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PREPARATION AND ALKYLATION OF CAPPED HYDROPHOBIC VITAMIN B_{12}

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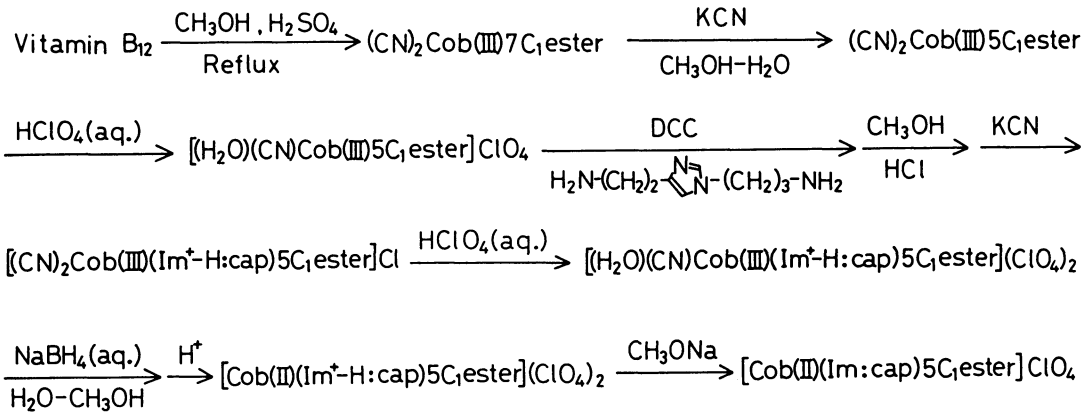
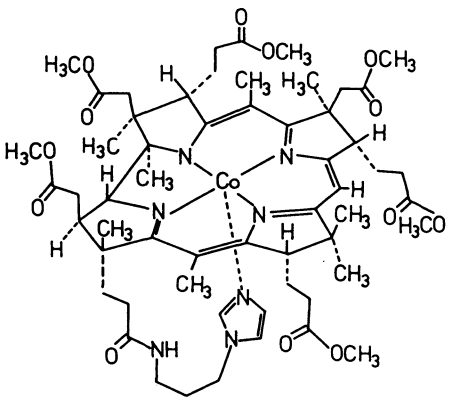
The pentamethyl cobyrinate complex capped with a fragment involving the imidazolyl moiety was prepared and characterized by spectroscopic means. Its alkylation reactions with alkyl bromides were carried out in organic solvents and compared with those of other hydrophobic vitamin B_{12}'s from the kinetic viewpoint.

In order to simulate the catalytic functions of vitamin B_{12} placed in the hydrophobic microenvironments of enzymes concerned, vitamin B_{12} needs to be modified so that the model studies can be carried out in ordinary organic solvents. Furthermore, such vitamin B_{12} derivatives are required to hold a proximal base for characterization of the coordination effect provided by the benzimidazolyl group of vitamin B_{12} on such catalytic activities. To meet the above requirements for designing model complexes, we have previously prepared a hydrophobic vitamin B_{12} bearing a proximal base capable of coordinating to its nuclear cobalt, [Cob(II)-(Im)6C_1ester]ClO_4, and characterized its properties by spectroscopic and electrochemical means.[1] In the present study, we prepared a hydrophobic vitamin B_{12} capped with a fragment involving the imidazolyl moiety, [Cob(II)(Im:cap)5C_1ester]ClO_4. The capping fragment in the present complex is linked to the equatorial skeleton at its both ends, and the imidazole-nitrogen undergoes coordination to the nuclear cobalt more favorably by an entropy effect than that of the previous complex in which only one end of the imidazolyl segment is bound to the corrinoid skeleton. The alkylation reactions of the capped hydrophobic vitamin B_{12} in the Co^I state, Cob(I)(Im:cap)5C_1ester, with alkyl bromides were investigated in comparison with those of another hydrophobic vitamin B_{12} having a proximal base, Cob(I)(Im)6C_1ester, and heptamethyl cobyrinate without any proximal base, Cob(I)7C_1ester, from the kinetic viewpoint.

