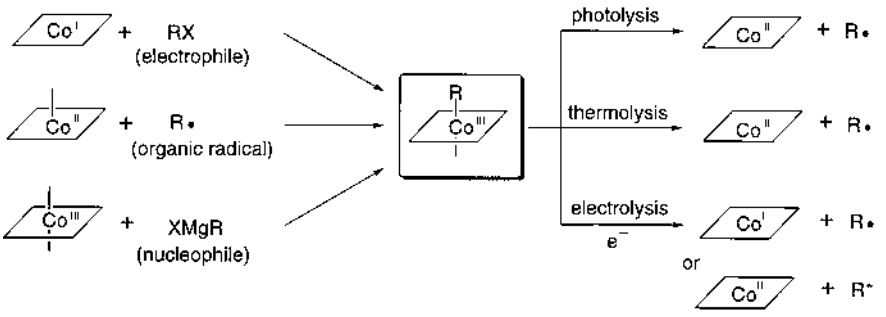
(1)

These reactions have attracted much attention because of their novel nature from the viewpoint of organic and organometallic chemistry. Carbon-skeleton rearrangement reactions, for example, mediated by methylmalonyl-CoA mutase is shown in Eq. (2).



(2)

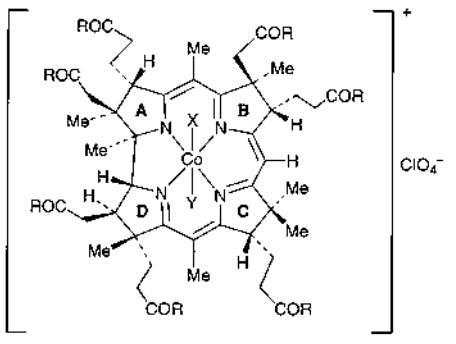
We have been studying the functional simulation of vitamin B_{12} enzymes by means of the electrochemical method [3–14]. The key intermediates are the compounds having a cobalt–carbon bond, which can be formed by the reactions between Co^{I} and an electrophile, Co^{II} and a radical species, or Co^{III} and a nucleophile as shown in Scheme 1. We have generally used the reactions between Co^{I} and an alkyl halide in this work. In this review, we summarized electrochemical molecular transformations mediated by vitamin B_{12} derivatives.



Scheme 1. Formation and cleavage of Co–C bond.

2. Preparation of vitamin B_{12} derivatives

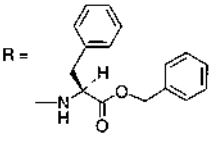
The naturally occurring apoproteins, which provide relevant reaction sites for vitamin B_{12}, are considered to perform additional important roles that lead to desolvation and close association of reacting species [15]. On this basis, we have been interested in the catalytic activity of vitamin B_{12} in hydrophobic microenvironments in order to simulate the catalytic functions of the holoenzymes concerned. Under such circumstances, we have prepared hydrophobic vitamin B_{12} derivatives which have ester groups in place of the peripheral amide moieties of natural vitamin B_{12} as shown in Scheme 2 [16–18]. Strapped hydrophobic vitamin B_{12}, [Cob(II)(c,10-PDA)6C_3ester]ClO_4, was prepared in order to control the enantioselectivity of reactions [19]. We also prepared a novel vitamin B_{12} derivative, [Cob(II)7Phe(OBzl)]ClO_4, having phenylalanine residues on the peripheral side chains in order to enhance the catalytic efficiency in 1,2-migration reactions [20].



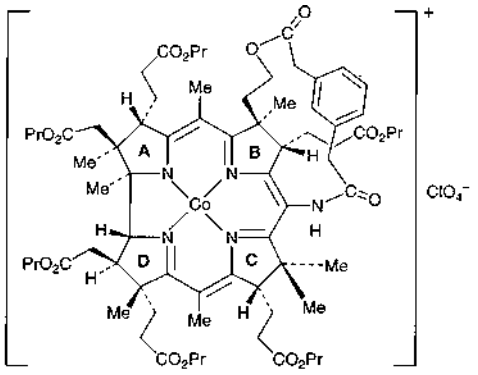
R=OMe, X=Y=None : [Cob(II)7C_1ester]ClO_4

