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Hydrophobic Vitamin B_{12}. XI. Preparation, Characterization, and Enantioselective Alkylation of Hydrophobic Vitamin B_{12} Bearing a Binaphthyl Moiety†

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Hydrophobic vitamin B_{12} derivatives bearing a chiral binaphthyl moiety, hexamethyl 7[1]-decarboxy-7[1]-[(*R*)-2′-methoxy-1,1′-binaphthyl-2-carboxymethyl]cobyrinate perchlorate [B_{12}–BINAP(*R*)] and hexamethyl 7[1]-decarboxy-7[1]-[(*S*)-2′-methoxy-1,1′-binaphtyl-2-carboxymethyl]cobyrinate perchlorate [B_{12}–BINAP(*S*)], were prepared from cyanocobalamin. These complexes were characterized by means of electronic and circular dichroism spectroscopy as well as by cyclic voltammetry in comparison with those data for a hydrophobic vitamin B_{12} without a binaphthyl moiety. The enantioselective alkylation of hydrophobic vitamin B_{12} derivatives at the β-axial site was examined in methanol with various 3-bromo-2-methylpropionic esters by means of ^{1}H NMR spectroscopy. All the hydrophobic vitamin B_{12} derivatives used here, the one bearing methoxycarbonyl groups as peripheral substituents without a binaphthyl moiety, B_{12}–BINAP(*R*), and B_{12}–BINAP(*S*), were found to bind (*S*)-2-methylpropionates more favorably than the corresponding *R*-enantiomers; the highest *S*-selectivity was observed with the latter two derivatives, 65% e.e. The cause of such *S*-enantioselectivity was discussed with attention to stereochemical configurations of the peripheral substituents placed in the corrin ring.

Naturally occurring apoproteins are considered to provide water-lacking and hydrophobic microenvironments for vitamin B_{12}[1,2] to enhance the coenzyme activity in various isomerization reactions,[3,4] in addition to their stereochemical functions to mediate the reactions. One of the efficient approaches to mimicking the catalytic functions of vitamin B_{12}-dependent holoenzymes is to develop vitamin B_{12} derivatives which can be utilized under dehydrated and/or hydrophobic conditions. In this regard, we have been dealing with hydrophobic vitamin B_{12} derivatives which have ester groups in place of the peripheral amide moieties of the naturally occurring vitamin B_{12}.[5-13]

Vitamin B_{12} derivatives and model compounds have been found to catalyze the reduction of alkyl halides,[14] nitriles,[15] α,β-unsaturated carbonyl derivatives,[16] and olefins.[17] These reactions proceed via formation of intermediates involving a Co–C bond that is subsequently cleaved and transformed into a C–H bond. On the other hand, one of the fascinating functions of naturally occurring vitamin B_{12} is referred to its potentiality as a chiral catalyst in asymmetric synthesis, since vitamin B_{12} creates a chiral reaction site provided by a corrin ring and peripheral substituents. In this regard, we became interested in the enantioselective alkylation of vitamin B_{12} derivatives. Meanwhile, Schrauzer et al. examined the asymmetric alkylation of cobalamin with DL-alanine in the presence of V^{3+} and oxygen radicals,[18] and obtained the alanine-bound cobalamin in a D/L alanine ratio of 56 to 44 mol% (refer to Eq. 1). They attributed such enantioselectivity to a specific stereochemical microenvironment provided on the β-axial site of the corrin ring, even though the effect is very small. Ogoshi et al. investigated the alkylation of cobalamin with the prochiral 1-acetyl-1-alkylcyclopropanes that induces an asymmetric center in the resulting alkyl ligands (refer to Eq. 2). However, such a structural framework of the corrin moiety does not achieve high enantioselectivity in nonenzymatic reactions. In this paper, we report on preparation and enantioselective alkylation of novel vitamin B_{12} derivatives.

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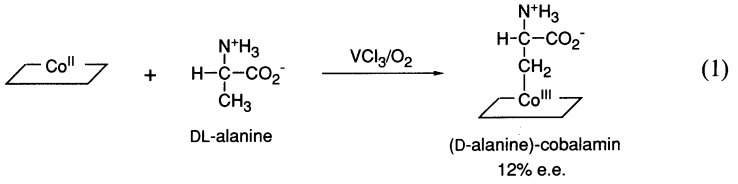
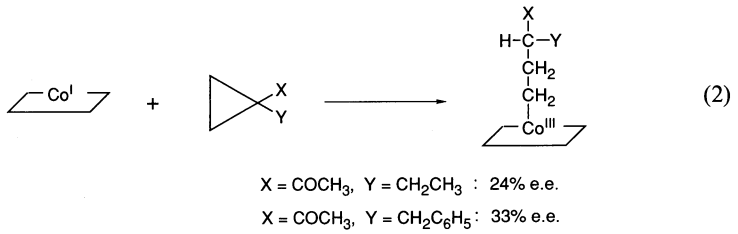
Experimental

General Analyses and Measurements. Elemental analyses were preformed at the Microanalysis Center of Kyushu University. IR spectra were taken on a JASCO IR-810 infrared spectrophotometer, while electronic absorption spectra were recorded on a Hitachi 220A or a Hitachi 340 spectrophotometer. Circular dichroism (CD) spectra were recorded on a JASCO J-500C spectropolarimeter. ^{1}H NMR spectra were taken on a Hitachi R-1500, a Bruker AC-250P, and a Bruker AMX-500 spectrometer installed at the Center of Advanced Instrumental Analysis of Kyushu University. Assignments of NMR signals for the cobalt complexes were performed by means of the 2D NMR technique (H–H COSY). Cyclic voltammograms were obtained on an apparatus composed of a Hokuto Denko HA-501 potentiostat/galvanostat and a Hokuto Denko HB-104 function generator.

Materials. 3-Bromo-2-methylpropionic acid was obtained by reaction of methacrylic acid with hydrogen bromide in acetic acid: Yield 91%; bp 110—111 °C/1000 Pa; IR (neat) 3000 (carboxylic OH) and 1710 cm^{-1} (carboxylic C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ=1.33 (3H, d, CH_3), 2.90 (1H, m, CH), 3.50 (2H, m, CH_2Br), and 10.97 (1H, s, CO_2H). Various 3-bromo-2-methylpropionic esters were prepared by esterification of 3-bromo-2-methylpropionic acid.

