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CARBON-SKELETON REARRANGEMENT OF ALKYL LIGANDS COORDINATED TO HYDROPHOBIC VITAMIN B_{12} DERIVATIVES IN MOLECULAR AGGREGATES

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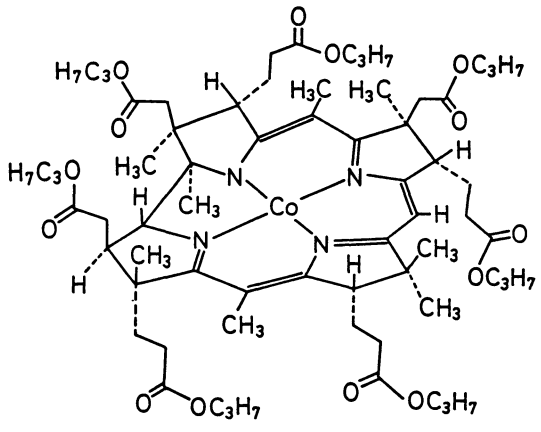
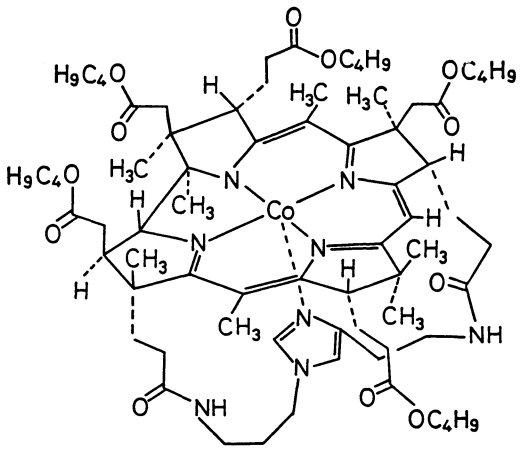
The carbon-skeleton rearrangement of alkyl ligands coordinated to hydrophobic vitamin B_{12} derivatives took place in molecular aggregates formed with CTAB, Triton X-100, or N,N-didodecyl-N^{α}-[6-(trimethylammonio)hexanoyl]-L-alaninamide bromide more favorably than the reaction in methanol or benzene under anaerobic conditions in the dark.

We have been interested in the catalytic activity of vitamin B_{12} placed in hydrophobic microenvironments so as to simulate catalytic functions of the holoenzymes concerned. Our previous findings are as follows:[1] (i) incorporation of a hydrophobic vitamin B_{12} derivative into single-compartment vesicles of N,N-didodecyl-N^{α}-[6-(trimethylammonio)hexanoyl]-L-alaninamide bromide ($N^{+}C_5Ala2C_{12}$) is progressively enhanced as the cobalt complex becomes less soluble in the aqueous bulk phase; (ii) the alkylation of a hydrophobic vitamin B_{12} with alkyl halides is much accelerated in molecular aggregates formed with hexadecyltrimethylammonium bromide (CTAB), α-[4-(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxypoly(oxyethylene) (Triton X-100), or $N^{+}C_5Ala2C_{12}$ relative to that in methanol. Consequently, it became necessary to examine the reactivity of alkylated hydrophobic vitamin B_{12}'s in various molecular aggregates which provide hydrophobic microenvironments in aqueous media. We report here on the carbon-skeleton rearrangement reaction of alkyl ligands coordinated to hydrophobic vitamin B_{12} derivatives in such reaction media.