R=OPr, X=Y=None : [Cob(II)7C_3ester]ClO_4

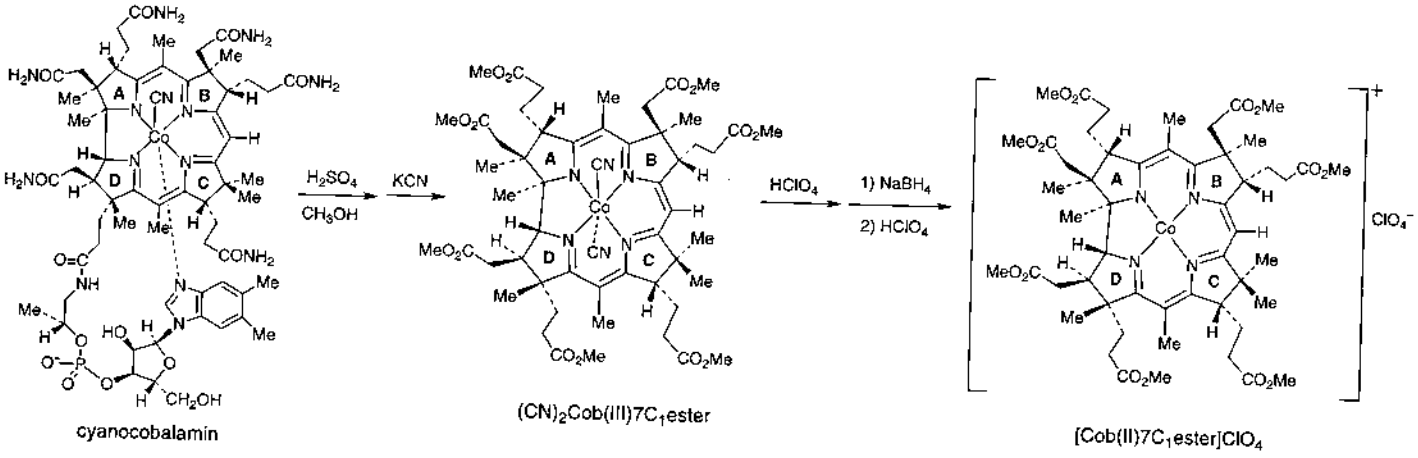
R=OMe, X=Me, Y=H_2O : [(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4



, X=Y=None : [Cob(II)7Phe(OBzl)]ClO_4



[Cob(II)(c,10-PDA)6C_3ester]ClO_4



Scheme 2. Preparation of hydrophobic vitamin B_{12} from cyanocobalamin.

3. Redox behavior of vitamin B_{12} derivatives in nonaqueous media

3.1. Hydrophobic vitamin B_{12}

The redox behavior of heptamethyl cobyrinate perchlorate, [Cob(II)7C_1ester]ClO_4, in various organic solvents has been reported. We have pointed out that this complex is readily reduced to the univalent cobalt species of highly nucleophilic character by electrochemical means in nonaqueous media [6]. A typical cyclic voltammogram is shown in Fig. 1. The redox potentials for Co(II)/Co(I) and Co(III)/Co(II) couples of [Cob(II)7C_1ester]ClO_4 in dimethyl sulfoxide (DMSO) were observed at -0.64 and $+0.41$ V vs. SCE, respectively [3]. Redox behavior of the strapped hydrophobic vitamin B_{12} in various organic solvents was also examined by means of cyclic voltammetry [19]. The Co(III)/Co(II) and Co(II)/Co(I) redox potentials in various media are summarized in Table 1. The Co(III)/Co(II) and Co(II)/Co(I) redox potentials for the strapped hydrophobic vitamin B_{12} are quite comparable to those for the simple hydrophobic vitamin B_{12}, [Cob(II)7C_3ester]ClO_4, in all the solvents used here. Since the liquid junction potential is subject to change by the nature of solvent systems, the redox potentials observed in various solvents cannot be directly compared with each other. Though liquid junction potentials between electrolyte solutions in various solvents have been extensively investigated, the most conventional and reliable means of eliminating the difference in liquid junction potential between various media is to adopt the observed redox potentials for the couple of ferrocenium/ferrocene ion in various media as references. Because the true redox potential for the couple of ferrocenium/ferrocene ion is considered to remain constant regardless of the nature of organic media [21–23], the redox potentials corrected for the difference in liquid junction

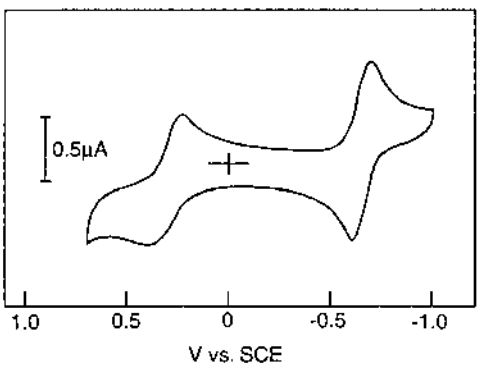


Fig. 1. Cyclic voltammogram of [Cob(II)7C_1ester]ClO_4 (5.2×10^{-4} mol dm^{-3}) in DMSO containing tetrabutylammonium perchlorate (TBAP, 5.1×10^{-2} mol dm^{-3}) at 20 ± 2°C; scan rate, 100 mV s^{-1}.

Table 1
Redox potentials for vitamin B_{12} derivatives in non-aqueous media [a]

