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Coenzyme B_{12} model studies : synthesis and axial ligation of alkyl(aquo)cobaloximes with biologically important ligands

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Alkyl(aquo)cobaloximes, $RCo(DH)_2OH_2$ (R = $BrCH_2$, CH_3, C_2H_5) have been prepared. These aquo complexes upon reacting with imidazoles, substituted imidazoles, histamine and histidine give alkyl(ligand)complexes [$RCo(DH)_2L$]. All the ligands are coordinated through endocyclic nitrogen (N_3). The characteristic absorption band of C=N of dimethylglyoximato ligand in the alkyl cobaloximes shifts to lower wave numbers as the donating power of the base ligand increases, where C=N shifts to higher wave numbers when the withdrawing power of alkyl group increases. The formation of alkyl ligand cobaloximes is confirmed by the spectral data.

Vitamin B_{12} and its derivatives are the most biologically important cobalt(III) compounds known and are essential in the nutrition of animals and humans[1]. The equatorial sites of vitamin B_{12} are occupied by a structurally unique corrin ring which is responsible for the exceptionally high lability of the axial sites of vitamin B_{12} compound compared to other Co^{III} complexes with N-donor equatorial ligands. The substitution rate constants for the β site of vitamin B_{12} are much greater than its model compounds.

Co–C bond cleavage occurs considerably faster[2] in the presence of the enzyme. There has been much speculation as to what is responsible for the rate enhancement, and it now appears that a major contribution of Co–C homolysis arises from conformational changes in the enzyme which occurs upon substrate binding leading to a sterically strained adenosyl group and ultimately to cleavage of the Co–C bond[3]. Factors[4] that determine of the rate of Co–C heterolysis are less well understood although it has been suggested that electronic factors are important. Studies using model compounds of vitamin B_{12} have shown than the nature of the ligand *trans* to the Co–C bond can play a role in the kinetic and thermodynamic stability of this bond[4]. Equilibria and kinetics of the reaction of $RCo(DH)_2OH_2$ (R = $BrCH_2$, ICH_2 and $C_6H_5CH_2$) with various aliphatic and aromatic N donor ligands were reported[5,6]. In the present work, we have isolated and characterized various alkyl(ligand)-cobaloximes.

Results and discussion

These alkyl(aquo)cobaloximes are photolabile, particularly in solution. They are soluble in alcohols and DMSO, less so in chloroform or water and virtually insoluble in ether and hydrocarbon solvents. IR spectra of all the complexes contain a weak broad band at 1700–1786 cm^{-1}, attributable to intramolecular hydrogen bridge[7]. This conclusion has been supported by ^1H NMR spectra[8]. The band at 1570 cm^{-1} is attributed to $\nu_{C=N}$ of dimethylglyoxime $(DH)_2$[7,9]. This band is shifted to lower wave number when the fifth ligand changes from SCN to H_2O to IMD. Burger *et al.*[10] reported on the basis of the frequency shifts of the C=N vibration that the lower the C=N vibration frequency, the stronger is the M → N=C donor π-bond. Our results suggest that the increase in electron density on the cobalt causes the increase of back-donation from Co^{III} to nitrogen atoms of dimethylglyoxime.

The peaks around 1235 and 1087 cm^{-1} are assigned to the N–O stretching vibrations[9]. These two bands are shifted to lower wavenumber when the fifth ligand changes in the order, IMD > H_2O, which is in the approximate order of the strength of electron donating power.

All the complexes show the weak broad IR band around 2360 cm^{-1} corresponding to another hydrogen bonded O–H frequency of $(DH)_2$ moiety[8]. The bands at around 1440 cm^{-1} are due to asymmetric and symmetric deformation vibrations, respectively, corresponding to methyl groups in dimethylglyoxime. The bands at 975 and 880 cm^{-1} may be attributed to deformation vibration of OH on bis-(dimethylglyoximato) moiety and the band at around 740 cm^{-1} to C=N–O deformation vibration.

The characteristic absorption due to the axial ligands are also observed. Imidazole derivatives show the weak bands at 3000–3150 cm^{-1} (C–H), 1560–1570 (C=N stretch of the ring) and 750–780 cm^{-1} (C–H deformation of imidazole). The C-H stretching of alkyl group linked to Co^{III} occur at 2930 cm^{-1}. Aquocobaloxime also shows the characteristic

bands due to H_2O molecule coordinating to Co^{III}, the ν_{O-H} at 3072 cm^{-1}. The band at 440–480 cm^{-1} are attributable to Co^{III}–N (of base) stretching vibrations. Appearance of this new band and disappearance of ν_{O-H} at 3072 cm^{-1} indicate coordination of imidazole to Co^{III} of cobaloxime.

As the donating power of the base ligand increases, the bands at ~1770 (O–H····O) and ~1560 cm^{-1} (C=N) shift to lower wavenumber region while bands at ~1230 and 1085 (N–O) and ~515 cm^{-1} (Co–N) shift to higher wavenumber region. These results can be interpreted as follows : the coordination of more electron-donating base to Co^{III} causes the increase in electron density in Co^{III} which facilitates the back-donation from Co^{III} to the nitrogen atoms of dimethylglyoximato ligands resulting in the increase in electron densities in C=N and N–O bonds. The increase in electron density in N–O bonds causes the stronger hydrogen bridges of O–H···O and higher frequency shifts of N–O stretching vibrations.

More electron-withdrawing ligand in the sixth position causes stronger interaction between the central metal and the fifth ligand in the *trans* position, which could be caused by decrease in the Co^{III} → base bond length. This is also supported by our binding studies[6,11]. As electron-donating power of (sixth ligand) alkyl group increases the binding constant decreases. These alkyl(ligand)cobaloximes are non-electrolytes in dilute solution[12] (10^{-3} *M*) of MeOH. The conductance is in the range 10–25 Ω^{-1} cm^2 mol^{-1}. The cobaloximes are diamagnetic, in agreement with the low-spin d^6 configuration of Co^{III} ion.