[Cob(Ⅲ)7C$_3$ester]ClO$_4$



[Cob(Ⅲ)(Im:cap)5C$_4$ester]ClO$_4$

Heptapropyl cobyrinate perchlorate, [Cob(II)7C_3ester]ClO_4,[1] and a capped hydrophobic vitamin B_{12} with five butoxycarbonyl groups, [Cob(II)(Im:cap)5C_4ester]ClO_4,[2] were used as model complexes; these are insoluble in water but solubilized in aqueous buffers through incorporation into molecular aggregates formed with N^+C_5Ala2C_{12}, CTAB, and Triton X-100. Alkylated hydrophobic vitamin B_{12} derivatives were prepared by the reaction of the univalent cobalt complexes with alkyl halides in a manner as reported previously:[3] [{$(CH_3O_2C)_2CHCH_2$}(H_2O)Cob(III)7C_3ester]ClO_4 (**1**), [{$(CH_3O_2C)_2CHCH_2$}(H_2O)Cob(III)(Im:cap)5C_4ester]ClO_4 (**2**), [{$(C_2H_5O_2C)_2(CH_3)CCH_2$}$(H_2O)$Cob(III)7$C_3$ester]$ClO_4$ (**3**), and [{$(C_2H_5O_2C)_2(CH_3)CCH_2$}$(H_2O)$Cob(III)(Im:cap)5$C_4$ester]$ClO_4$ (**4**).[4] The cobalt—carbon bond involved in the alkylated complexes was gradually cleaved in solution by stirring under nitrogen atmosphere in the dark, and this thermal decomposition was completed in 48 h as shown in Fig. 1. The final spectra in all media were identical with those for the bivalent cobalt complexes.

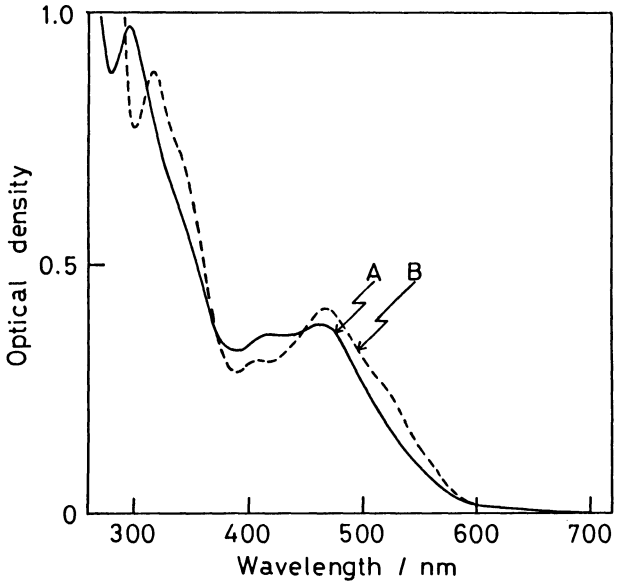
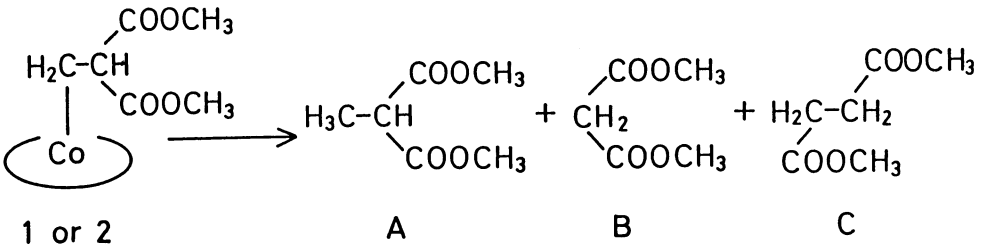


Fig. 1. Electronic spectra of hydrophobic vitamin B_{12} derivatives in benzene: A, alkylated complex **3** (3.8×10^{-5} mol dm^{-3}); B, **3** being allowed to stand in the dark for 48 h at 30 ± 2 °C to afford [Cob(II)-7C_3ester]ClO_4.

