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Novel catalytic functions of hydrophobic vitamin B_{12} in electrochemical carbon-skeleton rearrangements

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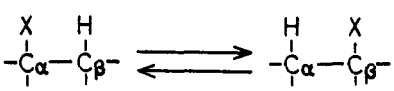
Abstract - The carbon-skeleton rearrangements as catalyzed by hydrophobic vitamin B_{12} derivatives were investigated under electrochemical conditions. The controlled-potential electrolyses of alkyl halides with various electron-withdrawing groups were carried out, and the electrochemical carbon-skeleton rearrangements proceeded via formation of anionic intermediates. Substrates with two electron-withdrawing groups placed on the β-carbon atom with combination 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 apparent migratory aptitude of electron-withdrawing groups was found to decrease in the order: COSR > COR > CO_2R > CN. A hydrophobic vitamin B_{12} with the cyano moiety at the axial site of cobalt further enhanced the electrochemical carbon-skeleton rearrangement.

INTRODUCTION

The vitamin B_{12}-dependent enzymes catalyze various molecular rearrangements, which can be formulated generally as the exchange of a hydrogen atom for substituent X on an adjacent carbon, as shown by Eq. 1. These reactions include three carbon-skeleton rearrangements, and



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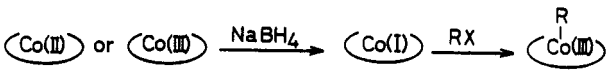
they are the reversible interconversions: methylmalonyl-CoA ⇌ succinyl-CoA, β-methylaspartate ⇌ glutamate, and methylitaconate ⇌ α-methyleneglutarate (ref. 1). These reactions are not explained clearly from the viewpoints of organic and organometallic chemistry so far studied, so that clarification of reaction mechanisms involved therein has become a target in bioinorganic chemistry by utilizing relevant model systems (ref. 2).

Various cobalt complexes have been synthesized as model complexes (ref. 3), but most of those complexes cannot be qualified as favorable models. The corrin moiety, which is the ligand for vitamin B_{12}, is remarkably different from porphyrin in ligation nature, so that the following aspects must be noted in designing model complexes. (i) Redox behavior of the central cobalt, which is primarily controlled by basicity of an equatorial ligand, must be similar to that observed for the naturally occurring vitamin B_{12}; corrin is a monoanionic ligand. (ii) Electronic properties must be equivalent to those of the natural B_{12}, which are provided by the corrin moiety with eight double bonds and a direct linkage between A and D rings. (iii) Steric effects, which are caused by the methyl group and the hydrogen atom at C(1) and C(19) positions in the corrin moiety, respectively, and by four propanamides and three acetamides placed at the α- and β-peripheral sites, respectively, must be retained by model complexes.

On the other hand, model studies of coenzyme B_{12}-dependent enzymatic reactions have been carried out in aqueous media since vitamin B_{12} is soluble in water but hardly in apolar solvents. In order to simulate catalytic functions of vitamin B_{12} as exerted in the hydrophobic active sites of enzymes concerned, vitamin B_{12} needs to be modified so that model studies can be carried out in ordinary apolar organic solvents. Therefore, we have synthesized hydrophobic vitamin B_{12} derivatives which have ester groups in place of the peripheral amide moieties of the naturally occurring vitamin B_{12} (ref. 4) in reference to the method of Werthemann et al. (ref. 5).

Most of vitamin B_{12} model reactions so far carried out are concerned merely with cleavage of

the Co-C bond of the corresponding alkylated complexes and cannot be regarded as catalytic ones (Eqs. 2 and 3). Because the alkylated complexes in those reactions were prepared from cobalt complexes and alkyl halides (RX) in the presence of chemical reductants such as sodium tetrahydroborate, it was difficult to establish the catalytic cycle and to eliminate an un-



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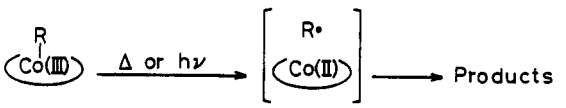