Medium [b]	DN [c]	E_T^N [d]	Complex [e]	$E_{1/2}$ vs. SCE (V)		$E_{1/2}$ vs. (Fc^+/Fc) [f] (V)	
				Co(III)/Co(II)	Co(II)/Co(I)	Co(III)/Co(II)	Co(II)/Co(I)
CH_3CN	14.1	0.460	Cob(II)7C_1ester	+0.45	−0.64	+0.01	−1.10
			Cob(II)7C_3ester	+0.54	−0.57	+0.08	−1.03
			Strapped B_{12}	+0.58	−0.53	+0.12	−0.99
			Cob(II)7Phe(OBzl)	+0.50	−0.63	+0.04	−1.09
CH_3COCH_3	17.0	0.355	Cob(II)7C_1ester	+0.77	−0.53	+0.25	−1.05
			Cob(II)7C_3ester	+0.82	−0.47	+0.30	−0.99
			Strapped B_{12}	+0.87	−0.47	+0.35	−0.99
DMF	26.6	0.404	Cob(II)7C_1ester	+0.40	−0.61	−0.04	−1.05
			Cob(II)7C_3ester	+0.43	−0.62	−0.01	−1.06
			Strapped B_{12}	+0.41	−0.61	−0.03	−1.05
			Cob(II)7Phe(OBzl)	+0.50	−0.70	−0.06	−1.14
DMSO	29.8	0.444	Cob(II)7C_1ester	+0.30	−0.64	+0.11	−1.05
			Cob(II)7C_3ester	+0.28	−0.66	−0.13	−1.07
			Strapped B_{12}	+0.41	−0.65	+0.00	−1.06
			Cob(II)7Phe(OBzl)	+0.40	−0.70	−0.01	−1.11

[a] Measured at 20 ± 2°C; scan rate, 100 mV s^{-1}.
[b] Abbreviations: DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide.
[c] Donor number of a solvent; refer to Ref. [21].
[d] Solvent polarity parameter; refer to Ref. [22].
[e] Abbreviations: Cob(II)7C_1ester, [Cob(II)7C_1ester]ClO_4; Cob(II)7C_3ester, [Cob(II)7C_3ester]ClO_4; Strapped B_{12}, [Cob(II)(c,10-PDA)6C_3ester]ClO_4; Cob(II)7Phe(OBzl), [Cob(II)7Phe(OBzl)]ClO_4.
[f] Abbreviations: Fc, ferrocene; Fc^+, ferrocenium ion.

potential in the light of the observed redox potentials for ferrocenium/ferrocene ion are shown in Table 1. Redox potentials for Co(II)/Co(I) and Co(III)/Co(II) of hydrophobic vitamin B_{12} derivatives are considered to be essentially unchanged in various organic solvents. This means that the electronic state of the nuclear cobalt atom remains primarily unchanged even after the strapping modification of the hydrophobic vitamin B_{12} is carried out.

3.2. Hydrophobic vitamin B_{12} with Co–C bond

Savéant et al. reported the redox behavior of methylcobinamide and showed that even at -20°C, a single irreversible cathodic wave of methylcobinamide was observed at low sweep rate (1 V s^{-1}) corresponding to the reductive cleavage of the cobalt–carbon bond in *N*,*N*-dimethylformamide (DMF)-1-propanol (1:1 v/v). Upon raising the sweep rate (10–200 V s^{-1}), the cathodic wave becomes progressively reversible, clearly showing the existence of the one-electron reduction intermediate before cleavage of the cobalt–carbon bond at $E_{1/2} = -1.46$ V vs. SCE [24].

The redox behavior of heptamethyl methylcobyrinate perchlorate, $[(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4$, which has a Co–C bond, was examined in DMF by means of cyclic voltammetry as shown in Fig. 2 [4]. The cyclic voltammogram is similar in appearance to those for methylcobalamin and methylcobinamide reported previously [24,25]. In the course of the initial sweep of cyclic voltammetry, a single irreversible reduction peak, which is assigned to the one-electron reduction intermediate, was observed at -1.32 V vs. SCE, while a very weak peak (-0.53 V vs. SCE) and a more intense peak (-0.53 V vs. SCE) were

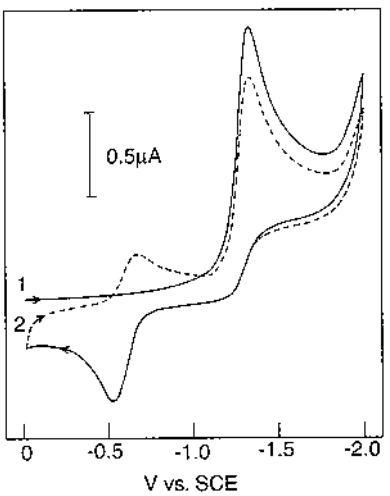
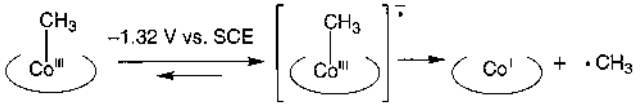


Fig. 2. Cyclic voltammogram of $[(CH_3)(H_2O)Cob(III)7C_1ester]ClO_4$ (6.1×10^{-4} mol dm^{-3}) in DMF containing tetrabutylammonium tetrafluoroborate (TBAF, 5.0×10^{-2} mol dm^{-3}) at 20 ± 2°C in the dark; scan rate, 100 mV s^{-1}.

observed in the anodic sweep; the latter being attributed to the Co(I)/Co(II) oxidation. The second cathodic sweep, curve 2 in Fig. 2, showed two reduction peaks at -0.69 V, assigned to the Co(II)/Co(I) reduction, and at -1.32 V vs. SCE. The $E_{1/2}$ value for Co(II)/Co(I) is -0.61 V vs. SCE and in agreement with that for [Cob(II)7C_1ester]ClO_4, measured in DMF. The characteristic feature of redox behavior observed in the subsequent repeated cyclic sweeps remained the same. This redox behavior indicates that the methylated complex is decomposed to afford Cob(I)7C_1ester and the methyl radical in a potential range more cathodic than -1.32 V vs. SCE as shown in Eq. (3).