Methyl 3-Bromo-2-methylpropionate: Yield 90%; bp 72—73 °C/2500 Pa; IR (neat) 1740 cm^{-1} (ester C=O); 60 MHz





^{1}H NMR ($CDCl_3$, TMS) δ=1.28 (3H, d, CH_3), 2.84 (1H, m, CH), 3.47 (2H, m, CH_2Br), and 3.66 (3H, s, CO_2CH_3).

Ethyl 3-Bromo-2-methylpropionate: Yield 80%; bp 82—85°C/2500—2700 Pa; IR (neat) 1740 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ=1.28 (3H, t, $CH_2C\underline{H}_3$), 1.30 (3H, d, CH_3), 2.85 (1H, m, CH), 3.48 (2H, m, CH_2Br), and 4.15 (2H, q, $C\underline{H}_2CH_3$).

Butyl 3-Bromo-2-methylpropionate: Yield 77%; bp 88—90°C/1300 Pa; IR (neat) 1740 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ=0.50—1.90 (7H, m, $CH_2CH_2CH_3$), 1.29 (3H, d, CH_3), 2.87 (1H, m, CH), 3.51 (2H, m, CH_2Br), and 4.15 (2H, t, $C\underline{H}_2CH_2CH_2CH_3$).

Octyl 3-Bromo-2-methylpropionate: Yield 79%; bp 120°C/1000 Pa; IR (neat) 1740 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ=0.64—1.93 [15H, m, $(CH_2)_6CH_3$], 1.26 (3H, d, CH_3), 2.84 (1H, m, CH), 3.50 (2H, m, CH_2Br), and 4.08 [2H, t, $C\underline{H}_2(CH_2)_6CH_3$].

Cyclohexyl 3-Bromo-2-methylpropionate: Yield 66%; bp 122.5—123.5°C/1300 Pa; IR (neat) 1740 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ=1.00—2.16 [10H, m, $(CH_2)_5$], 1.27 (3H, d, CH_3), 2.84 (1H, m, CH), 3.50 (2H, m, CH_2Br), and 4.83 [1H, m, CH(cyclohexyl)].

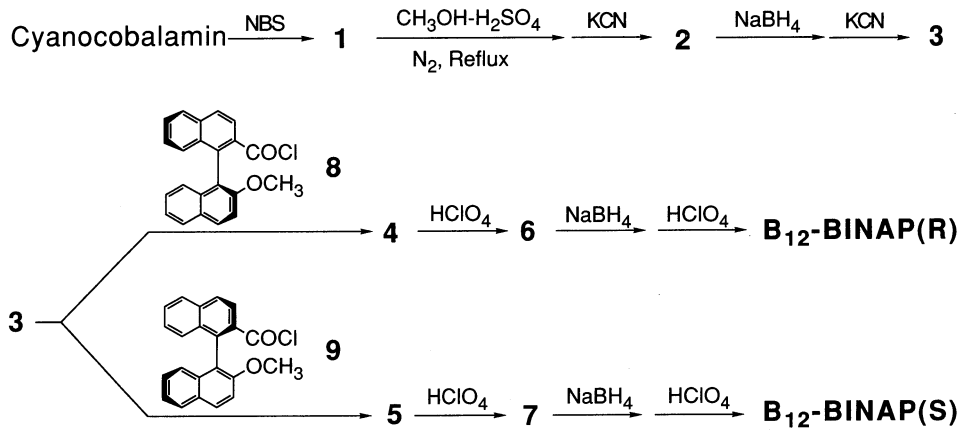
Benzyl 3-Bromo-2-methylpropionate: Yield 83%; bp 151.0—152.0°C/1300 Pa; IR (neat) 1740 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ=1.30 (3H, d, CH_3), 2.92 (1H, m, CH), 3.50 (2H, m, CH_2Br), 5.14 (2H, s, $C\underline{H}_2Ph$), and 7.34 (5H, s, phenyl).

Phenethyl 3-Bromo-2-methylpropionate: Yield 69%; bp 135°C/1000 Pa; IR (neat) 1740 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ=1.22 (3H, d, CH_3), 2.94 (2H, t, $C\underline{H}_2CH_2Ph$), 2.94 (1H, m, CH), 3.45 (2H, m, CH_2Br), 4.33 (2H, t, $CH_2C\underline{H}_2Ph$), and 7.25 (5H, s, phenyl).

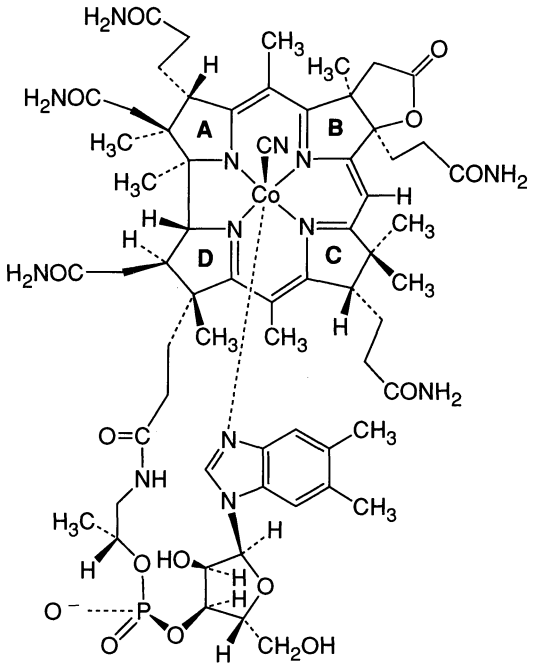
Neopentyl 3-Bromo-2-methylpropionate: Yield 68%; bp 105°C/1000 Pa; IR (neat) 1740 cm^{-1} (ester C=O); 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ=0.96 [9H, s, $CH_2(C\underline{H}_3)_3$], 1.30 (3H, d, CH_3), 2.94 (1H, m, CH), 3.56 (2H, m, CH_2Br), and 3.83 [2H, s, $C\underline{H}_2(CH_3)_3$].

All the 3-bromo-2-methylpropionates were confirmed to be sufficiently pure by GLC before use. Cyanocobalamin was a donation of Nippon Oil Company (Tokyo, Japan). Preparation of heptamethyl cobyrinate perchlorate (**B_{12}-ESTER**)[20] has been described previously.[5] Hydrophobic vitamin B_{12} derivatives having a binaphthyl group placed at one of the peripheral sites were prepared by following the reaction steps shown in Scheme 1.

