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Isomerization of an Axial Ligand Coordinated to Hydrophobic Vitamin B_{12} as Effected by Cyanide Ion and Microenvironment

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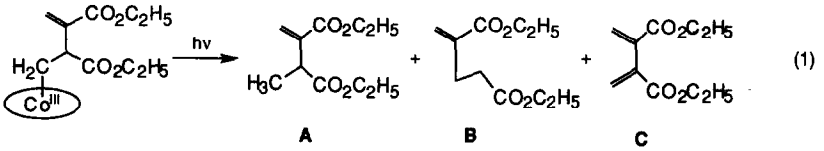
Abstract: The cyanide ion enhanced a carbon-skeleton rearrangement of the 2,3-bis(ethoxycarbonyl)-1-butene moiety bound to hydrophobic vitamin B_{12} derivatives in single-compartment bilayer vesicles under photolysis conditions *via* formation of the anionic substrate intermediate.

In connection with various carbon-skeleton rearrangement reactions catalyzed by vitamin B_{12}-dependent enzymes, we have been investigating microenvironmental effects on the catalytic activity of hydrophobic vitamin B_{12} derivatives under photolysis and electrochemical conditions in bilayer membranes and organic solvents, respectively.[1,2] The results indicate that the rearrangement reactions of model substrates proceed much readily *via* formation of anionic intermediates as compared with those *via* formation of radical ones, even though the reactions are generally considered to proceed *via* radical mechanisms *in vivo*. In this communication, we report that the cyanide ion enhances the formation of anionic substrate species from substrate-bound vitamin B_{12} model complexes under photolysis conditions and that a model reaction of α-methyleneglutarate mutase (eq. 1) proceeds readily as a consequence.

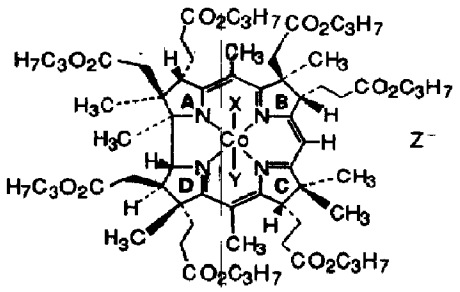


(1)

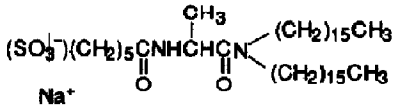
Complexes **1** and **6** were converted to the corresponding divalent cobalt complexes **3** and **8** *via* formation of **2** and **7**, respectively, after the methods reported previously.[1,3,4] Alkylated complexes **4** and **9** were derived from **3** and **8**, respectively, according to methods similar to those described previously.[1,4] Complex **4**: yield 68%; $\lambda_{max}(CH_3OH)$ 264, 304, and 462 nm. Found: C, 58.93; H, 7.59; N, 3.79%. Calcd for $C_{76}H_{118}ClCoN_4O_{23}$: C, 58.89; H, 7.67; N, 3.61%. Complex **9**: yield 59%; $\lambda_{max}(CH_2Cl_2)$ 266, 306, 403, and 468 nm. Found: C, 61.76; H, 8.60; N, 4.38%. Calcd for $C_{118}H_{196}ClCoNaN_7O_{28}S$: C, 61.35; H, 8.55; N, 4.24%.

We examined a carbon-skeleton rearrangement of the 2,3-bis(ethoxycarbonyl)-1-butene moiety bound to the hydrophobic vitamin B_{12} derivatives, **4** and **9**, in the single-walled bilayer membrane formed with $(SO_3^-)C_5Ala2C_{16}$ as well as in methanol under anaerobic photolysis conditions. After each of the alkylated complexes was completely decomposed by photolysis as confirmed by electronic spectroscopy, products were extracted with dichloromethane and analyzed by GLC (refer to eq. 1 and Table 1). The analytical results