(3)

On the basis of above information, catalytic cycles were established as shown in Fig. 3. An alkylated complex, generated by the reaction of a univalent cobalt complex and an alkyl halide, is generally decomposed by photolysis or electrolysis to afford reduction and/or rearrangement products [5,6,10].

4. Electrochemical catalytic reactions

4.1. Catalytic simulation of methylmalonyl-CoA mutase

2,2-Bis(ethoxycarbonyl)-1-bromopropane has been adopted as a model substrate

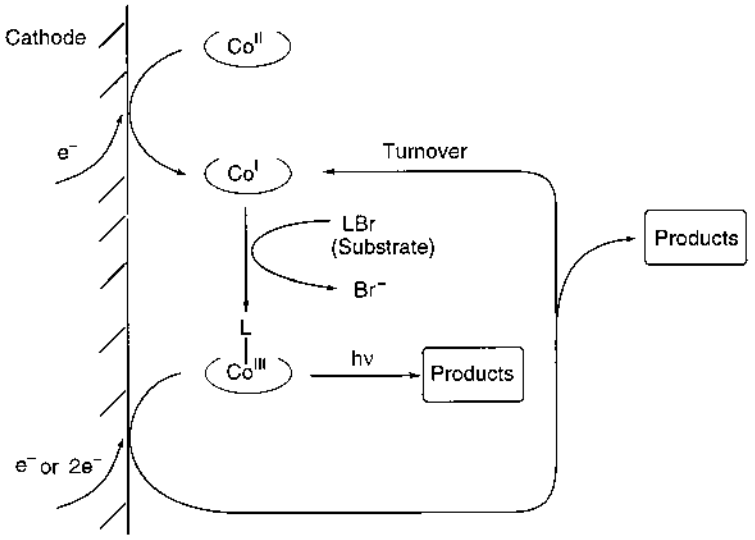


Fig. 3. Electrochemical reactions mediated by hydrophobic vitamin B_{12}.

for methylmalonyl-CoA mutase. The redox behavior of [Cob(II)7C_1ester]ClO_4 in DMF containing the substrate in a large excess and tetrabutylammonium tetrafluoroborate (TBAF) as a supporting electrolyte was examined by means of cyclic voltammetry as shown in Fig. 4. The redox potential for the Co(II)/Co(I) couple was observed at -0.59 V vs. SCE in the presence of the substrate. An irreversible reduction peak was observed at ca. -1.3 V vs. SCE and assigned to the formation of the one-electron reduction intermediate of the alkylated complex, which was generated by the reaction between Co^{I} species and the substrate. In addition, the second irreversible reduction peak was observed at ca. -1.8 V vs. SCE. This peak was assigned to the formation of the two-electron reduction intermediate of the alkylated complex. The first reduction peak for the substrate was observed at -2.7 V vs. SCE in DMF without the hydrophobic vitamin B_{12}, so that the peaks observed in the range -2.0–0 V vs. SCE do not originate from the substrate itself. This redox behavior indicates that different intermediates will be formed at -1.0, -1.5, and -2.0 V vs. SCE, respectively.

Electrolysis of the substrate was carried out upon addition of a catalytic amount (below 1% mol) of [Cob(II)7C_1ester]ClO_4 in DMF under various conditions, and products were analyzed by GLC (refer to Eq. (4)) [6]. The catalysis was quite efficient at -2.0 V vs. SCE as reflected in the yields of the rearrangement product; turnover numbers based on an initial amount of the hydrophobic vitamin B_{12} per hour are shown in the equation, which depend on an actual area of the cathode electrode.

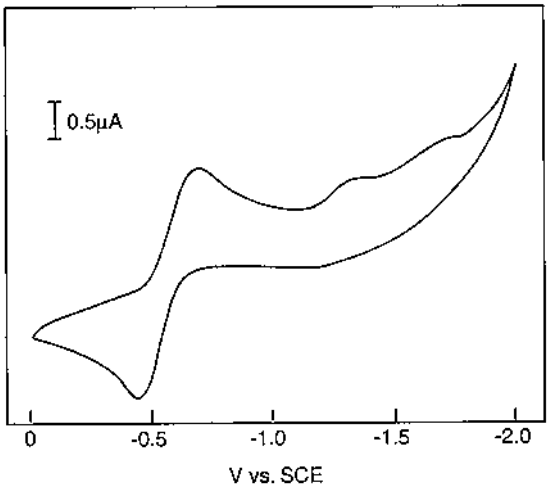
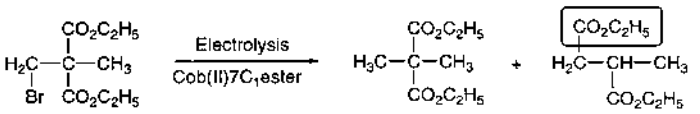


Fig. 4. Cyclic voltammogram of [Cob(II)7C_1ester]ClO_4 (7.2×10^{-4} mol dm^{-3}) in DMF containing 2,2-bis(ethoxycarbonyl)-1-bromopropane (0.10 mol dm^{-3}) and TBAF (0.10 mol dm^{-3}) at 20 ± 2°C in the dark; scan rate, 100 mV s^{-1}.