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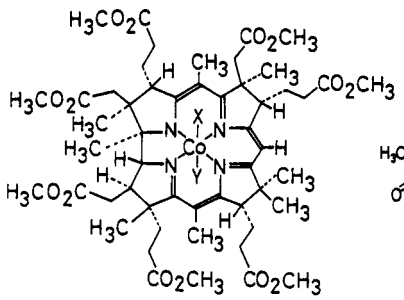
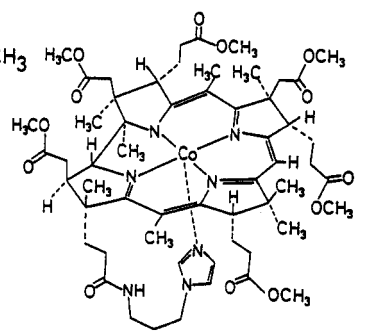
desirable effect caused by reductants on the reaction. In order to overcome these difficulties and set up clean reaction systems, we have adopted electrochemical means for reduction. Recently, electrochemical reactions catalyzed by vitamin B_{12} derivatives or model complexes have been carried out rather extensively (ref. 6), but catalytic isomerization reactions accompanied with the carbon-skeleton rearrangement have not been successfully performed yet by other research groups. This article describes the rearrangement reactions by electrochemical means as catalyzed by the following hydrophobic vitamin B_{12} derivatives.



X = Y = None : 1
X = CH_3, Y = H_2O : 2
X = CN, Y = H_2O : 3
X = Y = CN : 4



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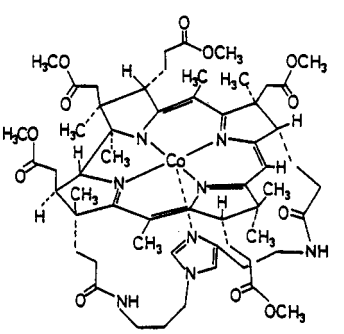

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REDOX BEHAVIOR

We have previously reported on the redox chemistry of heptamethyl cobyrinate perchlorate (1) and pointed out that this cobalt complex is readily reduced to the univalent cobalt species of highly nucleophilic character by electrochemical means in nonaqueous media (ref. 7). The cyclic voltammetry of heptamethyl methylaquacobyrinate perchlorate (2) indicated that the cobalt-carbon bond is cleaved by electrochemical reduction (ref. 8). In the light of these informations, catalytic cycles were established as shown in Fig. 1 (refs. 9 and 10). An alkylated complex, generated by the reaction between a univalent cobalt complex and an alkyl halide, is generally decomposed by photolysis or electrolysis to afford reduction and/or rearrangement products.

We firstly adopted 2,2-bis(ethoxycarbonyl)-1-bromopropane (7) which is considered to be a model substrate for methylmalonyl-CoA mutase. The redox behavior of 1 in N,N-dimethylformamide (DMF) containing 7 in a large excess and tetrabutylammonium tetrafluoroborate (TBAF) as a supporting electrolyte was examined by means of cyclic voltammetry (ref. 9). The outline of reduction processes is shown in Fig. 2. The redox potential for the Co(II)/Co(I) couple of 1 in DMF was observed at -0.56 V vs. Ag/AgCl (-0.59 V vs. SCE) in the presence of the alkyl bromide. 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 of the Co^{I} species with 7. This potential value is in agreement with the one for 2 in DMF; -1.29 V vs. Ag/AgCl. 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. Consequently, the electrochemical scheme shown in Fig. 2 indicates generation of mutually different intermediates upon electrolyses at -1.0, -1.5, and -2.0 V vs. SCE.

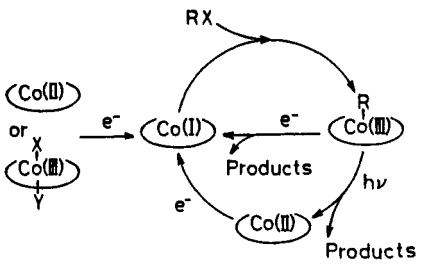

Fig. 1. Schematic representation of catalytic cycles.

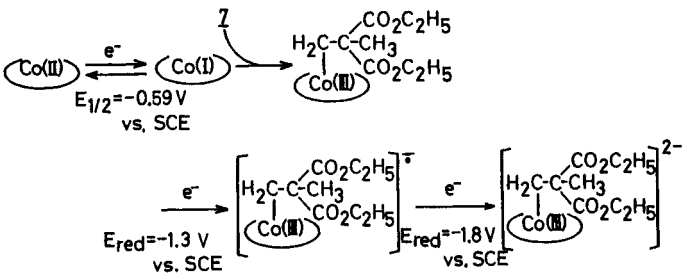

Fig. 2. Electrochemical processes for 1 and 7 in DMF.