The reaction was carried out as follows: an aqueous buffer (20 mL; phosphate—borate, pH 9.18) containing N^+C_5Ala2C_{12} (or CTAB, Triton X-100) (1.0×10^{-3} mol) was sonicated for 2 min with a probe-type sonicator at 30-W to give a clear solution. After the solution was deoxygenated with nitrogen gas, ca. 0.2 mL of a methanol solution containing an alkylated complex (2.9×10^{-5} mol) was added to it. An alkylated complex incorporated into the single-compartment vesicle or the micelle in such a manner was allowed to undergo reaction in the dark under nitrogen atmosphere at 30 ± 2 °C. After the alkylated complex was completely decomposed as confirmed by electronic spectroscopy (in 24—48 h), the products were extracted with dichloromethane and analyzed by GLC. As for the reaction in organic solvents, a reaction mixture was evaporated to dryness in vacuo before the extraction treatment with hexane. We identified the following products: 1,1-bis(methoxycarbonyl)-ethane (A), bis(methoxycarbonyl)methane (B), and 1,2-bis(methoxycarbonyl)ethane (C) from complexes **1** and **2** (refer to Eq. 1); 2,2-bis(ethoxycarbonyl)propane (D) and 1,2-bis(ethoxycarbonyl)propane (E) from complexes **3** and **4** (refer to Eq. 2). The product analyses for the reactions in various media are summarized in Tables 1 and 2. These analytical results indicate that the carbon-skeleton rearrangement to afford C and E takes place more favorably in the molecular aggregates than in homogeneous solutions, and the axial base placed intramolecularly in a hydrophobic vitamin B_{12} did not affect the product composition. However, cleavage of the

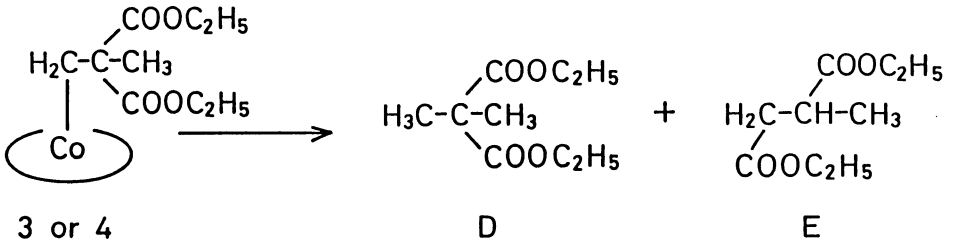


(1)

Table 1. Product analyses for the decomposition of complexes **1** and **2** in various media in the dark at 30 ± 2 °C[a)]

Complex[b)]	Medium[c)]	Yield/%		
		A	B	C
1	CH_3OH	81 - 91	1.3 - 2.1	0
	C_6H_6	82 - 90	1.0 - 2.0	0.8 - 1.3
	$N^+C_5Ala2C_{12}$ vesicle	56 - 66	11 - 15	4.2 - 6.2
2	CH_3OH	81 - 93	1.3 - 2.2	0
	C_6H_6	81 - 93	1.0 - 2.0	0.9 - 1.5
	$N^+C_5Ala2C_{12}$ vesicle	54 - 64	8 - 14	4.6 - 6.6

a) Reaction period, 48 h. b) 1.45 x 10^{-3} mol dm^{-3}. c) $N^+C_5Ala2C_{12}$ (5.0 x 10^{-2} mol dm^{-3}) in phosphate (5.0 x 10^{-3} mol dm^{-3})—borate (4.75 x 10^{-2} mol dm^{-3}) buffer; pH 9.18.



(2)

Table 2. Product analyses for the decomposition of complexes **3** and **4** in various media in the dark at 30 ± 2 °C[a)]

Complex[b)]	Medium[c)]	Yield/%	
		D	E
3	CH_3OH	82 - 94	0
	C_6H_6	81 - 91	0.9 - 1.5
	CTAB micelle	71 - 81	5 - 9
	Triton X-100 micelle	73 - 83	4 - 8
	$N^+C_5Ala2C_{12}$ vesicle	70 - 80	7 - 11
4	CH_3OH	79 - 93	0
	C_6H_6	81 - 93	1.3 - 1.9
	CTAB micelle	72 - 80	6 - 10
	Triton X-100 micelle	70 - 80	6 - 10
	$N^+C_5Ala2C_{12}$ vesicle	69 - 81	7 - 13

a) Reaction period, 48 h. b) 1.45 x 10^{-3} mol dm^{-3}. c) Amphiphiles (5.0 x 10^{-2} mol dm^{-3}) in phosphate (5.0 x 10^{-3} mol dm^{-3})—borate (4.75 x 10^{-2} mol dm^{-3}) buffer; pH 9.18.