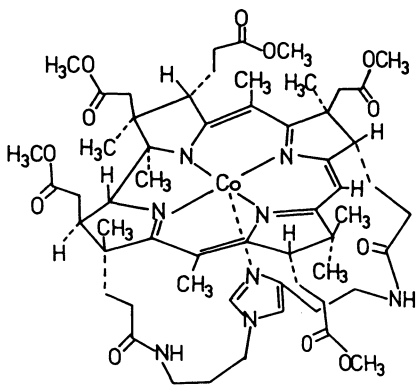
The capped hydrophobic vitamin B_{12}, [Cob(II)(Im:cap)5C_1ester]ClO_4, was prepared according to the procedure shown in Scheme 1 based on modification of cyanocobalamin (vitamin B_{12}). [$(CN)_2$Cob(III)(Im^+-H:cap)5C_1ester]Cl was prepared by (i) condensation of [(H_2O)(CN)Cob(III)5C_1ester]ClO_4 with 4-(2-aminoethyl)-1-(3-aminopropyl)imidazole[2] in the presence of N,N'-dicyclohexylcarbodiimide (DCC) after the method adopted for the preparation of $(CN)_2$Cob(III)(Im)6C_1ester[1] and (ii) the subsequent treatment with hydrogen chloride and potassium cyanide in methanol: yield 38%; UV_{max} (CH_3OH) 319 (ε 6.4 x 10^3), 369 (1.2 x 10^4), 502 (4.0 x 10^3), 545 (3.7 x 10^3), and 584 nm (3.8 x 10^3); CD (CH_3OH) 252 ($\Delta\varepsilon$ -4.11), 291 (-1.50), 323 (+2.00), 349 (-2.37), 396 (+5.05), 424 (+2.62), 466 (-1.81), and 583 nm (-1.62); IR (KBr)



Scheme 1.



[Cob(III)(Im)6C$_1$ester]ClO$_4$



[Cob(II)(Im:cap)5C$_1$ester]ClO$_4$

1730 (ester C=O) and 1630 cm^{-1} (amide C=O); ^{1}H-NMR (CD_3OD, TMS) δ=3.65 (15H, m, CO-OCH_3), 4.10 [2H, t, CH_2N(Im)], 5.70 (1H, s, H at C-10), 7.00 (1H, s, Im-5H), and 7.55 (1H, s, Im-2H). Found: C, 58.40; H, 7.05; N, 11.21; Cl, 2.9; Co, 4.60%. Calcd for $C_{60}H_{82}ClCoN_{10}O_{12}$: C, 58.60; H, 6.72; N, 11.39; Cl, 3.1; Co, 4.80%.

[Cob(II)(Im$^+$-H:cap)5C$_1$ester](ClO$_4$)$_2$ was prepared from [(CN)$_2$Cob(III)(Im$^+$-H:-cap)5C$_1$ester]Cl after the method adopted for the preparation of heptamethyl cobyrinate perchlorate:[3] yield 29%; UV_{max} (CH_3OH) 261, 313, 402, and 467 nm; IR (KBr) 1730 (ester C=O), 1630 (amide C=O), and 1120 and 625 cm^{-1} (ClO_4^-). [Cob(II)(Im:-cap)5C$_1$ester]ClO$_4$ was obtained by adding an equimolar amount of sodium methoxide to the above bivalent cobalt complex in methanol and isolated after the method described previously:[1] UV_{max} (CH_3OH) 261, 316, 356sh, 474, and 540sh nm. The final complex without the axial cyano ligands is readily oxidized to the Co^{III} species under aerobic conditions.

ESR spectra of [Cob(II)(Im$^+$-H:cap)5C$_1$ester](ClO$_4$)$_2$ and [Cob(II)(Im:cap)5C$_1$-ester]ClO$_4$ are shown in Fig. 1. The spectrum for the former complex is comparable to that for the base-off form of vitamin B_{12r}, while the spectrum for the latter is comparable to that for the base-on form of vitamin B_{12r} and indicates that the imidazolyl moiety is completely coordinated to the nuclear cobalt.