CATALYTIC REACTIONS AND MECHANISMS

The electrolysis of 7 was carried out upon addition of 1 under various conditions, and products were analyzed by GLC. The following findings were obtained on the basis of the product analyses given in Table 1 (refer to Eq. 4). (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 (8 in Eq. 4). (ii) At -1.5 V vs. SCE in the dark; the rearrangement product (9 in Eq. 4) was the major one when an efficient proton source such as acetic acid or propionic acid was added, while the reduction product (8) was largely obtained without any additive. (iii) At -1.5 V vs. SCE under irradiation with the visible light; the major product was the reduced one (8) even in the presence of acetic acid. (iv) At potentials more cathodic than -1.8 V vs. SCE in the dark; the rearrangement product (9) 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 equivalent to 100—110 times as much as a molar quantity of the hydrophobic vitamin B_{12} after 2 h of the reaction.

The reaction mechanisms for controlled-potential electrolyses were investigated by means of electronic spectroscopy and coulometry as well as by the spin-trapping ESR technique (ref. 10). These data are consistent with the overall feature of electrolyses shown in Fig. 3. The bivalent cobalt complex is first converted into the univalent cobalt species by the electrochemical reduction at -1.0 V vs. SCE. The alkylated complex is formed in the second place by the reaction of the super-nucleophilic Co^{I} species with 7. The complex is then decomposed by the visible light to give the bivalent cobalt species and the alkyl radical, which ab-

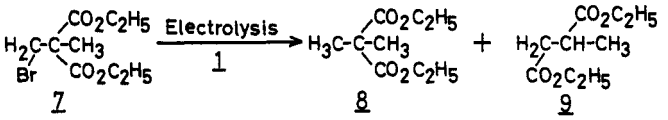

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TABLE 1. Product analyses for controlled-potential electrolysis of 7 as catalyzed by 1[a]

Entry	Electrolysis conditions					Yield[e]/%	
	Potential V vs. SCE	Irradiation[b]	Additive[c]	Charge[d] F mol^{-1}	Period h	8	9
1	-1.0	Irradiation	CH_3CO_2H	0.2	9	9—12	Trace
2	-1.5	Irradiation	CH_3CO_2H	3.0	12	36—41	3—10
3	-1.5	In the dark	CH_3CO_2H	3.0	6	16—18	40—46
4	-1.5	In the dark	None	1.0	23	25—36	ca. 1
5	-1.8	In the dark	CH_3CO_2H	2.0	6	12—13	32—36
6	-1.8	In the dark	None	2.0	23	24—28	23—31
7	-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: 1, 30 mg (2.6×10^{-5} mol); 7, 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_3CO_2H, 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_3CO_2H 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.

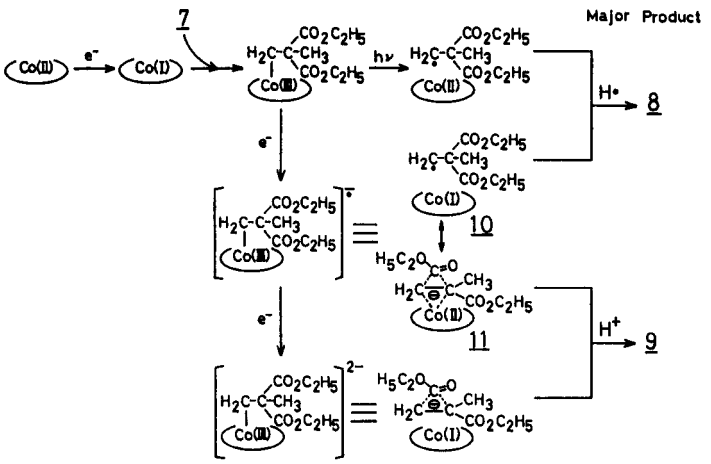


Fig. 3. Overall feature of electrolyses catalyzed by 1

stracts a hydrogen atom to afford the reduction product (8). 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 10 and 11 (refer to Fig. 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 (8) is mainly produced 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 the anionic species, and rearrangement product 9 is obtained from the latter. Therefore, the simple reduction product is primarily obtained from the radical species. Since the identical radical species, which is produced by the reaction of the present substrate with tributyltin hydride (ref. 11) or by the photolysis of the present substrate bound to cobaloxime (ref. 12), does not give the rearrangement product, the anionic reduction intermediates are the primary sources for the rearrangement product. As a consequence, these studies demonstrate the first example of the rearrangement as catalyzed by a vitamin B_{12} model under electrochemical conditions.