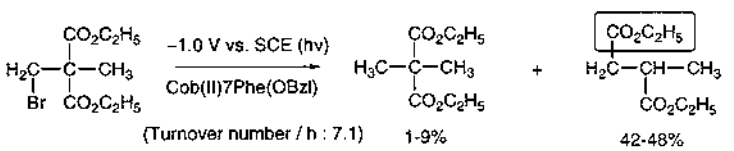


			Turnover number / h
1) −1.0 V vs. SCE (hv)	10%	trace	1.6
2) −1.5 V vs. SCE	30%	trace	1.9
3) −1.5 V vs. SCE (AcOH)	17%	43%	15
4) −2.0 V vs. SCE	15%	80%	20

(4)

Reaction mechanisms involved in the controlled-potential electrolysis were investigated by means of electronic spectroscopy and coulometry as well as by the spin-trapping ESR technique [5]. The results are consistent with the overall feature of electrolysis shown in Fig. 5. At -1.0 V vs. SCE, the divalent cobalt complex is first converted into the corresponding univalent cobalt species by electrochemical reduction. The alkylated complex is formed subsequently by reaction of the super-nucleophilic Co^{I} species with the alkyl halide. The complex is then decomposed by visible light to give the divalent cobalt species and the alkyl radical, and the latter abstracts a hydrogen atom to afford the simple reduction product. At -1.5 V vs. SCE, the alkylated complex is further reduced to form the one-electron reduction intermediate in the dark. An electronic structure of the intermediate seems to be represented by two canonical forms. A 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 the Co^{I} chelate and the alkyl radical in the absence of an efficient proton source. The reduction product is mainly derived from the alkyl radical by rapid abstraction of a hydrogen atom. At -2.0 V vs. SCE, the alkylated complex is converted into the two-electron reduction intermediate in the dark. This intermediate is decomposed to the Co^{I} chelate and an anionic species, and the rearrangement product is obtained from the latter. The simple reduction product is primarily obtained from the radical species. Since the identical radical species, which is produced by reaction of the present substrate with tributyltin hydride or by photolysis of the present substrate bound to cobaloxime, does not undergo the rearrangement reaction [26], both of the anionic reduction intermediates given in Fig. 5 are the primary sources for the rearrangement product.

When we used $[Cob(II)7Phe(OBzl)]ClO_4$ as a catalyst, a different result was obtained. On the electrolysis at -1.0 V vs. SCE under irradiation conditions, the ester migrated product was obtained as a major product as shown in Eq. (5) [20].



(5)

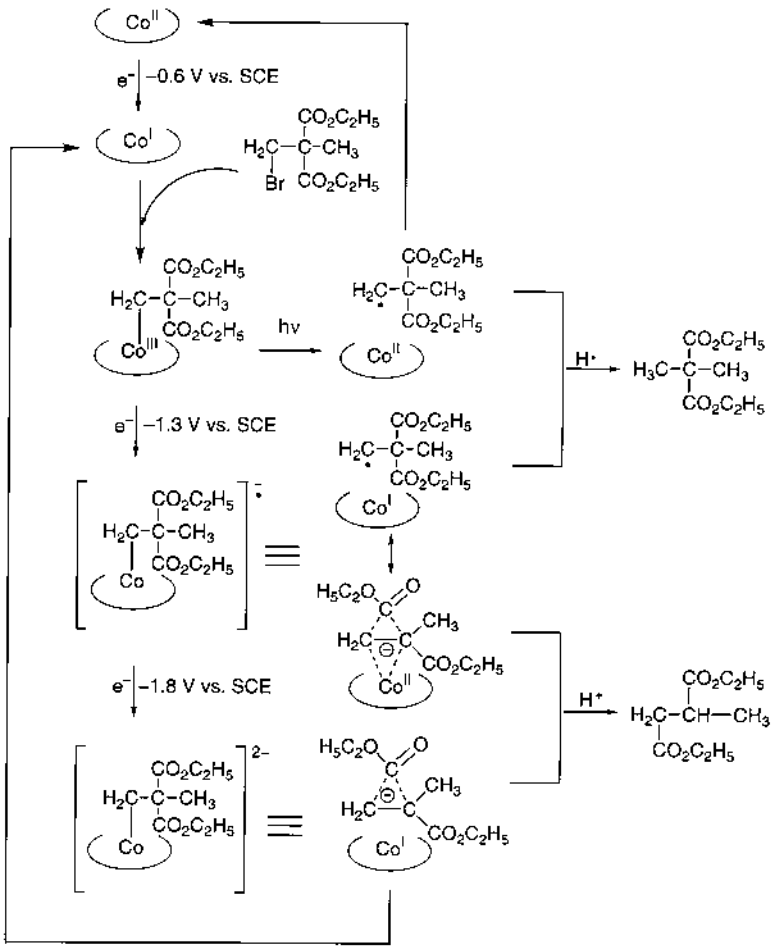


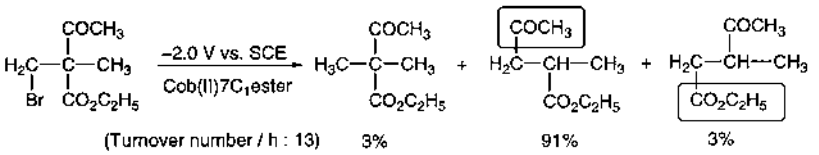
Fig. 5. Overall electrochemical catalytic reaction mediated by hydrophobic vitamin B_{12}.

