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THE COBALT-BISDEHYDROCORRIN COMPLEX AS A VITAMIN B_{12} MODEL†

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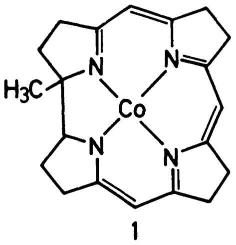
The (AD-bisdehydrocorrinato)dicyanocobalt(III) complex [Co(III)$(CN)_2$(BDHC)] was reduced with sodium borohydride to give the corresponding cobalt(I) complex, which underwent alkylation with an alkyl bromide or iodide at the axial position. The second-order rate constants for reactions of Co(I)(BDHC) with alkyl halides in aqueous THF at 25.0±0.1°C reveal that an extra steric effect, which is not expected for the cobalt corrinoid, is exerted by the 1,3-diaxial-type interaction between angular methyl groups placed at C_1 and C_{19} of BDHC and an alkyl groups bound to the nuclear cobalt. The present complex bears a resemblance to the cobalt corrinoid in various aspects.

The intrinsic equatorial ligand effect, which is exerted by the corrin framework on the central cobalt atom for the development of vitamin B_{12} functions, is not well understood despite rather extensive studies on the cobalt corrinoids$^{1)}$ (**1**, substituents at the peripheral positions are omitted). As an approach to the clarification of this problem, the cobalt complexes of some modified corrins such as **2** and **3** have been taken up as reference metal complexes. Additional double bonds located at the periphery of the corrin framework show remarkable effects on the redox and axial coordination properties of the nuclear cobalt atom. The (8,12-diethyl-1,2,3,7,13,17,18,19-octamethyltetradehydrocorrinato)cobalt complex (**3**, Co(TDHC)) is far from analogous to the cobalt corrinoid.$^{2)}$ A powerful oxidation ability is cited as one of the most striking properties of Co(TDHC); even with the unsolvated hydroxide ion, **3** in Co(II) state is readily reduced to the cobalt(I) species which lacks in nucleophilic reactivity even with methyl iodide.$^{2a)}$ We report here that a cobalt complex of AD-bisdehydrocorrin (**2**) is quite analogous to the cobalt corrinoid in various aspects.

Dicyano(8,12-diethyl-1,2,3,7,13,17,18,19-octamethyl-AD-bisdehydrocorrinato)-cobalt(III) [Co(III)$(CN)_2$(BDHC)] was prepared by the procedure of Johnson *et al.*$^{3)}$



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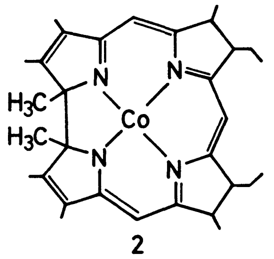

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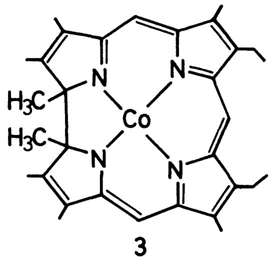

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with some modification. The crude material of Co(III)(CN)$_2$(BDHC) was obtained by hydrogenation of the corresponding (tetradehydrocorrinato)cobalt(II) perchlorate (0.6 g)[2c,3] in methanol (150 ml) containing acetic acid (1.6 g) over 10% palladium carbon (0.6 g) at 80-82°C and the initial hydrogen pressure of 85 kg/cm^2. The product was purified by repeated preparative tlc on silica gel (type 60) of E. Merck, Darmstadt, which contained sodium cyanide (2.3% by weight), with chloroform containing acetic acid (1% by volume) as eluant. The reddish purple fraction was extracted with chloroform, and the extract was evaporated at room temperature by bubbling with dry nitrogen after addition of sodium cyanide (50 mg). Extraction with chloroform followed by precipitation with petroleum ether gave the purified product, yield *ca.* 10%. IR (KBr disk): 2123 cm^{-1} (CN str.). NMR (CDCl$_3$, TMS): δ 5.97 (s, C$_5$-H and C$_{15}$-H), 5.91 (s, C$_{10}$-H), 3.7-2.7 (broad, H's on saturated carbons C$_7$, C$_8$, C$_{12}$, and C$_{13}$), 2.11 and 2.29 (s, CH$_3$'s on unsaturated carbons C$_2$, C$_3$, C$_{17}$, and C$_{18}$), 1.55-1.1 (d centered at 1.41, CH$_3$'s on saturated carbons C$_7$ and C$_{13}$; and overlapping m, C$\underline{H}_2$-CH$_3$), 0.97 (t, CH$_2$C$\underline{H}_3$), 0.84 (s, C$_1$-CH$_3$ and C$_{19}$-CH$_3$), and 1.65 (broad s, H$_2$O; integrated intensity corresponds to about two molecules and disappeared upon deuteration). Found: C, 64.01; H, 7.02; N, 13.02%. Calcd for $C_{33}H_{41}CoN_6 \cdot 2H_2O$: C, 64.29; H, 7.03; N, 13.63%.

