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Ring-Expansion Reactions Catalyzed by Hydrophobic Vitamin B_{12} in Synthetic Bilayer Membrane

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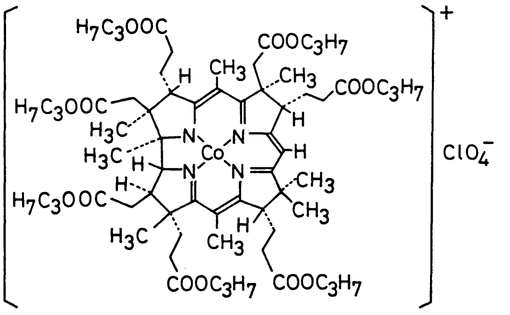
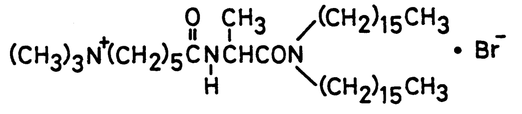
Heptapropyl cobyrinate perchlorate catalyzed the ring-expansion reactions, which convert 2-methyl-1,3-cyclopentanedione and 3-methyl-2-pyrrolidinone into 1,4-cyclohexanedione and 2-piperidinone, respectively, in single-compartment bilayer vesicles.

In order to simulate catalytic functions of vitamin B_{12} as exerted in the hydrophobic active sites of enzymes concerned, we have synthesized hydrophobic vitamin B_{12} derivatives by converting the amide groups of vitamin B_{12} into carboxylic esters.1) The naturally occurring apoproteins, which provide relevant reaction sites for vitamin B_{12}, are considered to play crucial roles in various isomerization reactions accompanied with carbon-skeleton rearrangements. We have been interested in the roles of such apoproteins and investigated various reactions of hydrophobic vitamin B_{12} derivatives in an octopus azaparacyclophane, having eight hydrocarbon chains, and single-compartment vesicles of peptide amphiphiles as apoprotein models.2,3) The effective 1,2-migration of functional groups, as model reactions for methylmalonyl-CoA mutase and glutamate mutase, was found to proceed in those apoprotein models. Our research interest is now focused on utilization of these artificial enzymes for novel organic syntheses. The ring expansion of α-(bromomethyl)-β-keto esters by one carbon unit and for syntheses of natural products has recently been examined rather extensively.4) In this connection, we investigated in this study the true catalytic conversion of five-membered ring ketons into the corresponding six-membered ones by adopting our artificial enzyme along with a novel substrate-activation process.

Hydrophobic vitamin B_{12} derivatives bearing various alkyl ligands at one of the axial sites of the nuclear cobalt can be prepared by various methods.3) Among them, a combination of molecular oxygen and vanadium(III) ions as oxidizing and reducing reagents, respectively, readily converts a methyl derivative into the corresponding radical species which then undergoes coupling with a Co^{II} species as reported by Schrauzer and his associates5)(Eq. 1). We adopted their method for preparation of hydrophobic vitamin B_{12}'s bearing alkyl ligands having five-membered ring moieties at one of the axial sites of the nuclear cobalt as follows. A methanol solution (100 mL) containing heptapropyl cobyrinate perchlorate, $[Cob(II)7C_3\text{-}ester]ClO_4$, (300 mg, 2.2×10^{-4} mol) and 2-methyl-1,3-cyclopentanedione (50 mg, 4.5×10^{-4} mol) was mixed with 60 mL of aqueous sodium carbonate buffer (0.02 mol dm^{-3},

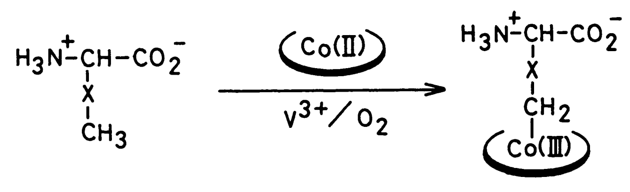


$[Cob(II)7C_3ester]ClO_4$



$$(CH_3)_3\overset{+}{N}(CH_2)_5\overset{O}{\overset{\|}{C}}\underset{H}{N}\overset{CH_3}{C}HCON\begin{matrix}(CH_2)_{15}CH_3\\(CH_2)_{15}CH_3\end{matrix}\cdot Br^-$$

$N^+C_5Ala2C_{16}$



(1)

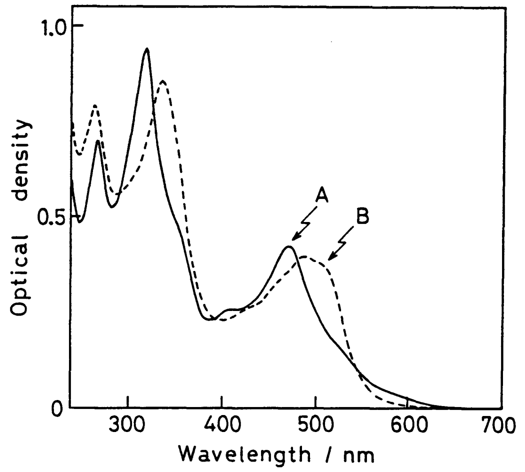


Fig. 1. Electronic spectral change caused by aerobic photolysis of **1** (3.9×10^{-5} mol dm^{-3}) in dichloromethane at 20.0 °C: A, before photolysis; B, after irradiation with a 500-W tungsten lamp for 1 min from a distance of 10 cm.

