CHEMISTRY LETTERS, pp. 877-880, 1989.

Carbon-Skeleton Rearrangement of an Alkyl Ligand Coordinated to Simple Vitamin B_{12} Model Complexes in Synthetic Bilayer Membrane†

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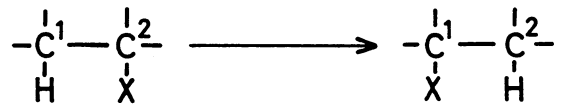
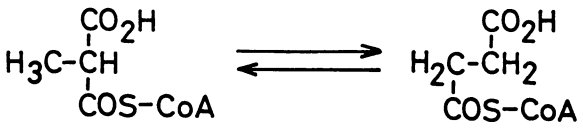
The carbon-skeleton rearrangement of an alkyl ligand coordinated to the nuclear cobalt of simple vitamin B_{12} model complexes formed with diimine-dioxime-type ligands took place efficiently in a synthetic bilayer membrane under irradiation with visible light.

Vitamin B_{12}-dependent enzymes catalyze various molecular rearrangements, which can be formulated generally as the exchange of a hydrogen atom for substituent X placed on the adjacent carbon, as shown by Eq. 1. These reactions include specific carbon-skeleton rearrangements; for example, methylmalonyl-CoA $\rightleftharpoons$ succinyl-CoA as shown by Eq. 2. Clarification of the reaction mechanisms by utilizing relevant model reaction systems is a current research target in bioinorganic chemistry. The naturally occurring apoproteins, which provide relevant reaction sites for vitamin B_{12}, are considered to play crucial roles in the molecular rearrangements.[1] However, studies of non-enzymatic reactions have been exclusively related to clarification of the catalytic functions of the coenzyme, vitamin B_{12}, and relevant apoprotein models have received little treatment. We have been interested in the catalytic activity of vitamin B_{12} in hydrophobic microenvironments and succeeded in constructing holoenzyme models, as composed of a synthetic bilayer membrane and a hydrophobic vitamin B_{12}.[2] This finding prompted us to develop simple model complexes, which catalyze the carbon-skeleton rearrangements in a similar membrane system. We report here on the carbon-skeleton rearrangement of an alkyl ligand coordinated to simple vitamin B_{12} model complexes which are structurally related to the Costa's complex.[3]



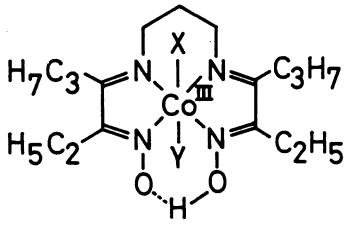
(1)



(2)

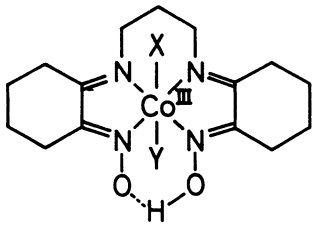
Two ligand species of the diimine-dioxime type, 3,11-bis(hydroxyimino)-4,10-dipropyl-5,9-diazatrideca-4,9-diene, $(C_2C_3)(DOH)_2pn$, and N,N'-bis(2-hydroxyiminocyclohexylidene)propane-1,3-diamine, $(ch)(DOH)_2pn$, and their cobalt complexes were prepared by referring to the reported procedures along with some modifications.[4]

† Contribution No. 903 from this Department.



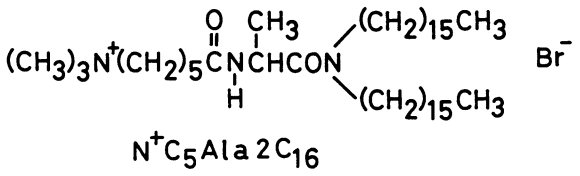
[Co^{III}\{(C_2C_3)(DO)(DOH)pn\}I_2] (**1**): X=Y=I