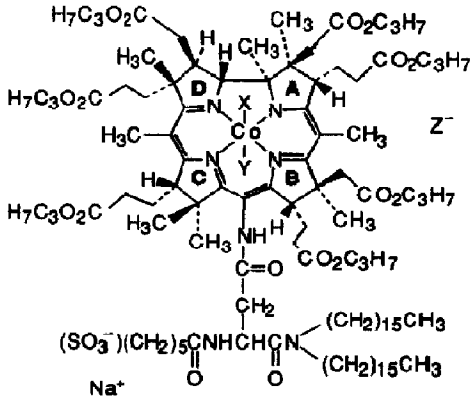
indicate that the cyanide ion markedly enhanced isomerization of the substrate bound to the hydrophobic vitamin B_{12}; particularly with **9** in the bilayer matrix of $(SO_3^-)C_5Ala2C_{16}$.



1 X=Y=CN, Z=None
2 X=CN, Y=H_2O, Z=ClO_4
3 X=Y=None, Z=ClO_4
4 X=$CH_2CH\{CCH_2(CO_2C_2H_5)\}(CO_2C_2H_5)$, Y=$H_2O$, Z=$ClO_4$
5 X=$CH_2CH\{CCH_2(CO_2C_2H_5)\}(CO_2C_2H_5)$, Y=CN, Z=$ClO_4$



$(SO_3^-)C_5Ala2C_{16}$



6 X=Y=CN, Z=None
7 X=CN, Y=H_2O, Z=ClO_4
8 X=Y=None, Z=ClO_4
9 X=$CH_2CH\{CCH_2(CO_2C_2H_5)\}(CO_2C_2H_5)$, Y=$H_2O$, Z=$ClO_4$

Table 1. Product Analyses for Photolysis of Alkylated Hydrophobic Vitamin B_{12} Derivatives in Various Media at 20 °C[a]

		Yield / %					
		TBACN[b] added			Without TBACN		
Medium	Complex	A	B	C	A	B	C
$(SO_3^-)C_5Ala2C_{16}$ vesicle[c]	9	22.0	43.8	6.5	1.3	3.4	80.3
$(SO_3^-)C_5Ala2C_{16}$ vesicle[c]	4	34.2	30.8	3.3	2.1	0	71.1
Methanol	4	55.8	27.2	0	32.2	0	57.3

a) A solution containing the alkylated complex (1.0×10^{-4} mol dm^{-3}) was irradiated with a 500-W tungsten lamp for 1 h at a distance of 30 cm under anaerobic conditions. Products were analyzed by GLC. Total yields are less than 100% due to losses during extraction treatments. b) Tetra-*n*-butylammonium cyanide (TBACN), 3.0×10^{-3} mol dm^{-3}. c) $(SO_3^-)C_5Ala2C_{16}$ in aqueous phosphate buffer (0.00 mol dm^{-3}; $\mu = 0.01$ with KCl) at pH 7.0 was sonicated with a probe-type sonicator at 30 W for 15 min to afford the single-compartment vesicle (5.0×10^{-3} mol dm^{-3}).

The coordination of cyanide ions to methylcobalamin at the residual axial site of cobalt atom has been claimed to enhance reduction of a methyl group to the corresponding carbanion species upon photolysis.[5,6] In order to confirm such heterolytic cleavage of the cobalt–carbon bond, we adopted spectroscopic measurements for photolysis of the alkylated hydrophobic vitamin B_{12}. When complex **4** incorporated into the $(SO_3^-)C_5Ala2C_{16}$ vesicle in aqueous phosphate buffer (0.001 mol dm^{-3}; $\mu = 0.01$ with KCl) at pH 7.0 was irradiated with visible light in the presence of cyanide ions under anaerobic conditions, its spectrum