Cyanocobalamin-c,8-lactone (1). This compound was prepared by reaction of cyanocobalamin (2.0 g, 1.5×10^{-3} mol) with *N*-bromosuccinimide (NBS) (0.32 g, 1.8×10^{-3} mol) in aqueous acetic acid (500 mL, 0.5 mol dm^{-3}) after a reported procedure:[21] Yield 1.7 g (84%); λ_{max}(CH_3OH) 279 (ε 8.06×10^3),



Scheme 1.



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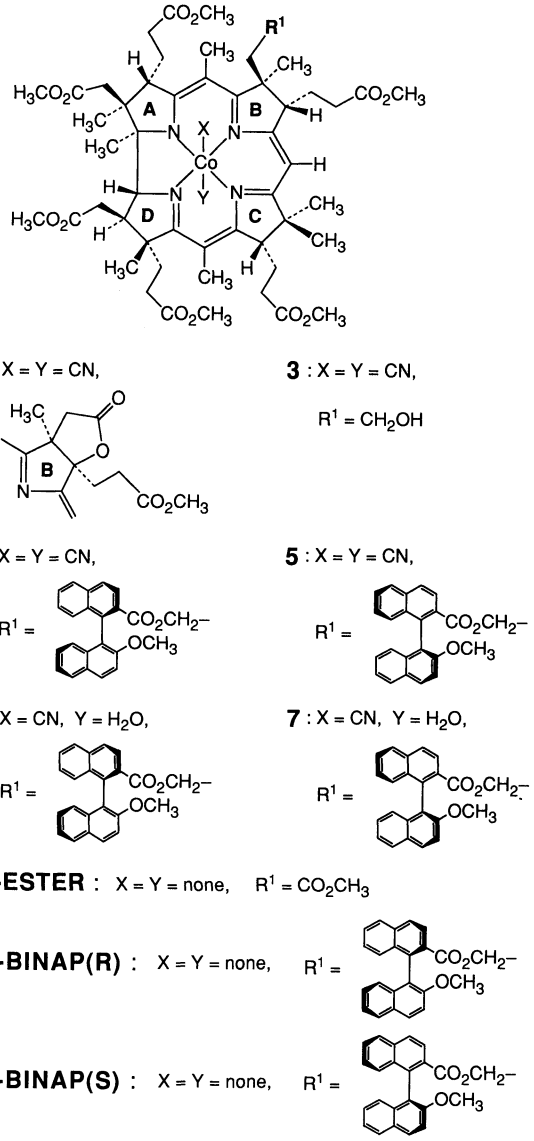
306 (8.77×10³), 321 (7.92×10³), 359 (2.68×10⁴), 410 (3.33×10³), 520 (7.56×10³), and 551 nm (8.06×10³); CD (CH_3OH) $\Delta\varepsilon$=−13 (251 nm), −4.0 (309 nm), +2.2 (328 nm), −12 (355 nm), +12 (427 nm), and −1.6 deg cm² dmol⁻¹ (555 nm); IR (KBr) 1785 (lactone C=O) and 1655 cm⁻¹ (amide C=O). Found: C, 54.97; H, 6.23; N, 13.37%. Calcd for $C_{63}H_{85}CoN_{13}O_{15}\cdot H_2O$: C, 55.13; H, 6.39; N, 13.27%.

Hexamethyl Coα,Coβ-Dicyano-7¹-de(carboxymethyl)-7¹, 7²-dihydro-7²-oxofuro[3,2-*g*]cobyrinate (2). Compound **1** (4.0 g, 3.0×10⁻³ mol) in dry methanol (400 mL) was mixed with cold concd sulfuric acid (40 mL) and dry methanol (200 mL). The solution was refluxed for 120 h in the dark. The reaction mixture was concentrated to ca. 150 mL, diluted with cold water (300 mL), and quickly neutralized with sodium carbonate powder. After an aqueous solution (20 mL) of potassium cyanide (5.0 g, 7.7×10⁻² mol) being added, the reaction mixture was extracted with carbon tetrachloride (150 mL×3). The extract was dried over sodium sulfate and evaporated to dryness at room temperature. The residue was dissolved in benzene, and the product was recovered by reprecipitation with hexane as a purple powder: Yield 2.5 g (84%); $\lambda_{max}(CH_3OH)$ 275 (ε 9.1×10³), 314 (8.3×10³), 366 (1.8×10⁴), 414 (8.3×10³), 545 (7.9×10³), and 586 nm (8.9×10³); IR (KBr) 2130 (C≡N), 1785 (lactone C=O), and 1735 cm⁻¹ (ester C=O); CD (CH_3OH) $\Delta\varepsilon$=+0.27 (286.4 nm), +5.68 (304.0 nm), −2.01 (324.4 nm), −8.68 (346.4 nm), +15.3 (391.2 nm), and −3.43 deg cm² dmol⁻¹ (577.6 nm).

Hexamethyl Coα,Coβ-Dicyano-7¹-decarboxy-7¹-(hydroxymethyl)cobyrinate (3). Distilled water (50 mL) was added to compound **2** (500 mg, 4.7×10⁻⁴ mol) dissolved in methanol (150 mL). The solution was deoxygenated by bubbling nitrogen gas through it for 30 min, and treated with sodium tetrahydroborate (1.0 g, 2.6×10⁻² mol) with vigorous stirring



for 5 min. An excess amount of sodium tetrahydroborate was decomposed by adding aqueous perchloric acid [60% (w/w), 5 mL] carefully to the mixture. The resulting cobalt complex was extracted with dichloromethane (50 mL×3) and washed with distilled water and saturated aqueous sodium carbonate. After the dichloromethane solution was shaken with 20 mL of aqueous potassium cyanide (3.0 g, 4.6×10⁻² mol), the layers separated. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by TLC on silica gel (Kiesel gel 60, Merck) with dichloromethane–methanol (95:5 v/v) containing 0.05% (w/w) potassium cyanide. The second purple fraction was collected, dissolved in methanol, and evaporated to dryness. The residue was dissolved in benzene, and the product was recovered by reprecipitation with hexane as a purple powder: Yield 160 mg (32%); $\lambda_{max}(CH_3OH)$ 280 (ε 8.6×10³), 316 (8.1×10³), 368 (2.3×10⁴), 548 (7.5×10³), and 587 nm (9.0×10³); IR (KBr) 2130 (C≡N) and 1735 cm⁻¹ (ester C=O); CD (CH_3OH) $\Delta\varepsilon$=−0.36 (286.0 nm), −5.77 (304.4 nm), +0.47 (320.4 nm), −10.9 (346.0 nm), +15.3 (394.8 nm), and −4.12 deg cm² dmol⁻¹

(580.4 nm). Found: C, 57.95; H, 6.57; N, 7.61%. Calcd for $C_{53}H_{73}CoN_6O_{14}\cdot H_2O$: C, 58.12; H, 6.90; N, 7.67%.