The Co(II)/Co(I) redox couple for [Cob(II)(Im:cap)5C$_1$ester]ClO$_4$ was observed

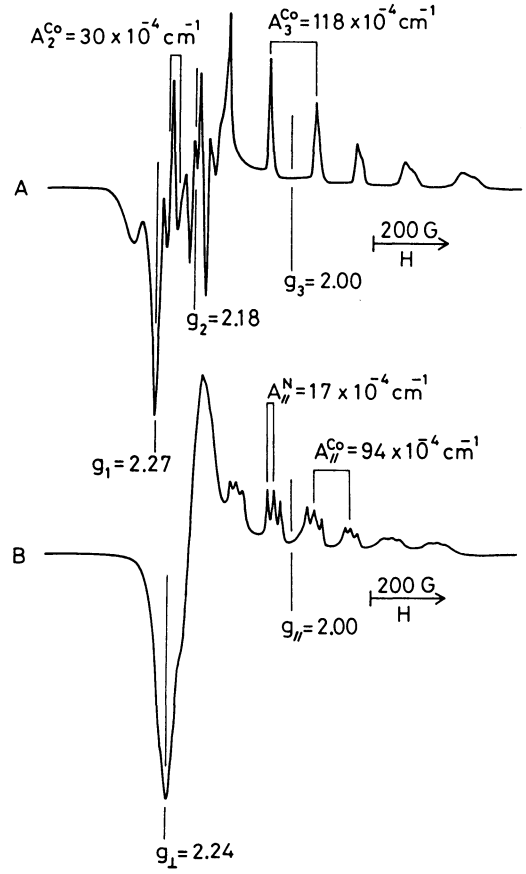


Fig. 1. ESR spectra of hydrophobic vitamin B_{12}'s in ether–methanol (1:1 v/v) at 77 K: A, [Cob(II)(Im^+-H:-cap)$5C_1$ester]$(ClO_4)_2$ (9.0×10^{-3} mol dm^{-3}); B, [Cob(II)(Im:cap)$5C_1$ester]-ClO_4 (9.0×10^{-3} mol dm^{-3}).

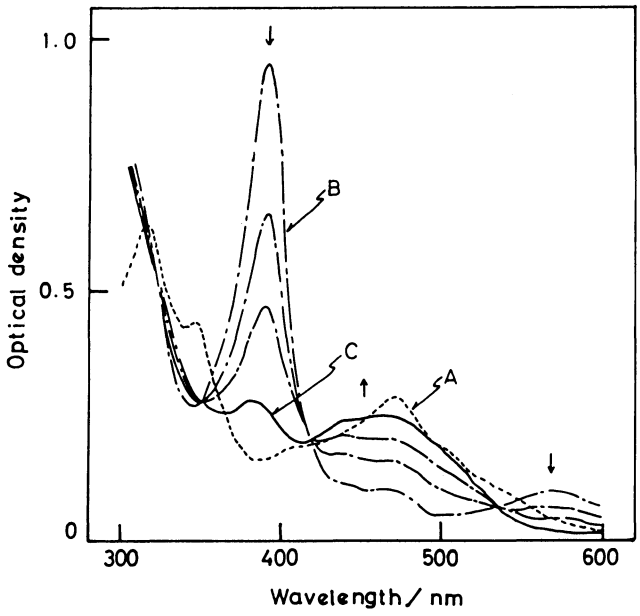


Fig. 2. Electronic spectral change for the reaction of Cob(I)(Im:cap)$5C_1$-ester with ethyl bromide at 20.5 ± 0.1 °C: A, Cob(II)(Im:cap)$5C_1$ester (2.1×10^{-5} mol dm^{-3}) in methanol (3 mL) containing 150 μL of a methanol solution of NaOH (0.1 mol dm^{-3}); B, Cob(I)(Im:-cap)$5C_1$ester formed upon addition of $NaBH_4$ to A; C, C_2H_5-Cob(III)(Im:cap)-$5C_1$ester formed upon addition of C_2H_5Br (2.1×10^{-4} mol dm^{-3}) to B. Trends of spectral change with time after addition of C_2H_5Br to B are shown by arrows.

at -0.69 V vs. SCE in dimethyl sulfoxide (DMSO) by means of cyclic voltammetry, while that for heptamethyl cobyrinate perchlorate having no axial base has been observed at -0.64 V vs. SCE.[4] Therefore, the intramolecular coordination of the imidazolyl group to the nuclear cobalt shifts the redox potential to the cathodic side by 50 mV; the same magnitude as observed for [Cob(II)(Im)$6C_1$ester]ClO_4.[1]