When [Cob(II)7C_1ester]ClO_4 was used, the product was simply the reduced one at -1.0 V vs. SCE as shown in Eq. (4). ESR measurements indicate that these reactions proceed via radical intermediates. Peripheral amino acid residues may effectively assist 1,2-migration of the carboxylic ester.

4.2. 1,2-Migration of functional groups

In order to further characterize the catalytic proficiency of the hydrophobic vitamin B_{12} and to clarify the migratory aptitude of functional groups in the electrochemical rearrangement reaction, several kinds of substrates were used [6]. These substrates and the corresponding products are summarized in Eqs. (6) and

(7). 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. In the light of the results, the apparent migratory aptitude of electron-withdrawing groups decreases in the following sequence: COR > CO_2R > CN. Both steric bulkiness and electronic character of the migrating groups would be responsible for this tendency.



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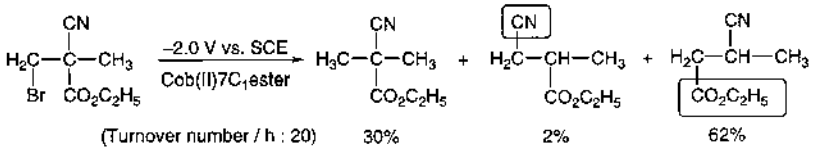
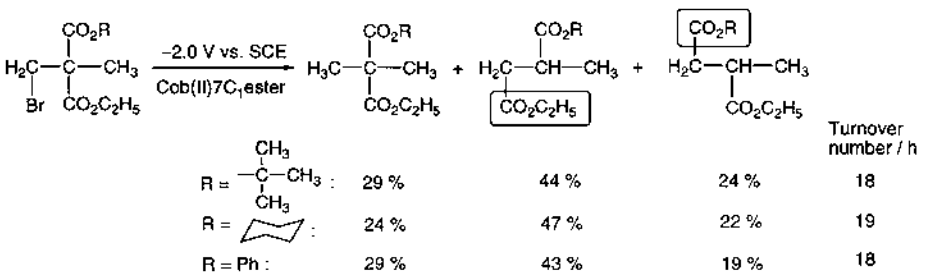


(7)

A steric effect in the carbon-skeleton rearrangement catalyzed by [Cob-(II)7C_1ester]ClO_4 was investigated under the same conditions [13]. The controlled-potential electrolyses of alkyl halides having two carboxylic ester groups of different bulkiness on the same carbon atom were carried out in DMF (refer to Eq. (8)). As regards a correlation between bulkiness of an ester group and migratory aptitude, a smaller ester group tends to migrate to the adjacent carbon atom more readily than a larger one. This steric effect is understood by a stereo-electronic effect.



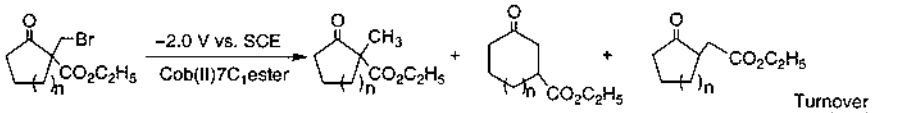
(8)

4.3. Ring-expansion reactions

The ring-expansion of cyclic α-(bromomethyl)-β-keto esters by one carbon unit has been examined rather extensively by generating radical species with Bu_3SnH [27–30]. Torii et al. have investigated ring-expansion reactions of 2-alkyl-2-(bromomethyl)cycloalkanones, which have 5- and 6-membered rings, mediated by cobaloxime in methanol at 55–60°C by constant-current electrolysis under irradiation with visible light [31]. Other ring-expansion reactions can apply to vitamin B_{12}

derivatives. [Cob(II)7C$_1$ester]ClO$_4$ was utilized to catalyze ring-expansion reactions under conditions of controlled-potential electrolysis.

The electrolyses of alkyl halides with a cyclic ketone (5, 6, 7, and 8-membered ring) and an ester group were carried out in DMF in the presence of [Cob(II)7C$_1$ester]ClO$_4$ at -2.0 V vs. SCE (refer to Eq. (9)) [14].