Hexamethyl Coα,Coβ-Dicyano-7^1-decarboxy-7^1-[(*R*)-2′-methoxy-1,1′-binaphthyl-2-carboxymethyl]cobyrinate (4). (*R*)-2′-Methoxy-1,1′-binaphthyl-2-carbonyl chloride (**8**)[22] (400 mg, 1.2×10^{-3} mol), triethylamine (0.5 mL), and 4-dimethylaminopyridine (10 mg) were added to compound **3** (200 mg, 1.9×10^{-4} mol) dissolved in dry dichloromethane (20 mL) under nitrogen atmosphere. The solution was stirred for 12 h at room temperature and then refluxed over 12 h. After the reaction mixture was washed with aqueous hydrochloric acid (2 mol dm^{-3}, 50 mL×2) and distilled water (50 mL×3), the unreacted binaphthyl derivative was removed by column chromatography (Kiesel gel 60, CH_2Cl_2). The product was purified by TLC on silica gel (Kiesel gel 60) with dichloromethane–methanol (94:6 v/v) containing 0.05% (w/w) potassium cyanide. The second purple fraction was collected, dissolved in methanol, and evaporated to dryness. The residue was dissolved in benzene, and the product was recovered by reprecipitation with hexane as a purple powder: Yield 173 mg (67%); λ_{max}(CH_3OH) 282 (ε 2.3×10^4), 369 (2.9×10^4), 515 (6.2×10^3), 526 (9.7×10^3), 588 nm (1.2×10^4); IR (KBr) 2125 (C≡N), 1735 (ester C=O), and 770 cm^{-1} (aromatic CH); CD (CH_3OH) $\Delta\varepsilon$=+107 (225.6 nm), −137 (239.4 nm), +14.9 (284.5 nm), −5.7 (305.6 nm), +3.9 (326.2 nm), −8.8 (348.5 nm), +14.4 (395.5 nm), and −0.83 deg cm^2 dmol^{-1} (580.6 nm). Found: C, 64.60; H, 6.18; N, 5.87%. Calcd for $C_{75}H_{87}CoN_6O_{16}$: C, 64.93; H, 6.32; N,6.06%.

Hexamethyl Coα,Coβ-Dicyano-7^1-decarboxy-7^1-[(*S*)-2′-methoxy-1,1′-binaphthyl-2-carboxymethyl]cobyrinate (5). This compound was prepared with (*S*)-2′-methoxy-1,1′-binaphthyl-2-carbonyl chloride (**9**)[22] in place of **8** after a method identical with that employed for the preparation of **4**: Yield 66%; λ_{max}(CH_3OH) 282 (ε 2.3×10^4), 369 (2.9×10^4), 515 (6.2×10^3), 526 (9.7×10^3), and 588 nm (1.2×10^4); IR (KBr) 2125 (C≡N), 1735 (ester C=O), and 770 cm^{-1} (aromatic CH); CD (CH_3OH) $\Delta\varepsilon$=−91 (225.6 nm), +200 (239.4 nm), −9.8 (279.7 nm), −10.1 (290.4 nm), −8.4 (305.6 nm), −10.9 (345.9 nm), +15.1 (395.5 nm), and −0.83 deg cm^2 dmol^{-1} (580.6 nm). Found: C, 64.42; H, 6.14; N, 5.88%. Calcd for $C_{75}H_{87}CoN_6O_{16}$: C, 64.93; H, 6.32; N, 6.06%.

Hexamethyl Coα,Coβ-Cyanoaqua-7^1-decarboxy-7^1-[(*R*)-2′-methoxy-1,1′-binaphthyl-2-carboxymethyl]cobyrinate Perchlorate (6). A purple solution of **4** (90 mg, 6.4×10^{-5} mol) dissolved in dichloromethane (50 mL) was shaken with 30% (w/w) aqueous perchloric acid (80 mL). The orange dichloromethane layer was separated, washed with distilled water (100 mL×2), dried over sodium sulfate, and evaporated to dryness at room temperature. The residue was dissolved in benzene, and the product was recovered by reprecipitation with hexane as an orange powder: Yield 100 mg (95%); λ_{max} (CH_3OH) 275 (ε 1.32×10^4), 296 (1.05×10^4), 354 (1.76×10^4), 403 (3.14×10^3), 494 (5.80×10^3), and 528 nm (5.62×10^3); IR (KBr) 2130 (C≡N), 1735 (ester C=O), and 1120 and 630 cm^{-1} (ClO_4^-); CD (CH_3OH) $\Delta\varepsilon$=+97.7 (228.6 nm), −126 (239.8 nm), +10.4 (289.6 nm), +3.13 (329.6 nm), +5.41 (427.2 nm), and −3.01 deg cm^2 dmol^{-1} (487.2 nm). Found: C, 59.56; H, 5.82; N, 5.04%. Calcd for $C_{74}H_{89}ClCoN_5O_{21}\cdot0.5H_2O$: C, 59.73; H, 6.10; N, 4.71%.

Hexamethyl Coα,Coβ-Cyanoaqua-7^1-decarboxy-7^1-[(*S*)-2′-methoxy-1,1′-binaphthyl-2-carboxymethyl]cobyrinate Perchlorate (7). This compound was prepared after a method identical with that employed for the preparation of **6**: Yield 95%; λ_{max}(CH_3OH) 275 (ε 1.32×10^4), 296 (1.05×10^4), 354 (1.76×10^4), 403 (3.14×10^3), 494 (5.80×10^3), and 528 nm (5.62×10^3); IR (KBr) 2130 (C≡N), 1735 (ester C=O), and 1120 and 630 cm^{-1} (ClO_4^-); CD (CH_3OH) $\Delta\varepsilon$=−98.6 (226.4 nm), +150 (239.8 nm), −11.9 (289.6 nm), −7.0 (336 nm), +2.63 (353.2 nm), +10.8 (425.6 nm), −6.02 (487.2 nm), and +1.61 deg cm^2 dmol^{-1} (541.2 nm). Found: C, 59.44; H, 5.92; N, 4.72%. Calcd for $C_{74}H_{89}ClCoN_5O_{21}\cdot H_2O$: C, 59.38; H, 6.13; N, 4.68%.