After reduction of [Cob(II)(Im:cap)$5C_1$ester]ClO_4 with sodium tetrahydroborate to Cob(I)(Im:cap)$5C_1$ester, the second-order rate constants (k_2) for the reactions with alkyl bromides were determined according to the method described previously.[5] The spectral change for the alkylation in methanol is shown in Fig. 2 for a selected run. The second-order rate constants in methanol, DMSO, and methyl acetate are listed in Table 1 along with those for Cob(I)(Im)$6C_1$ester and Cob(I)$7C_1$ester. The rate constant for each complex species undergoes variation by the nature of solvents employed. The observed solvent effect cannot be explained by the solvent polarity alone: $E_T(30)$ values are 40.0, 45.0, and 55.5 for methyl acetate, DMSO, and methanol, respectively. A specific cage effect provided by each of the present

Table 1. Second-order rate constants for the reactions of Co^{I} complexes with alkyl bromides at 20.5 ± 0.1 °C

Alkyl bromide	Solvent[a)]	k_2/mol^{-1} dm^3 s^{-1}		
		Complex 1[b)]	Complex 2[c)]	Complex 3[d)]
C_2H_5Br	CH_3OH	9.6	7.7	12.0
C_3H_7Br	CH_3OH	2.6	2.7	3.7
C_2H_5Br	DMSO	77	72	127
C_3H_7Br	DMSO	26	40	61
C_2H_5Br	CH_3COOCH_3	13	13	25
C_3H_7Br	CH_3COOCH_3	6.0	6.5	11

a) Each solvent (3 mL) contains 150 μL of a methanol solution of NaOH (0.1 mol dm^{-3}). b) Cob(I)7C_1ester. c) Cob(I)(Im)6C_1ester. d) Cob(I)(Im:cap)5C_1ester.

solvents seems to be responsible for the reactivity control, even though the intrinsic nature of such solvent cages is not clear at present. Since the univalent cobalt assumes the square-planar coordination geometry with coordination number of 4, the proximal base in both Cob(I)(Im)6C_1ester and Cob(I)(Im:cap)5C_1ester is free from metal-coordination. This is in fact reflected on the reactivity. A significant difference in reaction rate between Cob(I)7C_1ester and Cob(I)(Im)6C_1ester was not observed when both reaction medium and alkyl bromide are identical (Table 1). The reactivity of Cob(I)(Im:cap)5C_1ester is somewhat larger than those of the other two complexes as shown in Table 1. In view of the fact that the imidazolyl group in the former complex is fixed in a close vicinity of the nuclear cobalt, a polar effect by the group seems to be transmitted to the reaction site.

When the hydrophobic vitamin B_{12}'s are alkylated, the nuclear cobalt becomes tervalent and inevitably assumes the hexacoordination geometry, which allows the coordination of the proximal base at the axial site trans to the alkyl ligand. Thus, various reactions of the alkylated hydrophobic vitamin B_{12}'s must be subjected to the coordination effect provided by the proximal base. Our studies are in progress along this line.

References

1) Y. Murakami, Y. Hisaeda, and T. Ozaki, Chem. Lett., submitted for publication.
2) 4-(2-Aminoethyl)-1-(3-aminopropyl)imidazole was prepared as follows: 4-[N-(t-butoxycarbonyl)aminoethyl]-1-(2-cyanoethyl)imidazole, which was obtained by the reaction of acrylonitrile with histamine having the amino group protected with t-butoxycarbonyl, was reduced with hydrogen gas in the presence of Raney nickel. The product was isolated as the trihydrochloride salt by the treatment with methanolic hydrogen chloride and identified by IR, ^{1}H-NMR, and elemental analysis.
3) Y. Murakami, Y. Hisaeda, and A. Kajihara, Bull. Chem. Soc. Jpn., 56, 3642 (1983).
4) Y. Murakami, Y. Hisaeda, A. Kajihara, and T. Ohno, Bull. Chem. Soc. Jpn., 57, 405 (1984).
5) Y. Murakami, Y. Hisaeda, and T. Ohno, Bull. Chem. Soc. Jpn., 57, 2091 (1984).

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