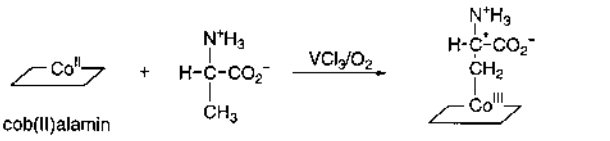
				Turnover number / h
n = 1 (5-membered ring)	1.5 %	43 %	0 %	8.6
n = 2 (6-membered ring)	14 %	49 %	12 %	6.1
n = 3 (7-membered ring)	3 %	44 %	trace	5.4
n = 4 (8-membered ring)	2 %	21 %	4 %	4.4

(9)

Products were analyzed by GLC; simple reduced products, ring-expanded products, and ester-migrated products were detected. The major product was a ring-expansion product for all the substrate. The following facts become obvious on the basis of these data: (i) The ring-expansion reactions are effectively catalyzed by the hydrophobic vitamin B$_{12}$. Turnover numbers for these substrates are 27–66 for 8 h under the present conditions; (ii) As for the reactivity of substrates, an alicyclic ketone with a larger ring size (8-membered one) is less reactive than those with smaller ring sizes (5-, 6-, and 7-membered ones). The formation of alkylated complex with the substrate ($n = 4$) seems to be less favorable relative to that with other substrates due to steric reasons; (iii) As for the product selectivity, major products are ring-expanded ones for all substrates. When even numbered substrates ($n = 2$ and 4) are used, ester-migrated products are obtained to some extent. Since the 6-membered ring is structurally stable, the 5-membered substrate ($n = 1$) readily underwent ring expansion to afford the ring-expansion product. On the other hand, molar ratios of non-expanded products vs. the ring-expansion product are much larger for reactions with the 6-membered substrate ($n = 2$) than those for other reactions examined here.

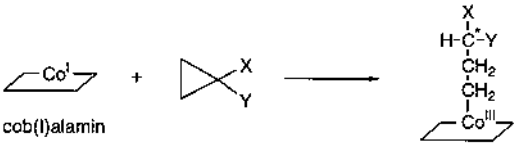
4.4. Enantioselective reactions

One of the fascinating functions of naturally occurring vitamin B$_{12}$ is its potentiality as a chiral catalyst in asymmetric synthesis, since vitamin B$_{12}$ creates a chiral reaction site provided by a corrin ring and peripheral substituents. Schrauzer et al. investigated the asymmetric alkylation of cob(II)alamin with DL-alanine in the presence of V^{3+} and oxygen radicals, and obtained the alanine-bound cobalamin in a 12% e.e. of the D-alanine-bound complex, as shown in Eq. (10) [32].



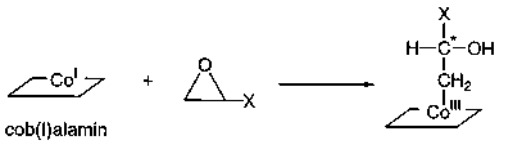
(10)

Ogoshi et al. studied the alkylation of cob(I)alamin with prochiral 1-acetyl-1-alkylcyclopropanes that induces an asymmetric center in the resulting alkyl ligands, as shown in Eq. (11), and found a 24% e.e. for X = Ac and Y = Et, a 33% e.e. for X = Ac and Y = CH_2Ph [33]. Golding and his co-workers carried out the alkylation of cob(I)alamin with *tert*-butyloxirane and methyloxirane as shown in Eq. (12), affording preferentially (*R*)-alkyl-bound products in 62 and 50% e.e., respectively [34,35].



(11)

X = $COCH_3$, Y = C_2H_5 : 24% e.e.
X = $COCH_3$, Y = CH_2Ph : 33% e.e.

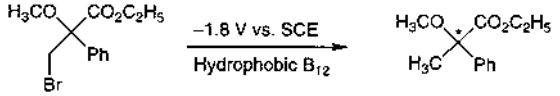


(12)

X =CH_3 : 50% e.e. (*R*-config)
X = $C(CH_3)_3$: 62% e.e. (*R*-config)

Scheffold et al. reported an asymmetric isomerization of 1,2-epoxycyclopentane to (*R*)-2-cyclopenten-1-ol via formation of the corresponding alkylated cobalamin, ca. 60% e.e. [36]. Murakami et al. have investigated the enantioselective alkylation of hydrophobic vitamin B_{12} derivatives, which bear a chiral binaphthyl moiety, with various racemic 3-bromo-2-methylpropionic esters in methanol, and the *S*-enantioselectivity as high as 65% e.e. was observed regardless of the chiral nature of the binaphthyl moiety [37,38]. The higher *S*-enantiomer selectivity with a novel hydrophobic vitamin B_{12}, modified by introducing a 1,3-phenylenediacetyl moiety into the peripheral site around the corrin's B ring, has been reported as shown below.

A strapped hydrophobic vitamin B_{12}, [Cob(II)(c,10-PDA)6C_3ester]ClO_4, has been prepared in order to change the enantioselectivity [19]. The controlled-potential electrolysis of racemic ethyl 3-bromo-2-methoxy-2-phenylpropionate was carried out at − 1.8 V vs. SCE in DMF, as mediated by a simple hydrophobic vitamin B_{12}, [Cob(II)7C_3ester]ClO_4, and a strapped hydrophobic vitamin B_{12}, [Cob(II)(c,10-PDA)6C_3ester]ClO_4, to afford ethyl 2-methoxy-2-phenylpropionate and ethyl 2-methoxy-3-phenylpropionate in the dark [39]. The simple hydrophobic vitamin B_{12} acted to afford ethyl (*S*)-2-methoxy-2-phenylpropionate, the hydrogen-substituted product, in 55% e.e., while the strapped hydrophobic vitamin B_{12} formed the corresponding *R* enantiomer in 26% e.e. as shown in Eq. (13).