The formation of cobalt-carbon σ-bond is the attractive criterion for vitamin B$_{12}$ models. Sodium borohydride was used for the reduction of Co(III)(CN)$_2$(BDHC) in water or 50%(v/v) aqueous tetrahydrofuran. The univalent cobalt complex thus obtained, Co(I)(BDHC), was air-sensitive and oxidized quantitatively to give the original dicyanocobalt(III) complex in the presence of sodium cyanide. Co(I)(BDHC) was readily converted to an organometallic derivative in which the axial position of cobalt was alkylated on treatment with an alkyl iodide or bromide. As generally expected for organo-cobalt derivatives, the resulting alkylated complexes were photolabile. The methyl derivative [CH$_3$-Co(III)(BDHC)] was stable for hours in dark but readily photolyzed upon irradiation in seconds to yield Co(III)(CN)$_2$(BDHC) in the presence of sodium cyanide, the recovery of which was larger than 82%. Alkyl derivatives showed NMR signals in a relatively higher field range, which are assignable to protons of an alkyl group bound to the nuclear cobalt and disappeared on photolysis: CH$_3$-Co(III)(BDHC), a singlet at δ -0.04; CH$_3$CH$_2$CH$_2$-Co(III)(BDHC), a triplet at δ +0.48, an unresolved multiplet at +0.3 — 0, and multiplets at -0.31 and -0.81. The chemical shifts for the alkyl protons are quite analogous to those for the corresponding alkylcobinamide,[4] thus indicating that BDHC may provide a diamagnetic shielding effect to an extent similar to that of the corrin ring. The highest two signals of the *n*-propyl derivative may be assigned to the nonequivalent β-CH$_2$ protons, since a similar phenomenon has been observed for *n*-propylcobinamide. The nonequivalent NMR behavior of two protons of the β-CH$_2$ group may be attributed to the restricted rotation about C$_\alpha$-C$_\beta$ bond.[4a] The formation of *iso*-propyl derivative was confirmed by electronic spectroscopy but an attempt of its isolation was not successful. The formation of alkyl derivatives of Co(BDHC) means that the equatorial ligand effect exerted by BDHC on the nature of cobalt resembles to that of the corrin ring, in marked contrast to the more highly π-conjugated analog, TDHC (**3**). This was further appreciated by the electronic spectral measurements for the cobalt complexes of both ligands[5] as shown in Figure. Both systems show quite similar spectral features.

Table. Second-order rate constants for reactions of Co(I)(BDHC)a) and vitamin B_{12s} b) with alkyl halides c)

Alkyl halide	k(BDHC)/$M^{-1}s^{-1}$	k(B_{12s})/$M^{-1}s^{-1}$	k(BDHC)/k(B_{12s})
CH_3I	3.0×10^4	3.4×10^4	0.88
CH_3CH_2I	3.1×10^2	——	——
$CH_3CH_2CH_2I$	1.1×10^2	——	——
$(CH_3)_2CHI$	0.71	2.3×10^2	3.1×10^{-3}
CH_3Br	8.5×10^2	1.6×10^3	0.53
CH_3CH_2Br	3.9	3.1×10	0.13
$CH_3CH_2CH_2Br$	1.8	1.4×10	0.13
$(CH_3)_2CHBr$	7×10^{-4}	1.8	4×10^{-4}

a) In 50%(v/v) aqueous tetrahydrofuran. b) In methanol containing 0.10 F NaOH. c) Co(I)(BDHC), at 25.0±0.1°C; vitamin B_{12s}, at 25±2°C with ethyl, *n*-propyl, and *iso*-propyl halides, and at 25.0°C with methyl halides. The kinetic data for B_{12s} are cited from Ref. 6.

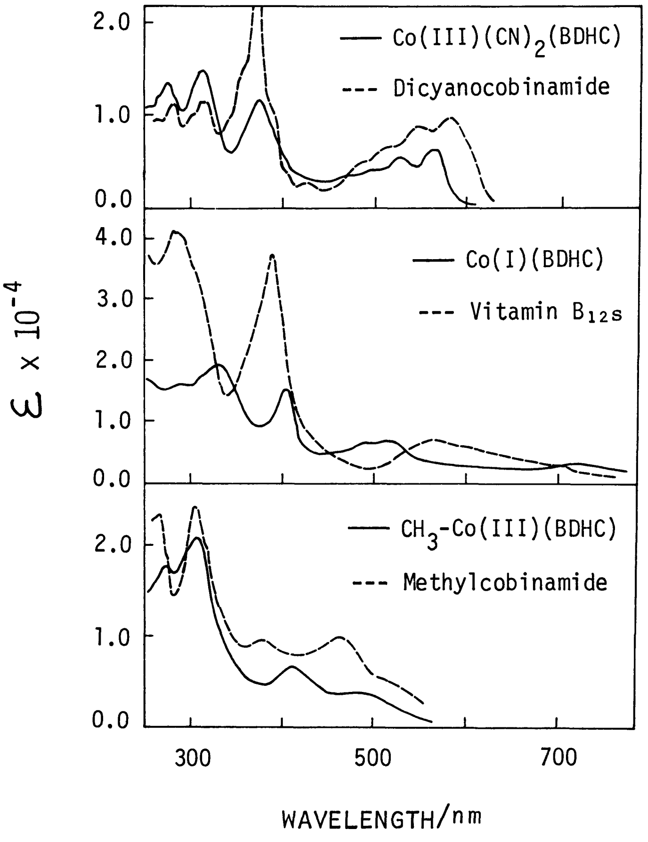

Figure. Electronic absorption spectra of the cobalt complexes of BDHC and corrinoid in water at room temperature.