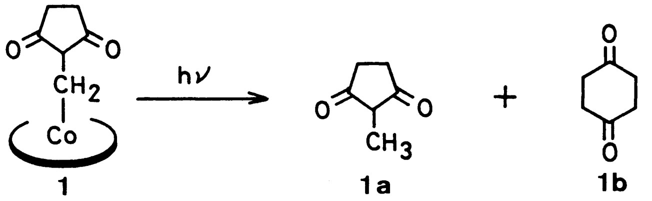
pH 11.2), and 25 mL of 15%(w/w) aqueous perchloric acid containing vanadium trichloride (50 mg, 3.2×10^{-4} mol) was added to the solution. The mixture was stirred vigorously for 5 min at room temperature, air was introduced into it for 2 min, and stirring was continued further for 1 h at the same temperature. The reaction product was extracted with dichloromethane and purified by gel-filtration chromatography on a column of Sephadex LH-20 with methanol as an eluant to give brownish powder; yield 101 mg (31%). This alkylated complex, $\overline{COCH_2CH_2COCH}CH_2$-Cob(III)7$C_3$-ester (**1**), showed an electronic spectrum characteristic of a complex with the cobalt-carbon bond and was converted into the corresponding tervalent cobalt complex upon cleavage of the cobalt-carbon bond by aerobic photolysis (Fig. 1). Product **2**, $\overline{CH_2CH_2NHCOCH}CH_2$-Cob(III)7$C_3$ester, was also prepared from $[Cob(II)7C_3ester]ClO_4$ and 3-methyl-2-pyrrolidinone by the same procedure; yield 28%.

The reactions shown by Eqs. 2 and 3 were carried out in the single-compartment vesicle of N,N-dihexadecyl-N^{α}-[6-(trimethylammonio)hexanoyl]-L-alaninamide bromide, $N^+C_5Ala2C_{16}$, at 20.0 °C under anaerobic irradiation with the visible light in a manner identical with that described previously,[3] and the products, 2-methyl-1,3-cyclopentanedione (**1a**), 1,4-cyclohexanedione (**1b**), 3-methyl-2-pyrrolidinone (**2a**), and 2-piperidinone (**2b**), were analyzed by GLC. The product analyses for the reactions in various media are summarized in Table 1. These analytical results indicate that the conversions of the five-membered ring compounds into the corresponding six-membered ones take place much more favorably in the $N^+C_5Ala2C_{16}$ vesicle, relative to those in methanol and benzene. Tada et al. reported that photolysis reactions of 1-substituted 2-oxocyclopentylmethylcobaloximes gave six-membered cyclic olefins (Eq. 4). However, the corresponding olefins were not detected under the present experimental conditions.

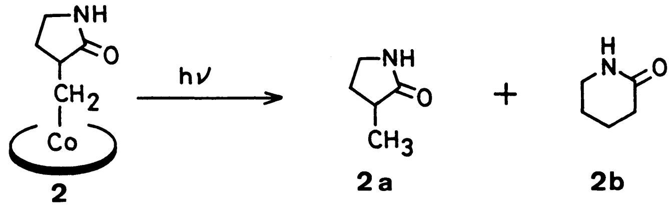
Table 1. Product analyses for photolysis of **1** and **2** in various media at 20.0 ± 0.1 °C[a)]

Medium	Yield/%[b)]		Yield/%[c)]	
	1a	**1b**	**2a**	**2b**
Methanol	69	19	83	3.0
Benzene	57	28	76	9.0
$N^+C_5Ala2C_{16}$ vesicle[d)]	19	67	63	24

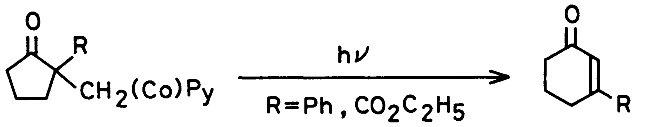
a) A solution containing **1** or **2** (5.0×10^{-5} mol dm^{-3}) was irradiated with a 500-W tungsten lamp for 1 h from a distance of 30 cm. b) Reactant, **1**. c) Reactant, **2**. d) $N^+C_5Ala2C_{16}$ (5.0×10^{-3} mol dm^{-3}) in aqueous phosphate-borate buffer (0.05 mol dm^{-3}, pH 9.2).