Hexamethyl 7^1-Decarboxy-7^1-[(*R*)-2′-methoxy-1,1′-binaphthyl-2-carboxymethyl]cobyrinate Perchlorate [B_{12}-BINAP-(*R*)]. A methanol solution (100 mL) of compound **6** (100 mg, 6.7×10^{-5} mol) was deoxygenated by bubbling nitrogen gas through it for 30 min, and sodium tetrahydroborate (100 mg, 2.6×10^{-3} mol) was added to the deoxygenated solution with vigorous stirring under nitrogen atmosphere. When the solution turned dark green, 60% (w/w) aqueous perchloric acid (3 mL) was added carefully to it in order to decompose an excess sodium tetrahydroborate and to convert the Co^I species into the corresponding Co^{II} species. The resulting cobalt complex was extracted with dichloromethane (25 mL×2). The extract was washed with distilled water, dried over sodium sulfate, and evaporated to dryness at room temperature. The residue was dissolved in benzene, and the product was recovered by reprecipitation with hexane as a brown powder: Yield 70 mg (72%); λ_{max}(CH_2Cl_2) 266, 286, 298, 315, 400, and 468 nm; IR (KBr) 1735 (ester C=O), and 1120 and 630 cm^{-1} (ClO_4^-); CD (CH_3OH) $\Delta\varepsilon$=+102 (226.2 nm), −133 (239.0 nm), +17.4 (292.8 nm), +17.4 (315.2 nm), −3.26 (426.4 nm), and +1.57 deg cm^2 dmol^{-1} (460.0 nm). Found: C, 59.19; H, 6.19; N, 4.41%. Calcd for $C_{73}H_{87}ClCoN_4O_{20}\cdot2H_2O$: C, 59.61; H, 6.24; N, 3.81%.

Hexamethyl 7^1-Decarboxy-7^1-[(*S*)-2′-methoxy-1,1′-binaphthyl-2-carboxymethyl]cobyrinate Perchlorate [B_{12}-BINAP-(*S*)]. This compound was prepared after a method identical with that employed for the preparation of B_{12}–BINAP(*R*): Yield 62%; λ_{max}(CH_2Cl_2) 266 (ε 2.0×10^4), 286 (1.9×10^4), 298 (1.9×10^4), 315 (2.0×10^4), 400 (5.8×10^3), and 468 nm (9.0×10^3); IR (KBr) 1735 (ester C=O), and 1120 and 630 cm^{-1} (ClO_4^-); CD (CH_3OH) $\Delta\varepsilon$=−85.9 (225.6 nm), +138 (239.4 nm), −10.04 (264.0 nm), −10.3 (281.2 nm), +12.0 (314.0 nm), −3.78 (423.6 nm), and +1.06 deg cm^2 dmol^{-1} (460.8 nm).

Cyclic Voltammetry. An electrochemical cell similar to that reported in literature[23] was used and equipped with platinum wire of 0.5 mm diameter as working and auxiliary electrodes. A saturated calomel electrode (SCE) was served as a reference which was separated from a bulk electrolyte solution by a salt bridge prepared with 1,2:4,5-*O*-dibenzylidene-D-glucitol[24] and an organic solvent containing tetrabutylammonium perchlorate (TBAP, 5.0×10^{-2} mol dm^{-3}). Acetonitrile, acetone, *N,N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were used as media for cyclic voltammetry. An organic solution containing a hydrophobic vitamin B_{12} derivative and TBAP were deaerated prior to each measurement, and the cell interior was maintained under argon atmosphere throughout each measurement. All the measurements were carried out at 20±2°C, and the scan rate was varied in a range from 50 through 500 mV s^{-1}. Half-wave potentials ($E_{1/2}$) and anodic and cathodic currents were evaluated according to the method described previously.[25]

Enantioselective Alkylation of Hydrophobic Vitamin B_{12}

Derivatives. Alkylated complexes were prepared by reaction of the hydrophobic vitamin B_{12} derivatives in the Co(I) state with various 3-bromo-2-methylpropionates in a manner similar to that described previously,[8] and identified by electronic and ^1H NMR spectroscopy. Preparation of the methyl 2-methylpropionate adduct of B_{12}–ESTER is described below as a representative example.

A methanol solution (50 mL) of B_{12}-ESTER (50 mg, 4.4×10^{-5} mol) was deoxygenated by bubbling nitrogen gas through it for 30 min, and sodium tetrahydroborate (100 mg, 2.6×10^{-3} mol) was added to the deoxygenated solution with vigorous stirring under nitrogen atmosphere. The following operations were carried out in the dark. When the solution turned dark green, methyl 3-bromo-2-methylpropionate (500 mg, 2.8×10^{-3} mol) was added to it. The resulting solution was stirred for 7 min at room temperature, and 60% (w/w) aqueous perchloric acid (3 mL) was added carefully to it in order to decompose an excess sodium tetrahydroborate. The resulting mixture was extracted with dichloromethane (25 mL×3), and the extract was washed with distilled water. After being dried over sodium sulfate, the extract was evaporated to dryness at room temperature. The product was purified by gel-filtration chromatography on a column of Sephadex LH-20 with methanol as eluent in the dark. The first brown fraction was collected and evaporated to dryness at room temperature under reduced pressure. The residue was dissolved in benzene, and the product was recovered by reprecipitation with hexane as a brown powder: Yield 44 mg (67%); $\lambda_{max}(CH_2Cl_2)$ 264 (ε 2.22×10^4), 302 (2.24×10^4), 378 (7.86×10^3), and 456 nm (8.51×10^3); IR (KBr) 1730 (ester C=O), and 1100 and 620 cm^{-1} (ClO_4^-). Found: C, 54.43; H, 6.52; N, 4.56%. Calcd for $C_{57}H_{84}ClCoN_4O_{21}$: C, 54.52; H, 6.74; N, 4.46%.