The second-order rate constants for reactions of Co(I)(BDHC) with alkyl halides in 50%(v/v) aqueous tetrahydrofuran at 25.0±0.1°C were determined spectrophotometrically at 400 nm as listed in Table along with those for Co(I)-corrinoid (vitamin B_{12s}) in methanol at 25°C.6) These data indicates that the S_N2 mechanism is operative in the reaction of Co(I)(BDHC); the iodides are more reactive with the cobalt complex than the bromides, and the rate decreases with increasing the bulkiness of an alkyl donor. The steric effect is far more pronounced for Co(I)(BDHC) than for vitamin B_{12s} as confirmed by the rate ratios for Co(I)(BDHC) *vs.* B_{12s}, k(BDHC)/k(B_{12s}), listed in Table. The significant steric effect seems to arise from the 1,3-diaxial-type interaction between angular methyl groups placed at C_1 and C_{19} positions of the macrocyclic ligand and an approaching alkyl group which is finally bound to the cobalt atom. A methyl group is placed only at C_1 in the corrinoid system and an alkyl halide may approach from the less hindered side of the equatorial skeleton to avoid the steric interaction with CH_3-C_1.

In order to get further insight into the ligand effects of BDHC and TDHC, and to differentiate them, the Co(III)-Co(I) reduction potentials for the dicyano-complexes were measured by cyclic voltammetry in *N*,*N*-dimethylformamide at 20.0±0.1°C under argon atmosphere with tetra(*n*-butyl)ammonium perchlorate as a supporting electrolyte: Co(III)$(CN)_2$(TDHC), -0.58 V; Co(III)$(CN)_2$(BDHC), -1.38 V *vs.* SCE. The reduction potential for the latter complex is comparable to those for dicyanocobalamin (-1.33 V *vs.* SCE in water)1) and of dicyanocobinamide (-1.18 V *vs.* SCE in water).7) The observed difference in reduction potential between TDHC and BDHC complexes is as large as 0.8 V, and reflected on the marked difference in nucleophilicity between the cobalt(I) complexes of both ligands.

The intrinsic resemblance of BDHC and corrins as equatorial ligands has been characterized in this work. Since the BDHC complex becomes soluble in a wide range of solvents by introduction of various types of substituents at the periphery of the macrocyclic skeleton, such BDHC complexes may provide means of elucidating reaction mechanisms involved in the B_{12} catalysis and also may be incorporated into the more elaborated enzyme model systems.

REFERENCES

1) J. M. Pratt, "Inorganic Chemistry of Vitamin B_{12}," Academic Press, London (1972).

2) (a) Y. Murakami and Y. Aoyama, *Bull. Chem. Soc. Jpn.*, 49, 683 (1976). (b) Y. Murakami, Y. Aoyama, and S. Nakanishi, *Chem. Lett.*, 1976, 857. (c) Y. Murakami, Y. Aoyama, and S. Nakanishi, *Inorg. Nucl. Chem. Lett.*, 12, 809 (1976).

3) D. Dolphin, R. L. N. Harris, J. L. Huppatz, A. W. Johnson, and I. T. Kay, *J. Chem. Soc. (C)*, 1966, 30: the formation of Co(III)$(CN)_2$(BDHC) is not well characterized in this paper.

4) (a) J. D. Brodie and M. Poe, *Biochemistry*, 10, 914 (1971). (b) H. A. O. Hill, B. E. Mann, J. M. Pratt, and R. J. P. Williams, *J. Chem. Soc. (A)*, 1968, 564. The reported chemical shifts of alkyl protons are -0.36 in $[^2H_6]$DMSO4a) or -0.24 in D_2O4b) for methylcobinamide; and +0.26 (γ-CH_3), +0.46 and +0.05 (α-CH_2), and -0.25 and -0.85 (β-CH_2) for *n*-propylcobinamide in $[^2H_6]$DMSO.4a)

5) Dicyanocobinamide: P. O. Offenhartz, B. H. Offenhartz, and M. M. Fung, *J. Amer. Chem. Soc.*, 92, 2966 (1970). B_{12s}: G. H. Beaven and E. A. Johnson, *Nature*, 176, 1264 (1955). Methylcobinamide: R. A. Firth, H. A. O. Hill, J. M. Pratt, R. J. P. Williams, and W. R. Jackson, *Biochemistry*, 6, 2178 (1967).

6) G. N. Schrauzer and E. Deutsch, *J. Amer. Chem. Soc.*, 91, 3341 (1969).

7) H. P. C. Hogenkamp and S. Holmes, *Biochemistry*, 9, 1886 (1970).

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