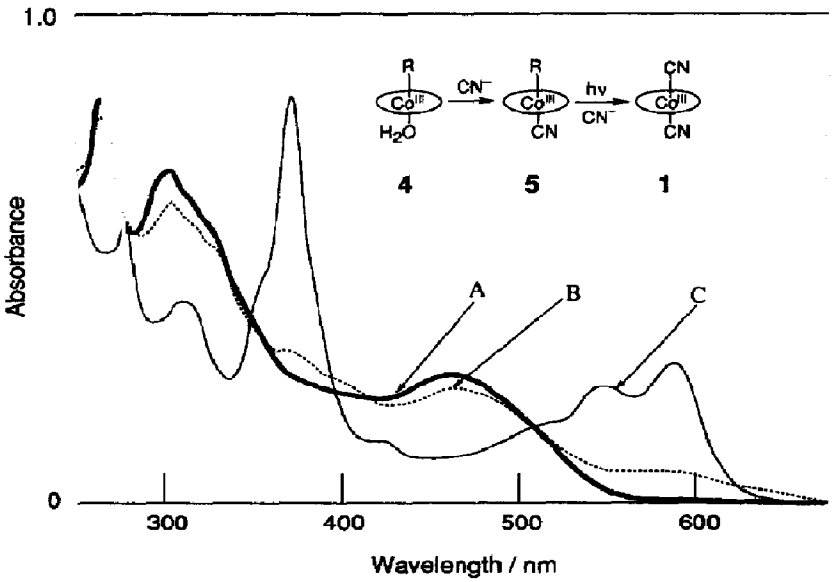


Fig. 1. Electronic spectra in the course of anaerobic photolysis of complex **4** incorporated into the single walled vesicle of $(SO_3^-)C_5Ala2C_{16}$ (1.5×10^{-3} mol dm^{-3}) in aqueous phosphate buffer (0.001 mol dm^{-3}; pH 7.0; $\mu = 0.01$ with KCl) at 20 °C: A, alkylated complex **4** (3.0×10^{-5} mol dm^{-3}) alone; B, after addition of TBACN (1.0×10^{-2} mol dm^{-3}) to **4** to afford **5**; C, **5** being irradiated with a 500-W tungsten lamp at a distance of 30 cm for 5 min under argon atmosphere to aford **1**.

underwent changes as shown in Fig. 1. Complex **4** was converted to complex **1** under anaerobic irradiation conditions in the presence of tetra-*n*-butylammonium cyanide (TBACN) (C in Fig. 1) *via* formation of complex **5** (B in Fig. 1). The reaction was also examined by the spin-trapping technique with α-phenyl-*N*-(*t*-butyl)nitrone (PBN). When **4** was irradiated with visible light, ESR signals attributable to the PBN spin adduct ($A_N = 15.1$ G, $A_H = 3.3$ G; G = 10^{-4} T) were clearly observed in methanol without cyanide ions (Fig. 2, a). The result apparently indicates that the alkyl radical is generated by the photolytic cobalt–carbon bond cleavage. On the other hand, ESR signals attributable to the PBN spin adduct were not observed when a mixture of **4** and PBN was irradiated in the presence of cyanide ions (Fig. 2, b). These ESR results clearly indicate