The electronic spectra of the alkyl(aquo)cobaloximes in MeOH or H_2O will show spin-allowed $^1A_{1g} \rightarrow {}^1T_{1g}$ transition[13] at ~22000 cm^{-1} due to R to Co^{III} σ-donation. This band disappears or drastically decreases in alkyl(ligand)-cobaloximes. The $^1A_{1g} \rightarrow {}^1T_{2g}$ band is masked by the intense charge transfer bands. The charge transfer spectra of the *trans*-[$RCo(DH)_2L$] complexes show a band at 33000 cm^{-1} due to intra-ligand π-π* transition of the coordinated dimethylglyoxime[14]. A band occurring at 27500 cm^{-1} is assigned to the imidazole → Co (LMCT) and that at 33000 cm^{-1} to the $d\pi(Co) \rightarrow \pi^*$ (DH) (MLCT) transition. The σ (DH) → σ* Co (LMCT) is masked by the intense short wavelength bands of alkyl(ligand)cobaloximes[15].

^1H NMR spectra of imidazoles[16] and substituted imidazole complexes are assigned[17]. All the hydrogens are α to the heteroatoms, hence they are shifted downfield. The H-2 is alpha to both nitrogens and is observed farthest downfield[18] (7.40). In the free ligand the H-4 and H-5 are averaged by rapid proton exchange and the H-4 and H-5 are together appear at δ 6.82 with double the intensity. Similarly, in the substituted imidazole in addition to H-2, H-4 and H-5, the substituent signals like C_2-CH_3 (δ 2.20), N_1-CH_3 (3.40) and C_2-CH_2-CH_3 (1.04t, 2.65q) are also observed in the upfield region. However, coordination of imidazole to Co^{III} center of alkylcobaloxime render the H-4 non-equivalent and separate signals are observed at δ 7.22 and 6.95, respectively. In these complexes, the electron donation from, N → Co^{III} leads to a pronounced deshielding of the proton adjacent to the N-3 nitrogen of imidazole (C_2-H, 7.20). H-4 and H-5 are also shifted to downfield but not as much as C_2-H. N_1-H signal of imidazole appears at δ 12.30. The characteristic signals for various substituted imidazoles are assigned. In case of 2-methylimidazole complex, C_2-CH_3 signal is observed at δ 2.38, C_4-H at 7.27 and C_5-H at 6.76. The ^1H NMR spectrum of [$BrCH_2Co(DH)_2$2-EtI[MD] is highly resolved showing a triplet at δ 1.00 corresponding to CH_3 group of CH_2-CH_3 and a quartet at 2.64 corresponding to CH_2 of 2-ethyl group of imidazole ring. Two more signals at downfield corresponding to C_4-H (δ 6.91) and C_5-H (6.62) also observed. ^1H NMR spectra of [$BrCH_2Co(DH)_2$1-MeIMd], [$BrCH_2Co(DH)_2$1,2-DMIMD]; [$CH_3Co(DH)_2L$] and [$C_2H_5Co(DH)_2L$] (where, L = IMD, 1-MeIMD, 1,2-DMIMD, 2-MeIMD or 2-EtIMD), and $RCo(DH)_2L$ (where, L = histamine or histidine and R = CH_2Br, CH_3, C_2H_5) complexes were also recorded.

Experimental

Imidazole, 1-methylimidazole, 2-methylimidazole, 2-ethylimidazole, 1,2-dimethylimidazole (all Across) and histidine, histamine and alkylating agents (Sigma-Aldrich) were used. Alkyl(aquo)cobaloximes were prepared by the reported procedure[19] :

$$Co(OAc)_2.4H_2O + 2(DH)_2 \rightarrow 1/2[Co^{II}(DH)_2OH_2]_2 + 2\ AcOH + 4\ H_2O \quad (1)$$

$$1/2[Co^{II}(DH)_2OH_2]_2 + 1/2\ H^- + 1/2\ H^+ \rightarrow HCo(DH)_2OH_2 \quad (2)$$

$$HCo(DH)_2OH_2 + RI \rightarrow RCo(DH)_2OH_2 + HI \quad (3)$$

(RI = CH_3I, C_2H_5I or Br_2CH_2)

All manipulations were performed under minimal illuminations due to photolability of organocobalt bond[20]. Formation of the product was monitored by TLC. The product migrated as a bright yellow-orange spot while unalkylated cobaloximes remained at the origin. When product formation was virtually complete, the reaction mixture was filtered, reduced the volume of the filtrate, diluted with water (100 ml), allowed to crystallise overnight at 4°. The red crystals were dried *in vacuo* over $CaCl_2$ to obtain alkyl(aquo)cobaloxime (yield ~80%).

Axial ligation of cobaloxime : These complexes were obtained by substitution of H_2O by N donor ligand (L), viz. IMD, 1-MeIMD, 2-MeIMD, 2-EtIMD, 1,2-DMIMD, HIAMN and HISDN :

$$RCo(DH)_2OH_2 + L \rightarrow RCo(DH)_2L + H_2O \quad (4)$$

(R = $BrCH_2$, CH_3 or C_2H_5)

The addition of equimolar or slightly excess of imidazole or substituted imidazoles to $RCo(DH)_2OH_2$ in methanol caused immediate colour change from reddish orange to yellow, indicating the formation of $[RCo(DH)_2L]$ cobaloxime, which was actually isolated in quantitative yields.

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