Although both Coα- and Coβ-axial ligand isomers are expected to be formed, the Coα-axial ligand isomer is much less likely formed because of remarkable steric hindrance between the angular methyl group at C(1) of the corrin ring and the axial ligand moiety bound to the nuclear cobalt. The alkylated complex prepared by the present method was confirmed to be the Coβ-bound isomer on the basis of ^1H NMR spectroscopy.[26]

The enantioselective alkylation for the hydrophobic vitamin B_{12} derivatives was examined by 500 MHz ^1H NMR spectroscopy, (+)-methyl (*R*)-3-bromo-2-methylpropionate and (−)-methyl (*S*)-3-bromo-2-methylpropionate (both from Aldrich Chemical Co., U.S.A.) being adopted as reference substrates. The enantioselectivity in alkylation was evaluated from ^1H NMR signal areas by the aid of a NMR1™ software (New Methods Research, Inc., U.S.A.) on a DEC 5000/200PX workstation .

Results and Discussion

Electronic and Circular Dichroism Spectra of Hydrophobic Vitamin B_{12} Bearing a Binaphthyl Moiety. Electronic and CD spectra of **4** and **5** in methanol are shown in Fig. 1. The electronic spectra of **4** and **5** with (*R*)- and (*S*)-binaphthyl moieties, respectively, are identical to each other, exhibiting a strong absorption band at 282 nm as caused by the binaphthyl moiety. These spectra are quite similar to that for heptamethyl dicyanocobyrinate, which does not bear a binaphthyl moiety, in the 350—700 nm range.[27] Such observations clearly indicate that the corrin ring hardly interacts electronically with the peripheral binaphthyl group.

The CD spectra of **4** and **5** are quite similar to each other in the 350—700 nm range, and this spectral pattern is comparable to that of cyanocobalamin in the same wavelength range.[28] The strong CD bands arising from the chiral binaphthyl moiety are observed in the 200—280 nm range; **4** and **5** exhibit spectral patterns nearly symmetrical with each other in this wavelength range. On the basis of theoretical calculation of the CD spectra for 2,2′-disubstituted-1,1′-binaphthalenes, the Cotton effects are expected to appear in the 230 nm range, as derived from the ^1B_b transition of the naphthalene chromophores.[29] In addition, the intensity of the Cotton effects derived from the ^1B_b transition was revealed to decrease with increase of the dihedral angle between the naphthalenes of the 1,1′-binaphthalene skeleton.[29] Since the intensity of Cotton effects in the 230 nm range for both **4** and **5** is similar to that for binaphthalenes **8** and **9**, a significant steric interaction does not seem to be operative between the corrin ring and the binaphthyl moiety.

Redox Behavior of Hydrophobic Vitamin B_{12} Bearing a Binaphthyl Moiety. Redox behavior of B_{12}–BINAP(*R*) and B_{12}–BINAP(*S*) in various organic solvents, such as acetonitrile, acetone, DMF, and DMSO, was

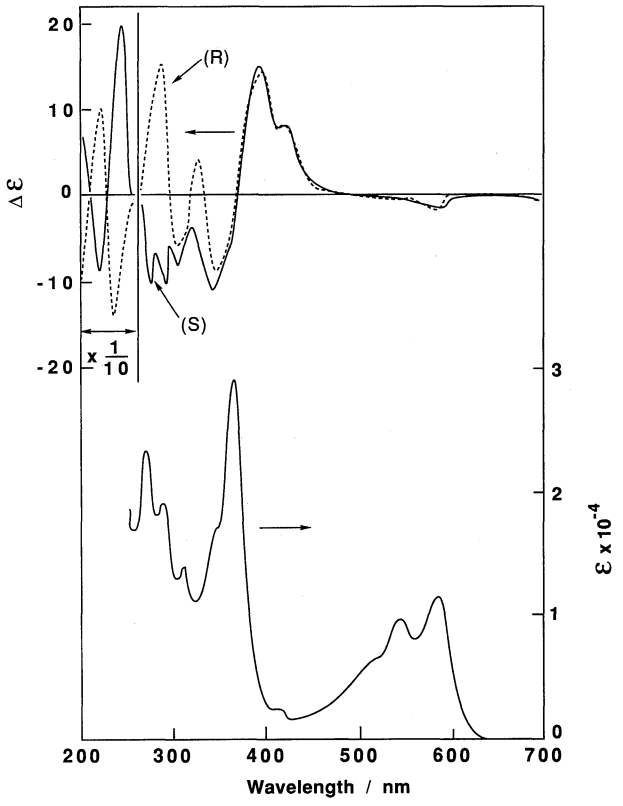


Fig. 1. Electronic and CD spectra of B_{12}–BINAP(*R*) and B_{12}–BINAP(*S*) in methanol: solid line, B_{12}–BINAP(*S*); broken line, B_{12}–BINAP(*R*). The $\Delta\varepsilon$ values are given in one tenth of real values for the 200—265 nm range.

Table 1. Redox Potentials for B_{12}–BINAP and B_{12}–ESTER in Nonaqueous Media[a]

Medium[b]	DN[c]	E_T^N[d]	$E_{1/2}$ vs. SCE/V	
			Co(III)/Co(II)	Co(II)/Co(I)
CH_3CN	14.1	0.460	+0.57 (+0.45)[e]	−0.54 (−0.64)[e]
CH_3COCH_3	17.0	0.355	+0.72 (+0.77)[e]	−0.45 (−0.53)[e]
DMF	26.6	0.404	+0.38 (+0.40)[e]	−0.58 (−0.61)[e]
DMSO	29.8	0.444	+0.32 (+0.30)[e]	−0.62 (−0.64)[e]

a) Measured at 20±2°C; scan rate, 100 mV s^{-1}. b) Abbreviations: DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide. c) Donor number of a solvent; refer to Ref. 30. d) Solvent polarity parameter; refer to Ref. 31. e) A redox potential ($E_{1/2}$) for B_{12}-ESTER is given in parentheses; refer to Ref. 6.

examined by means of cyclic voltammetry. A cyclic voltammogram of B_{12}–BINAP(*R*) in DMSO is shown in Fig. 2 as a typical example, whereas the identical voltammogram was observed for B_{12}–BINAP(*S*). The Co(III)/Co(II) and Co(II)/Co(I) redox potentials are summarized in Table 1.

The Co(III)/Co(II) and Co(II)/Co(I) redox couples for B_{12}–BINAP in acetonitrile [solvent basicity *DN*, 14.1][30] were observed at +0.57 and −0.54 V vs. SCE, respectively; the corresponding redox potentials ($E_{1/2}$) for B_{12}–ESTER were found at +0.45 and −0.64 V vs. SCE, respectively.[6] The redox potentials for B_{12}–BINAP(*R*) and B_{12}–BINAP(*S*) were shifted to an anodic side by ca.100 mV relative to the corresponding potentials for B_{12}-ESTER. A similar tendency, though to a less extent, was observed for those potentials observed in acetone as listed in Table 1. Therefore, the binaphthyl group furnishes a specific microenvironmental effect on the redox behavior of the nuclear cobalt when B_{12}–BINAP is treated in organic solvents of lower basicity.