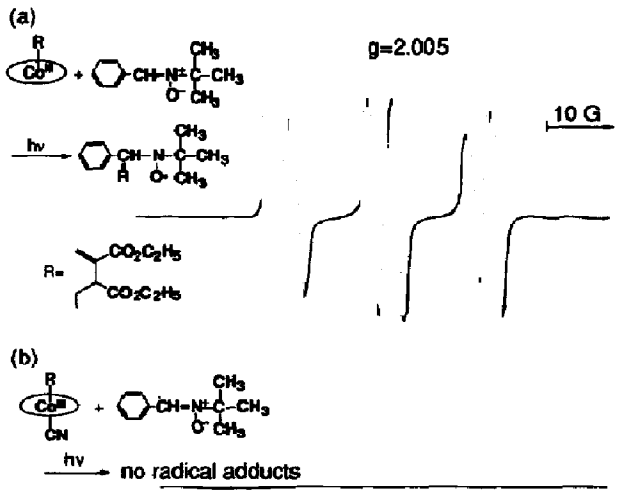
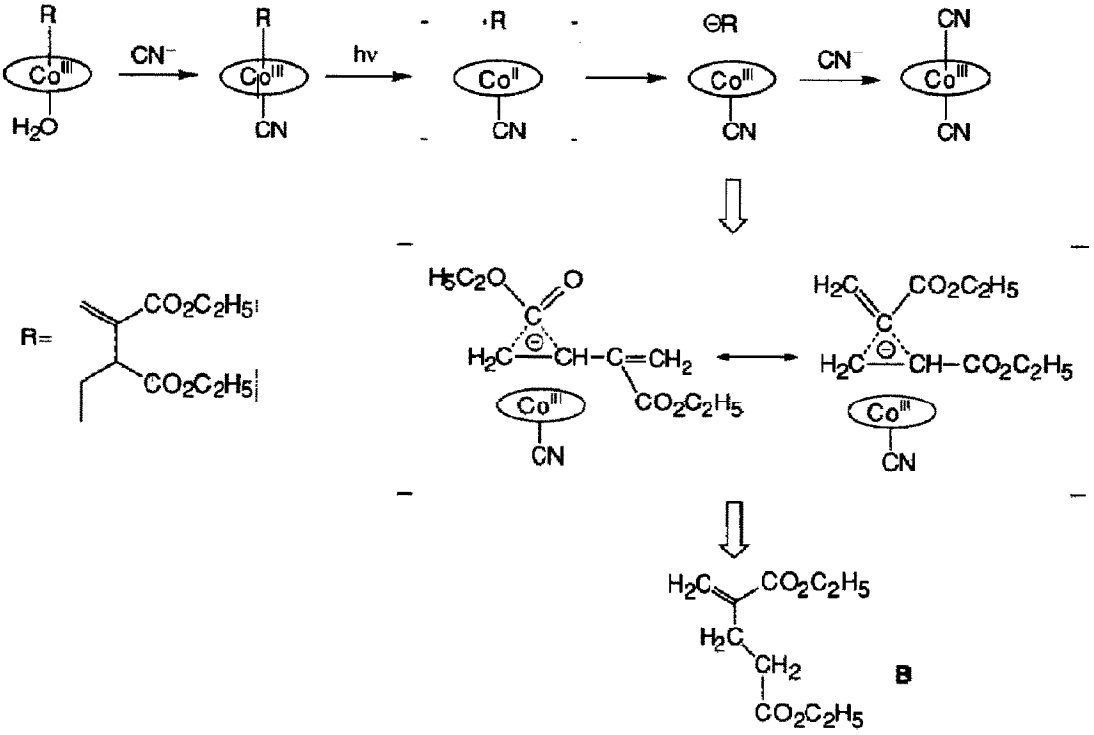


Fig. 2. ESR spectra for a system containing complex **4** (5.0×10^{-3} mol dm^{-3}) and PBN (5.0×10^{-1} mol dm^{-3}) in methanol under anaerobic irradiation with a 500-W tungsten lamp at a distance of 30 cm for 30 min: (a), without KCN; (b), in the presence of KCN (0.10 mol dm^{-3}).

that the photolysis of the substrate-bound complexes results in heterolytic cleavage of the cobalt–carbon bond to generate the Co^{III} species and the carbanion species under anaerobic conditions when the cyanide ion is coordinated to the nuclear cobalt atom of hydrophobic vitamin B_{12} derivatives (Scheme 1).



Scheme 1.

In conclusion, the cyanide ion induces the heterolytic cleavage of the cobalt–carbon bond involved in hydrophobic vitamin B_{12} derivatives to generate a carbanion intermediate under anaerobic irradiation conditions. This is apparently due to an electronic effect generated by the coordinated cyano moiety on an axial ligand *trans* to the cyano group through the coordinate bonds. The photochemical carbon-skeleton rearrangement of a substrate bound to the hydrophobic vitamin B_{12} proceeds much more readily as a consequence, and a microenvironmental effect provided by bilayer vesicles is in favor of the isomerization.

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