cobalt—carbon bond in the dark was accelerated by intramolecular coordination of the axial base as reflected on the first-order rate constants in the $N^+C_5Ala2C_{12}$ vesicle:[5] **3**, 2.2×10^{-5} s^{-1}; **4**, 5.0×10^{-5} s^{-1}. The extent of such rate enhancement originated from the intramolecular coordination of the imidazolyl moiety is comparable to that observed for the aerobic photolysis.[6]

The thermal cleavage of the cobalt—carbon bond involved in the alkylated hydrophobic vitamin B_{12}'s was examined by the spin-trapping technique with α-phenyl-N-(t-butyl)nitrone (PBN). ESR signals attributable to the PBN spin adducts were clearly observed in benzene and methanol. This apparently indicates that the radical species are generated by the cobalt—carbon cleavage in the dark. Although such ESR signals were not detected at room temperature in the presence of single-compartment vesicles, typical signals attributable to the bivalent cobalt species were observed during the reaction by ESR measurements of sample solutions at 77 K. Since a limited amount of PBN can be incorporated into the vesicles in aqueous media, the spin-adduct formation seems to be hardly detected by ESR. In the light of the above results, the alkylated hydrophobic vitamin B_{12} must undergo homolytic cleavage of the cobalt—carbon bond in all the reaction media to afford the corresponding bivalent cobalt complex and alkyl radical species in the dark.

In conclusion, the carbon-skeleton rearrangement takes place in molecular aggregates much more readily than the reaction in homogeneous organic solutions. This effect must come from an extended lifetime of the alkyl radical species generated by the cobalt—carbon cleavage, since a radical pair formed by the homolytic cleavage is generally stabilized in molecular aggregates[7] due to its slow diffusion from such cages. Although the axial base placed intramolecularly in the hydrophobic vitamin B_{12} does not affect the product composition, such coordination results in rate enhancement of the cobalt—carbon cleavage.

References

1) Y. Murakami, Y. Hisaeda, and T. Ohno, Bull. Chem. Soc. Jpn., 57, 2091 (1984).

2) $(CN)_2$Cob(III)(Im:cap)5C_4ester was prepared from [$(CN)_2$Cob(III)(Im^+-H:cap)5C_1-ester]Cl by transesterification and purified by gel-filtration chromatography on a column of Sephadex LH-20 with methanol as an eluant. Found: C, 64.64; H, 7.94; N, 9.96%. Calcd for $C_{75}H_{111}CoN_{10}O_{12}$: C, 64.17; H, 7.97; N, 9.98%. [Cob(II)(Im:cap)5C_4ester]ClO_4 was obtained from $(CN)_2$Cob(III)(Im:cap)5C_4ester in a manner as reported previously: Y. Murakami, Y. Hisaeda, T. Ohno, and T. Ozaki, Chem. Lett., 1985, 477.

3) Y. Murakami and Y. Hisaeda, Bull. Chem. Soc. Jpn., 58, 2652 (1985).

4) UV_{max} (CH_2Cl_2): **1**, 298 and 459 nm; **2**, 303 and 464 nm; **3**, 295, 415, and 460 nm; **4**, 305, 418, and 465 nm. These spectral data are consistent with the formation of the cobalt—carbon bond.

5) First-order rate constants were evaluated from amounts of products (D + E) analyzed by GLC at appropriate time intervals: initial concentrations of **3** and **4**, 1.45×10^{-3} mol dm^{-3}.

6) Y. Murakami, Y. Hisaeda, T. Ozaki, and T. Ohno, Chem. Lett., 1985, 1711.

7) N. J. Turro, M. Grätzel, and A. M. Braun, Angew. Chem., Int. Ed. Engl., 19, 675 (1980); N. J. Turro, Proc. Natl. Acad. Sci. U. S. A., 80, 609 (1983).

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