On the other hand, the redox potentials for B_{12}-ESTER and B_{12}–BINAP in DMF, a solvent of high basicity (*DN*=26.6),[30] are quite similar to each other; the Co(III)/Co(II) and Co(II)/Co(I) redox couples for B_{12}–BINAP in DMF were observed at +0.38 and −0.58 V vs. SCE, respectively, while the corresponding redox potentials for B_{12}-ESTER were at +0.40 and −0.61 V vs. SCE, respectively.[6] A similar tendency was observed for those potentials measured in DMSO (*DN*=29.8).[30] The solvent basicity is related to the axial ligation ability of solvent molecules; a sufficiently basic solvent tends to coordinate to the nuclear cobalt of a hydrophobic vitamin B_{12} derivative. Under such circumstances, the binaphthyl moiety of B_{12}–BINAP does not give out any meaningful microenvironmental effect on the redox behavior of the nuclear cobalt, and the redox potentials are primarily subjected to change by the solvent nature.

Enantioselective Alkylation of Hydrophobic Vitamin B_{12} Derivatives. The enantioselective alkylation of B_{12}-ESTER, B_{12}–BINAP(*R*), and B_{12}–BINAP(*S*) was examined by 500 MHz ^{1}H NMR spectroscopy, (+)-methyl (*R*)-3-bromo-2-methylpropionate and (−)-methyl (*S*)-3-bromo-2-methylpropionate (both from Aldrich Chemical Co., U.S.A.) being adopted as reference

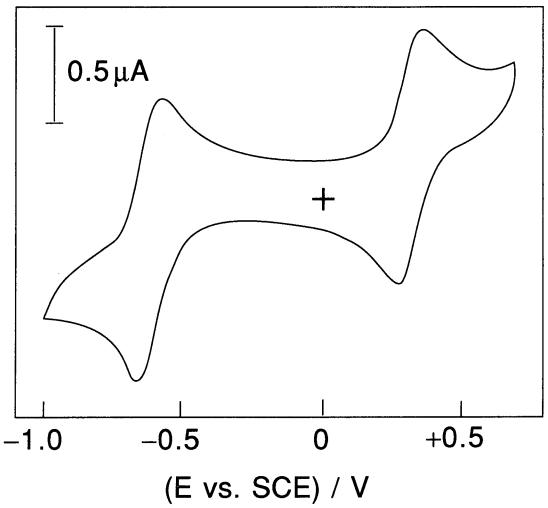
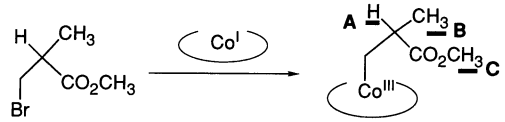


Fig. 2. Cyclic voltammogram of B_{12}–BINAP(*R*) (7.2×10^{-4} mol dm^{-3}) in DMSO containing 5.0×10^{-2} mol dm^{-3} TBAP at 20±2°C; scan rate, 50 mV s^{-1}.

Table 2. Assignments of ^{1}H NMR Signals for an Alkyl Moiety Placed at the Axial Site of B_{12}-ESTER in $CDCl_3$ at 25°C

Assignment[a]	Splitting	δ/ppm[b]	
		R-Configuration	*S*-Configuration
A	Multiplet	−0.68	−0.50
B	Doublet	0.26	0.43
C	Singlet	3.35	3.40

a) Refer to Eq. 3. b) Tetramethylsilane as an internal reference.



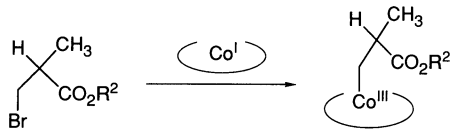
(3)

substrates. The major proton signals for the reference alkyl moieties placed at the β-axial site of the hydrophobic vitamin B_{12} were assigned as listed in Table 2 (refer to Eq. 3). All the signals for the alkyl moiety

Table 3. Enantioselectivity for the Reaction of Hydrophobic Vitamin B_{12} Derivatives with Various 3-Bromo-2-methylpropionic Esters in Methanol at Room Temperature[a)]

R^2 in 3-bromo-2-methylpropionate[b)]	Vitamin B_{12} derivative	Yield[c)]/%	Selectivity	
			% e.e.	Configuration
CH_3	B_{12}–ESTER	67	34	*S*
C_2H_5	B_{12}–ESTER	63	44	*S*
C_4H_9	B_{12}–ESTER	79	44	*S*
C_8H_{17}	B_{12}–ESTER	60	51	*S*
$(CH_3)_3CCH_2$	B_{12}–ESTER	66	45	*S*
Cyclohexyl	B_{12}–ESTER	86	55	*S*
$C_6H_5CH_2CH_2$	B_{12}–ESTER	66	47	*S*
$C_6H_5CH_2$	B_{12}–ESTER	68	49	*S*
$C_6H_5CH_2$	B_{12}–BINAP(*R*)	60	64	*S*
$C_6H_5CH_2$	B_{12}–BINAP(*S*)	54	65	*S*

a) Each reaction was carried out at a 1:5 molar ratio of a vitamin B_{12} derivative to a 3-bromo-2-methylpropionic ester; a vitamin B_{12} derivative, 50 mg. b) Refer to Eq. 4. c) Isolated yield, as purified by gel-filtration chromatography on a column of Sephadex LH-20 with methanol as eluent in the dark; crude yield, above 80%.