[Co^{III}\{(C_2C_3)(DO)(DOH)pn\}\{$CH_2C(CO_2C_2H_5)_2CH_3$\}Br] (**2**): $X=CH_2C(CO_2C_2H_5)_2CH_3$, Y=Br



[Co^{III}\{(ch)(DO)(DOH)pn\}I_2] (**3**): X=Y=I

[Co^{III}\{(ch)(DO)(DOH)pn\}\{$CH_2C(CO_2C_2H_5)_2CH_3$\}Br] (**4**): $X=CH_2C(CO_2C_2H_5)_2CH_3$, Y=Br



$N^+C_5Ala2C_{16}$

Amounts of the cobalt complexes incorporated into single-compartment vesicles were determined by the following procedure. A dichloromethane solution (1 mL) containing N,N-didodecyl-N^{α}-[6-(trimethylammonio)hexanoyl]-L-alaninamide bromide, $N^+C_5Ala2C_{16}$, (1.0×10^{-5} mol) and complex **1** or **3** (2.0×10^{-7} mol) was evaporated in vacuo to remove the solvent completely, and an aqueous potassium iodide solution (1 mL, 5.0×10^{-4} mol dm^{-3}) was added to the residue. The resulting mixture was sonicated for 30 s with a probe-type sonicator at 30 W to give a clear solution. An extent of incorporation of the cobalt complex into the single-compartment vesicle was examined by gel-filtration chromatography at an appropriate temperature on a column of Sephadex G-50 with an aqueous potassium iodide solution (5.0×10^{-4} mol dm^{-3}) as an eluant. The bound complex was eluted first in the void volume of column, and an amount of the incorporated complex was determined by electronic spectroscopy. As for complexes **2** and **4**, a methanol solution (10 μL) of each complex was injected into the vesicular solution which was prepared in a manner as stated above so that the possible cleavage of the cobalt-carbon bond by sonication may be avoided. Complexes **1**, **2**, **3**, and **4** were incorporated into the $N^+C_5Ala2C_{16}$ vesicle at 82—90, 55—60, 16—20, and 54—56% of their total amounts (2.0×10^{-7} mol) in molar ratio, respectively. The amounts of the complexes incorporated into the vesicle were little affected by temperature change for the range of 5—50 °C. The extents of solubility of these complexes in water were found as follows: **1**, 1.1×10^{-4} mol dm^{-3}; **2**, 2.0×10^{-4} mol dm^{-3}; **3**, 3.1×10^{-4} mol dm^{-3}; **4**, 8.1×10^{-4} mol dm^{-3}. We have already found that the incorporation of hydrophobic vitamin B_{12} derivatives into the $N^+C_5Ala2C_{16}$ vesicle becomes increasingly favored as the solubility of those complexes decreases in an aqueous bulk phase.[5] However, the solubility parameter alone can not provide a reasonable explanation for the incorporation behavior of the present complexes.

The cobalt-carbon bond involved in alkylated complexes **2** and **4** was cleaved in the vesicular solution upon irradiation with visible light as shown in Fig. 1. The reaction was carried out as follows. $N^+C_5Ala2C_{16}$ (5.0×10^{-5} mol) was dispersed in aqueous potassium bromide (10 mL, 5.0×10^{-4} mol dm^{-3}), and the dispersion sample was then sonicated for 2 min with a probe-type sonicator at 30 W to give a clear solution of single-compartment vesicles. A methanol solution (10 μL) of the alkylated complex (**2** or **4**, 5.0×10^{-7} mol) was added to the vesicular solution. Then, the resulting solution was irradiated with a 500-W tungsten lamp at a distance of 30 cm and at an appropriate temperature. After the alkylated complex was completely decomposed as confirmed by electronic spectroscopy, the products were extracted with dichloromethane (10 mL x 3) and analyzed by GLC.

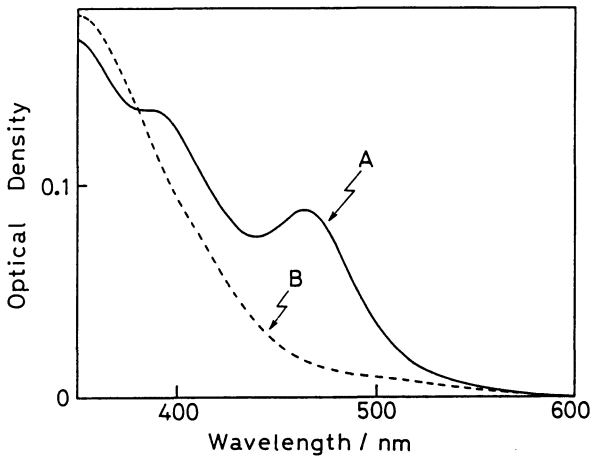
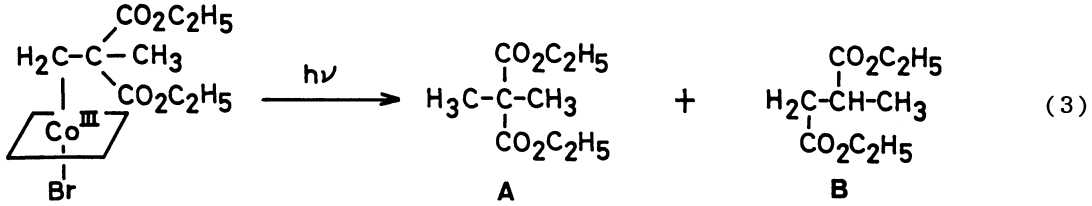


Fig. 1. Photolysis of **2** in $N^+C_5Ala2C_{16}$ (5.0×10^{-3} mol dm^{-3}) vesicular solution: A, **2** (5.0×10^{-5} mol dm^{-3}); B, A being irradiated with visible light.