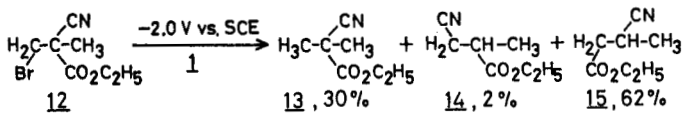
MIGRATORY APTITUDE

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, various substrates were also used. These substrates and the corresponding products are shown in Eqs. 5—10. The following aspects became apparent for the electrolyses. (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. 4, 5, and 6). (ii) Substrates with only one of the electron-withdrawing groups do not give the rearrangement products (refer to Eqs. 7, 9, and 10), except for the substrate with one thioester group (refer to Eq. 8). (iii) The rearrangement reaction readily proceeds under electrochemical conditions which allow the formation of anionic intermediates.

In the light of the above results, the apparent migratory aptitude of electron-withdrawing groups decreases in the following sequence: COSR > COR > CO_2R > CN. Both steric bulkiness and electronic character of the migrating groups would be responsible for this tendency. In order to estimate the effect of steric bulkiness of the migrating groups on the rearrangement reaction, the electrolyses of substrates with bulky ester groups were carried out (Eq. 11). We expected that a more bulky substituent on the β-carbon atom is placed at the anti-position to the cobalt atom when the alkylated complex is formed (refer to Eq. 12), so that such a bulky group readily migrates via formation of the quasi-cyclopropane ring. However, such preferential migration of a bulky group was not actually observed. On the other hand, attack of the α-carbanion on the β-substituent group is progressively enhanced as the substituent becomes more electron-withdrawing and leads to formation of the quasi-cyclopropane ring in the intermediate stage (refer to Eq. 13). 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 as a consequence.

EFFECTS OF AXIAL LIGANDS

The effect of an axial base on the electrochemical carbon-skeleton rearrangement was esti-



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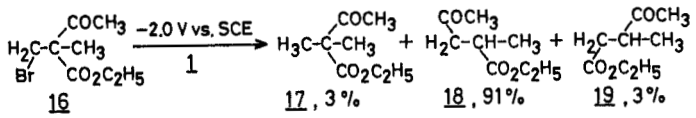

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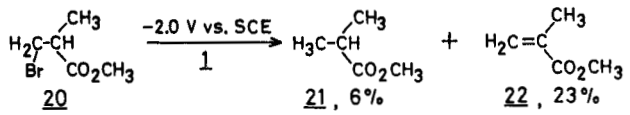

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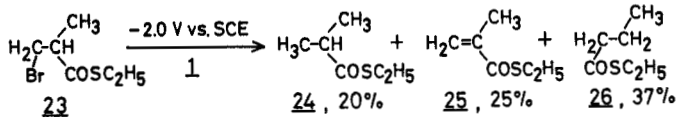

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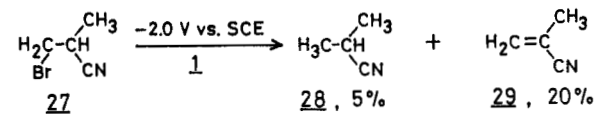

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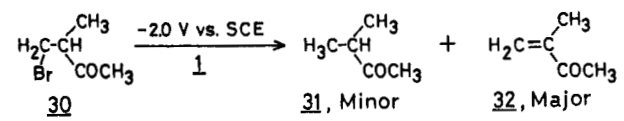

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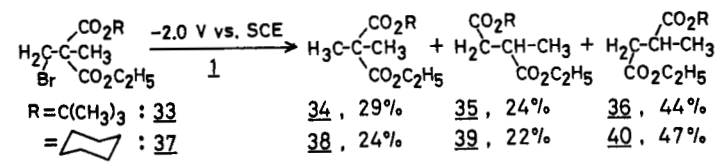

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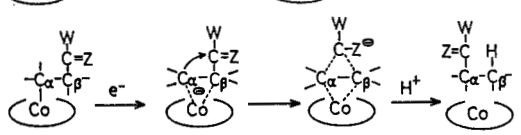