(13)

[Cob(II)7C_1ester]ClO_4 : 87% e.e. (*S*-config)
[Cob(II)7C_3ester]ClO_4 : 55% e.e. (*S*-config)
[Cob(II)(c,10-PDA)6C_3ester]ClO_4: 26% e.e. (*R*-config)

Since the reaction proceeds via formation of an intermediate in which the ethyl 2-methoxy-2-phenylpropionate moiety is bound to the hydrophobic vitamin B_{12}, the chiral microenvironment provided by the peripheral groups placed around the corrin framework is responsible for the enantioselective formation of the alkylated hydrophobic vitamin B_{12}. The best enantiomeric excess is 87% e.e. for [Cob-(II)7C_1ester]ClO_4 as shown in Eq. (13). This result indicates that hydrophobic vitamin B_{12} derivatives are effective catalysts for asymmetric reactions.

The enantioselective coordination of the substrate species was rationalized by means of molecular mechanic and dynamic computations as well as by a Monte Carlo conformational search [39]. Schematic representation of configuration for alkylated vitamin B_{12} derivatives are shown in Fig. 6; the simple hydrophobic vitamin B_{12} with the *S* substrate is lower in energy than the complex with the *R* substrate by 1.8 kJ mol^{-1}, while the strapped hydrophobic vitamin B_{12} with the *R* substrate is lower than the identical complex with the *S* substrate by 2.0 kJ mol^{-1}.

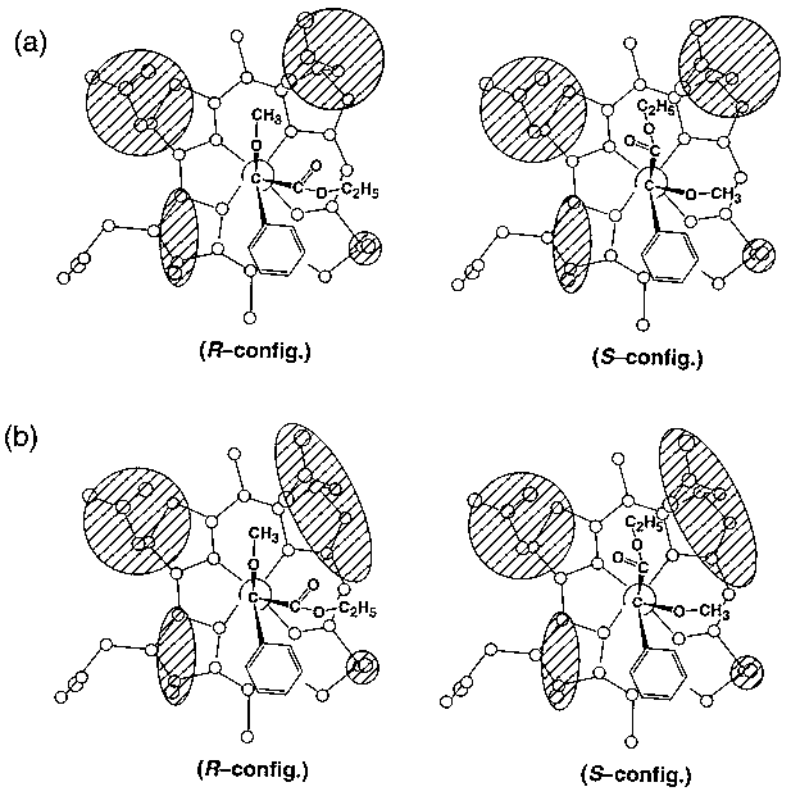


Fig. 6. The schematic representation of configuration for alkylated vitamin B_{12} derivatives having ethyl 2-methoxy-2-phenylpropionate as an β-axial ligand. (a) Simple hydrophobic vitamin B_{12}, Cob-(III)7C_3ester. (b) Strapped hydrophobic vitamin B_{12}, Cob(III)(c,10-PDA)6C_3ester.

These results suggested that the stability of alkylated complexes dominated the enantioselectivity of reduction products.

5. Conclusions

The carbon-skeleton rearrangements as mediated by vitamin B_{12} derivatives were investigated in non-aqueous medium under electrochemical conditions. In the light of the present study, one can conclude: (i) When the controlled-potential electrolyses of alkyl halides with various electron-withdrawing groups were carried out in the presence of vitamin B_{12} derivative, the electrochemical carbon-skeleton rearrangements proceeded effectively via formation of anionic intermediates under strong reduction conditions (-2.0 V vs. SCE); (ii) These reactions can be also applied to the ring-expansion reactions; (iii) A novel vitamin B_{12} derivative, having seven benzyl phenylalanine residues on the peripheral side chains, catalyzed 1,2-migration of carboxylic ester under mild reduction conditions (-1.0 V vs. SCE) with visible light; (iv) Strapped hydrophobic vitamin B_{12} was prepared in order to change the enantioselectivity. Vitamin B_{12} derivatives show characteristic enantioselectivity by reductive chiral resolution. Hydrophobic vitamin B_{12} derivatives are expected to be widely utilized as specific catalysts for fine organic syntheses via the 1,2-migration process of various functional groups.

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