Cobalt Chelates as Models for Methyl Donors and Acceptors in Vitamin B_{12}-dependent Transmethylation. Direct Methylation of Vitamin B_{12a}

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Summary The dimethyl derivative of 1,3-bis(biacetylmonoximeimino)propanecobalt (III)† $[(CH_3)_2Co\{(DOH)(DO)pn\}]$, behaves as a methylating reagent toward electrophilic metal atoms and protons, thus allowing the preparation of several methyl-cobalt derivatives from the corresponding Co^{III} complexes by a reaction which involves the transfer of a methyl carbanion and is related to the catalytic action of the Vitamin B_{12a} in transmethylases.

THE mechanism of the biosynthesis of methionine by methyl transfer from N^5-methyltetrahydrofolate to homocysteine, catalysed by several transmethylases, appears to imply formation and rupture of a Co–CH_3 bond in the Vitamin B_{12a} prosthetic group. The requirement of a reducing system and the easy alkylation of reduced Vitamin B_{12} by oxidative addition suggest the involvement of a Co^I complex (Vitamin B_{12s}), but the activation of the resulting Co–C bond still remains obscure.[1]

We recently showed that the reversible electron transfer to the cobalt atom[2] and the chemical reduction of the methyl aquo-derivative[3] $[CH_3Co\{(DOH)(DO)pn\}H_2O]^+$ induce carbanionic reactivity of the organic group.

The CH_3–Co^I chelate, regardless of how it is formed, reacts with the parent Co^{III} complex to give compound (III) (reaction 1).

$$[CH_3Co\{(DOH)(DO)pn\}H_2O]^+ (I) + [CH_3Co\{(DOH)(DO)pn\}]^- (II) \rightarrow [(CH_3)_2Co\{(DOH)(DO)pn\}]^0 (III) + [Co^I\{(DOH)(DO)pn\}H_2O]^0 \quad (1)$$

We have now found that (III) can act as a methylating agent (reaction 2).

$$(III) + [M]^+ \rightarrow [CH_3\text{–}M]^0 + (I) \quad (2)$$

Thus, (III) (1 mmol) readily reacts in water–tetrahydrofuran or methanol at room temperature with $[Co^{III}(chel)(H_2O)_2]^+$ (IV) (where chel = the dianions bae, salen, saloph‡),[4] $[Co^{III}\{(DOH)(DO)pn\}(H_2O)_2]^{2+}$, and Vitamin B_{12a} yielding

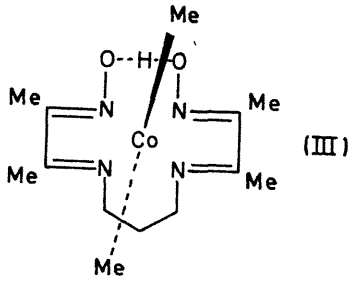
† A systematic name for this ligand is 3,3′-(trimethylenedi-imino)bis(butan-2-one oximato)[$(DOH)_2$pn].

‡ bae = *NN′*-ethylenebis(acetylacetoneiminato); salen = *NN′*-ethylenebis(salicylidene iminato); saloph = *NN′-o*-phenylenebis-(salicylideneiminato).

the corresponding methyl–cobalt derivative and (I) (70—90% yield).

All the reaction products were isolated and identified by comparison of their visible and i.r. spectra with those of authentic samples.[4] The reactions with the {(DOH)(DO)-pn} diaquo-complex and Vitamin B_{12a} were also followed by examining the visible spectra and appeared to be completed in 0·5—1 h, while reactions with the complexes (IV) were too fast to be followed by conventional spectrophotometry. Complex (III) also reacts with H^+ yielding CH_4 and with Ag^+ giving metallic silver together with C_2H_6. Intermediate formation of $AgCH_3$ can be safely assumed and explains C_2H_6 formation.[5]

These results unequivocally prove that (i) electrophilic Co^{III}, both in the model complexes and in Vitamin B_{12a} behaves as a methyl carbanion acceptor from a suitably activated methyl donor. This appears to be a novel route to the methylcobalamin alternative to the oxidative addition of CH_3X to Vitamin B_{12s}; (ii) methyl donor compounds are obtained either by electron transfer to the CH_3–Co^{III} chelate or by co-ordination of another CH_3 group in the *trans*-position to the first one. In the latter case activation of one CH_3 group is exerted by the very strong *trans*-effect of the other. Monomethyl derivatives undergo



(III)

a six–five co-ordination equilibrium which has been suggested for compounds of the Vitamin B_{12} group[6] as an extreme example of the *trans*-effect.

The methylating power of the methyl donor compounds decreases in the order (II) > (III) > (I).

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