(13)

mated by the use of 5 and 6 as catalysts. Each imidazolyl moiety of these complexes is completely coordinated to the nuclear cobalt in the bivalent and tervalent states as judged from their ESR data and redox behavior (ref. 13). In particular, the intramolecular base of 6 is fixed in a close vicinity of the nuclear cobalt regardless of its oxidation state (ref. 14). The formation ratios of 9/8 were 5.5, 2.3, and 0.7 for catalysts 1, 5, and 6, respectively, under controlled-potential electrolysis at -2.0 V vs. SCE. The axial base in the hydrophobic vitamin B_{12}'s apparently inhibits the electrochemical carbon-skeleton rearrangement. Formation of the two-electron reduction intermediate, which is capable of affording the rearrangement product, is depressed by the axial base. In other words, the one-electron reduction intermediate becomes quite labile by the presence of the axial base and undergoes the cobalt-carbon bond cleavage before the second electron comes in.

Next, we investigated the cyanide-ion effect on the electrolysis. It has been reported previously that coordination of the cyanide ion to methylcobalamin at the cobalt atom tends to increase an electron density of the metal and to favor reduction of the methyl group to the carbanion upon photolysis (ref. 15). Therefore, the cyano-coordinated hydrophobic vitamin B_{12} is expected to enhance the formation of anionic intermediates in the electrolysis. The controlled-potential electrolysis of 12 was carried out in the presence of three different hydrophobic vitamin B_{12}'s, 1, 3, and 4. The following findings were obtained (Table 2).

TABLE 2. Product analyses for controlled-potential electrolysis of 12 at -2.0 V vs. SCE in the dark[a]

Catalyst	Conditions		Yield[c]/%		Product ratio
	Charge[b] / F mol^{-1}	Period / h	13	14+15	(14+15)/13
1	2.0	8	28—32	62—67	2.2
3	2.0	3	18—20	78—80	4.2
4	2.0	8	13—17	74—77	5.0

[a]Electrolysis was carried out by the same procedure as given in Table 1. Starting solutions: catalysts, 2.6 x 10^{-5} mol; 12, 1.0 g (4.5 x 10^{-3} mol); 30 mL of DMF containing 0.5 mol dm^{-3} TBAF.
[b]Electrical charge passed per mol of the substrate.
[c]Based on an initial amount of the substrate; analyzed by GLC.

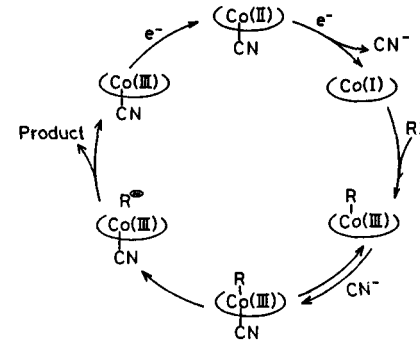

Fig. 4. Schematic representation of reaction cycle catalyzed by 3.

(i) The electrolysis catalyzed by 3 with one cyano group went to completion in a short period of time, and the ratio of rearrangement products, (14 + 15)/13, was large as compared with the ratio for the 1-catalyzed reaction. (ii) The (14 + 15)/13 ratio was further advanced by employing 4 with two cyano groups as a catalyst. However, a longer period of time was needed to complete the electrolysis, since the dicyano complex (4) requires a higher reduction potential for generation of the Co^{I} species. The reaction cycle catalyzed by 3 is consistent with the scheme shown in Fig. 4 on the basis of redox and spectroscopic measurements. The rearrangement reaction proceeded more readily since formation of the anionic intermediate was enhanced via coordination of the cyanide ion to the central cobalt atom.

CONCLUSION

We demonstrated for the first time the carbon-skeleton rearrangement reactions catalyzed by the hydrophobic vitamin B_{12} under electrochemical conditions in the dark. The electrochemical carbon-skeleton rearrangement was postulated to proceed via formation of the anionic intermediates. 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, and the reactivity of radical species may be subjected to change by the microenvironmental properties provided by apoenzymes at the reaction sites. In any event, it became apparent that electrochemical rearrangement reactions of model substrates readily proceed under stronger reduction conditions, and the apparent migratory aptitude of functional groups and the effects of axial ligands on the reaction were clarified.

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