We identified 2,2-bis(ethoxycarbonyl)propane (**A**), the simple hydrogenated product without rearrangement, and 1,2-bis(ethoxycarbonyl)propane (**B**), the rearranged one, which were obtained by the photolysis reactions of complexes **2** and **4** (refer to Eq. 3). The product analyses for the reactions carried out in various media are summarized in Table 1. The major product was the unrearranged one in benzene and methanol, but the rearranged product was largely obtained in the vesicular solution. These analytical results indicate that the carbon-skeleton rearrangement takes place more favorably in the vesicle relative to the reaction in homogeneous solutions. This favorable rearrangement in the vesicular solution must come from the microenvironmental effect provided by the $N^+C_5Ala2C_{16}$ vesicle in water, as verified for hydrophobic vitamin B_{12} derivatives placed in a similar vesicular phase.[5] In order to clarify the temperature effect, the photolysis reaction was examined at 5.0, 20.0, and 50.0 °C (Table 1). Since the single-compartment $N^+C_5Ala2C_{16}$ vesicle was found to show a broad phase transition at 20 ± 5 °C by differential scanning calorimetry, the synthetic bilayer membrane favors formation of the rearrangement product in the gel state.

The present study demonstrates that a vitamin B_{12}-dependent holoenzyme model can be made up by utilizing a synthetic bilayer membrane and a simple vitamin B_{12} model complex. It is clear that the carbon-skeleton rearrangement of an alkyl



(3)

Table 1. Product analyses for the photolysis of **2** and **4** in various media[a)]

Complex[b)]	Medium[c)]	Temp/°C[d)]	Yield/%[e)] A	Yield/%[e)] B
2	CH_3OH	20.0	74—77	8—11
	C_6H_6	20.0	76—80	5—9
	$N^+C_5Ala2C_{16}$ vesicle	5.0	41—44	46—50
		20.0	48—51	39—42
		50.0	54—59	31—33
4	CH_3OH	20.0	75—79	7—9
	C_6H_6	20.0	81—87	0—3
	$N^+C_5Ala2C_{16}$ vesicle	5.0	49—54	31—35
		20.0	59—63	21—25
		50.0	76—80	5—9

a) A solution containing **2** or **4** was irradiated with a 500-W tungsten lamp at a distance of 30 cm for 4 h. b) 5.0×10^{-5} mol dm^{-3}. c) $N^+C_5Ala2C_{16}$ (5.0×10^{-3} mol dm^{-3}) in aqueous potassium bromide (5.0×10^{-4} mol dm^{-3}). d) Accuracy, ±0.1 °C. e) Products were analyzed by GLC.

ligand coordinated to the simple vitamin B_{12} model takes place much favorably in the vesicular phase. Our studies are in progress toward development of such simplified artificial enzymes.

References

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3) G. Costa, Coord. Chem. Rev., 8, 63 (1972).
4) $(C_2C_3)(DOH)_2pn$ was synthesized by the condensation of 3-hydroxyimino-4-heptanone and 1,3-propanediamine, and $(ch)(DOH)_2pn$ was derived from 1,2-cyclohexanedione monooxime and 1,3-propanediamine. All the new compounds were characterized fully by analytical and spectroscopic methods; elemental analyses for the complexes are as follows. Found (**1**): C, 32.12; H, 4.92; N, 8.78%. Calcd for $C_{17}H_{31}I_2CoN_4O_2$ (**1**): C, 32.09; H, 4.91; N, 8.81%. Found (**2**): C, 47.87; H, 7.00; N, 8.53%. Calcd for $C_{26}H_{46}BrCoN_4O_6$ (**2**): C, 48.08; H, 7.14; N, 8.63%. Found (**3**): C, 29.94; H, 3.93; N, 9.50%. Calcd for $C_{15}H_{23}I_2CoN_4O_2$ (**3**): C, 29.82; H, 3.84; N, 9.27%. Found (**4**): C, 46.03; H, 6.23; N, 8.91%. Calcd for $C_{24}H_{38}BrCoN_4O_6 \cdot 0.5H_2O$ (**4**): C, 46.02; H, 6.28; N, 8.94%.
5) Y. Murakami, Y. Hisaeda, and T. Ohno, Bull. Chem. Soc. Jpn., 57, 2091 (1984).
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(Received February 28, 1989)