(2)



(3)



(4)

In order to set up the real catalytic cycle, a novel redox system, which is provided by vanadium trichloride in a large excess under aerobic irradiation conditions, was combined with the above stoichiometric reaction in the membrane system as illustrated in Fig. 2: **1a** is activated by vanadium trichloride and molecular oxygen, and the alkylated complex (**1**) thus formed as the intermediate undergoes photolysis to afford **1a** and **1b**; **1a** is re-cycled as the substrate. Vanadium trichloride acts not only as an activator for molecular oxygen but also as a reductant for the hydrophobic vitamin B_{12}, retaining the complex in the reactive Co^{II} state.[5)] The reaction was carried out as follows. Aqueous sodium carbonate buffer (0.02 mol dm^{-3}, pH 11.2; 20 mL) containing $N^+C_5Ala2C_{16}$ (3.0×10^{-3} mol dm^{-3}) was sonicated for 2 min with a probe-type sonicator at 30 W to give a clear solution of the single-compartment vesicle. Then, a methanol solution (0.2 mL) containing [Cob(II)-$7C_3$ester]ClO_4 (5.0×10^{-5} mol dm^{-3}) and **1a** (3.0×10^{-3} mol dm^{-3}) was added to the vesicle solution. Aqueous 10%(w/w) perchloric acid containing vanadium trichloride (0.10 mol dm^{-3}) was added to the resulting solution to an extent that pH of the solution was adjusted to 7.0. The reaction mixture was irradiated with the visible light along with air-bubbling at 20.0 °C, and samples were taken out at appropriate time intervals for product analysis by GLC. Substrate **1a** was converted efficiently into **1b** in the presence of [Cob(II)$7C_3$ester]ClO_4 as shown in Fig. 3 (refer to Eq. 5). The conversion of the heterocyclic **2a** into **2b** proceeded efficiently under the identical conditions (refer to Eq. 6). On the other hand, only a small amount of **1b** or **2b** was detected without the hydrophobic vitamin B_{12} under otherwise identical

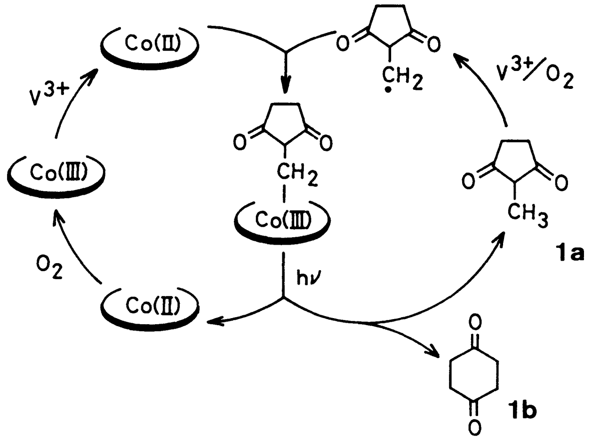


Fig. 2. Schematic representation of catalytic ring-expansion reaction.

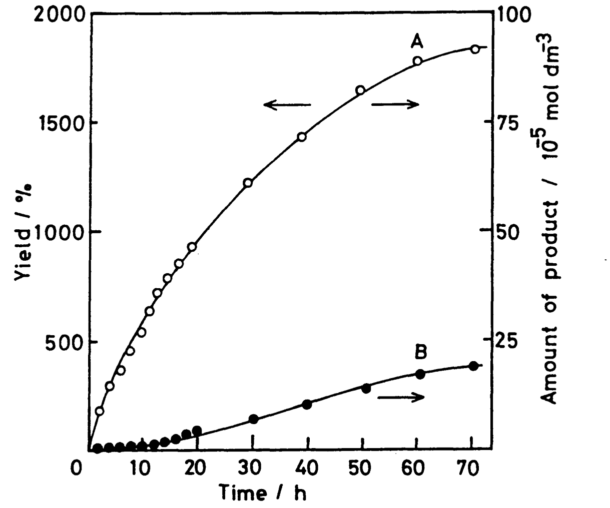
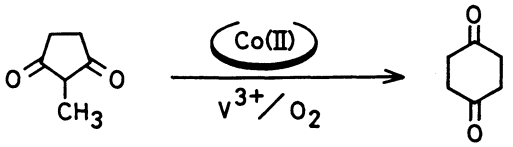
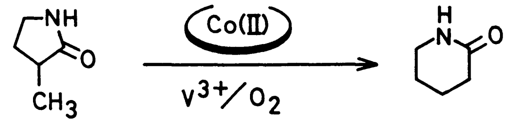


Fig. 3. Catalytic conversion of **1a** into **1b** in the $N^{+}C_5Ala2C_{16}$ vesicle under aerobic irradiation conditions, a 500-W tungsten lamp from a distance of 30 cm at 20.0 ± 0.1 °C: A, in the presence of [Cob(II)7C_3ester]ClO_4 (yield is based on the initial amount of the hydrophobic vitamin B_{12}; see the text for the conditions); B, without the hydrophobic vitamin B_{12}.



1a **1b** (5)



2a **2b** (6)

conditions.

In conclusion, the present catalytic system, composed of [Cob(II)7C_3ester]-ClO_4, $N^{+}C_5Ala2C_{16}$ vesicle, and vanadium trichloride, is expected to be applicable to other ring-expansion reactions without using activated substrates such as halogenated ones.

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