(4)

bound to the nuclear cobalt showed significant up-field shifts due to a shielding effect given by the corrin ring. The result indicates that the proton signals for the alkyl moiety with *R*-configuration appear in upper field ranges relative to those for the alkyl moiety with *S*-configuration. The enantioselectivity in alkylation was evaluated from the ^1H NMR signal areas. When the racemic 3-bromo-2-methylpropinate was used, the reactivity of the *S*-enantiomer in the alkylation prevails over that of the corresponding *R*-enantiomer. The enantioselectivity data for the formation of other alkylated complexes were evaluated by the identical method as summarized in Table 3.[32)]

The alkylation study reveals the following facts with respect to enantioselectivity (refer to Eq. 4 and Table 3). (i) B_{12}-ESTER affords the alkylated complexes by reaction with 3-bromo-2-methylpropionates in favor of binding *S*-enantiomers, and the selectivity is enhanced as the bulkiness of an R^2 group increases. (ii) The highest enantioselectivity is attained for the reaction of B_{12}-ESTER with a 3-bromo-2-methylpropionate bearing a cyclohexyl ester group, 55% e.e. (iii)The hydrophobic vitamin B_{12} derivatives having a binaphthyl group, B_{12}–BINAP(*R*) and B_{12}–BINAP(*S*), exhibit higher selectivity toward an (*S*)-3-bromo-2-methylpropionate than the simple hydrophobic vitamin B_{12}, B_{12}-ESTER, for the reaction with an alkyl bromide bearing a benzyl ester group, 65% e.e. This is the highest enantioselectivity in the alkylation so far observed for vitamin B_{12}-related compounds. However, both B_{12}–BINAP(*R*) and B_{12}–BINAP(*S*) having (*R*)- and (*S*)-binaphthyl groups, respectively, undergo substitution at the β-axial site with the *S*-enantiomer more preferably than the *R*-enantiomer at a comparable enantioselectivity. This seems to be caused by a conformational phenomenon that allows the binaphthyl group to rotate freely around the chain placed at the c-site of ring B. The results indicate that the stereoselectivity in the course of alkylation is apparently originated from a stereospecific arrangement of the bulky peripheral substituents placed around the corrin ring and not from the chiral nature of the specific peripheral substituent.

We examined stereochemical arrangements of (*R*)- and (*S*)-2-methylpropionate moieties bound to vitamin B_{12} in the light of X-ray crystal structures obtained for adenosylcobalamin and 2,3-dihydroxypropylcobalamin.[33,34)] A top view of the β-site of cobalamin, showing the corrin ring and the peripheral side chains at β-site based on X-ray analysis is illustrated in Fig. 3(a). The peripheral substituents of cobalamin placed in rings A, B, C, and D are shown with shaded circles in Fig. 3(b), in consideration of their effective bulkiness toward an alkyl moiety bound to the nuclear cobalt. According to the X-ray structural data for the above alkylated cobalamins, the most bulky group placed on the β-carbon atom of the alkyl moiety is directed toward a space intervening between rings C and D. In consideration of such a stereochemical state of affairs, (*S*)- and (*R*)-2-methylpropionate must be bound to the nuclear cobalt with their 3-carbon atoms as illustrated in Figs. 3(c) and 3(d), respectively, so that the steric hindrance between the alkyl moiety and the peripheral substituents of cobalamin is minimized. The stereochemical configuration of the *R*-enantiomer shown in Fig. 3(d) seems to be energetically less favorable than that of the *S*-enantiomer shown in Fig. 3(c), because a significant steric interaction would be expected between the 2-methyl group of the alkyl ligand and ring D. An alternative configuration for the *R*-enantiomer is illustrated in Fig. 3(e). However, B_{12}–BINAP, which bears a bulky binaphthyl group at the peripheral site of ring B, must give out a marked steric hindrance effect on the carboxylic ester group (CO_2R). On this ground, the

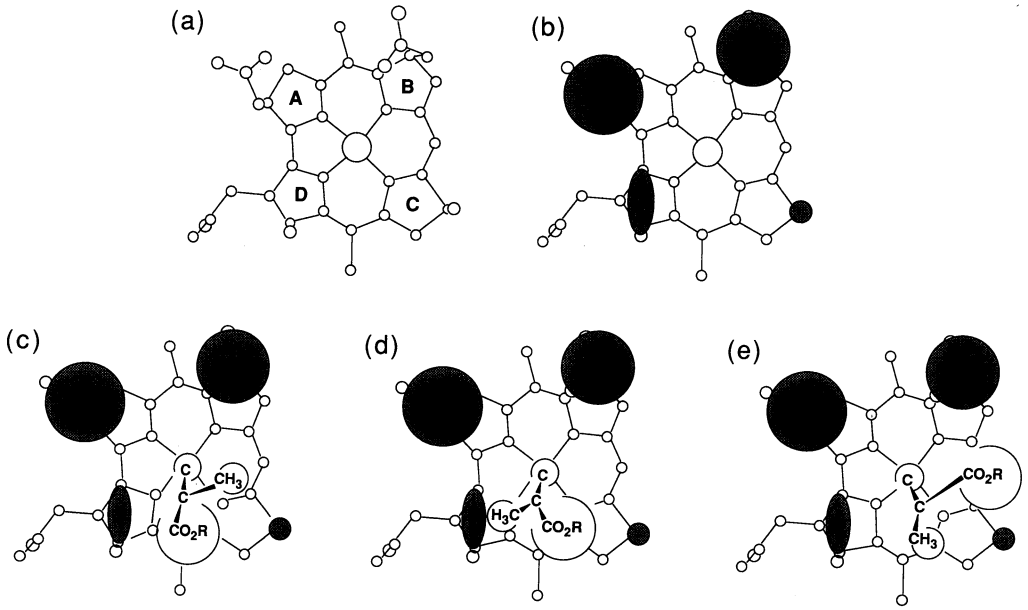


Fig. 3. Top views of cobalamin and its alkylated complex on the β-site: (a) and (b), structural representation of cobalamin based on X-ray analysis; (c), structural representation of cobalamin with an axial ligand of *S*-configuration; (d) and (e), structural representation of cobalamin with an axial ligand of *R*-configuration. Shaded circles indicate the peripheral substituents in their effective bulkiness toward the axial ligand.

stereochemical configuration of the *R*-enantiomer given in Fig. 3(e) turns out to be much less favorable than that shown in Fig. 3(d), and even can be excluded. As a consequence, the *S*-enantioselectivity in alkylation of B_{12}-ESTER becomes enhanced as the effective bulkiness of an carboxylic ester group placed in an alkyl ligand increases. The *S*-enantioselectivity is even more pronounced in the alkylation of B_{12}–BINAP due to the marked steric effect generated by the binaphthyl moiety introduced into ring B.

In conclusion, the enantioselectivity in alkylation of the hydrophobic vitamin B_{12} having a binaphthyl group is superior to that of the simple hydrophobic vitamin B_{12}. This means that the peripheral substituents of B_{12}–BINAP construct an effective chiral microenvironment for recognition of the *S*-enantiomer.

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