Hindered Rotation Leading to Nonequivalence in Cobaloximes

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Summary: The cobalt-bound CH_2 becomes diastereotopic and the dmgH methyl protons show nonequivalence at subzero temperature in benzylcobaloximes. The interaction of axial with equatorial ligands causes hindered rotation of the Co−C and/or C−Ph bond and leads to nonequivalence.

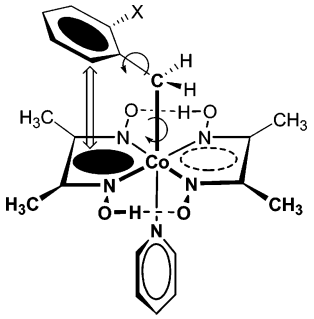
Coenzyme B_{12} has long fascinated chemists due to its complex structure and because it offers the only biological instance (alkylcobalamins) of a stable organometallic bond. Its unique property arises from the different catalytic activity of two different coenzymes. How the Co−C bond is activated toward homolysis or heterolysis is an enduring subject of research.[1] Randaccio has concluded his recent review article "which factors determine the different behavior of MeCbl and AdoCbl in the Co−C bond cleavage process?"[1b] Wider acceptance has recently been accorded to the possibility that a conformational change triggers the Co−C bond cleavage step in catalytic reactions involving coenzyme B_{12}. No direct information, however, exists on the nature of the conformational change. Jensen and Ryde[2] have shown that the Co−C bond cleavage is not the rate-determining step. The destabilization is due to the interaction of substrate with the coenzyme. The maximum distortion found is in the ribose moiety during the Co−C bond rupture, while the adenine moiety is stabilized due to its interaction with the corrin side chain and the enzyme.[2]

Studies on model compounds have continued to complement those on the more complex cobalamin and B_{12}-based proteins. Organocobaloximes, $RCo(dmgH)_2Py$ (*trans*-bis(dimethylglyoximato)pyridine(organo)cobalt(III)), have extensively been used to mimic the vitamin B_{12} coenzyme. Solution studies in alkylcobalamins and in organocobaloximes suggest that the Co−C bond length is responsive to both steric and electronic effects in organocobalt(III) compounds.[3]

Most of the recent studies have focused on the spectral and structural properties of cobaloximes, and NMR, in particular, has been extensively used for this purpose.[4,5] In the majority of the cobaloxime complexes, the dmgH methyl signal appears as a sharp singlet at around 2.0 ppm in the ^{1}H NMR spectra, indicating the chemical equivalence of all four methyl groups. A singlet is also expected on the basis of the mean C_{2v} symmetry of the cobaloxime and fast rotation of the Co−C bond, faster than the NMR time scale.

Nonequivalence of the dmgH methyl, however, has been observed in a few cases, when either of the axial ligands is asymmetric. For example, two sets of dmgH methyl resonances are observed in complexes of the type $Me(CN)CHCo(dmgH)_2Py$ and $MeCo(dmgH)_2NH(Me)CH_2Ph$.[6] A fast rotation of the Co−C bond produces two sets of diastereomers to show the dmgH methyls at a 1:1 ratio.

Scheme 1. Interaction between Axial Benzyl and Dioxime Ring Current



In a report, the hindered rotation of the axial 2-aminopyridine ligand in $(2\text{-}NH_2Py)Co(dmgH)_2CH_2CF_3$, caused by H-bonding of the NH_2 group to O−H···O bridges of the dmgH ligand, resulted in the splitting of the dmgH signals into two separate resonances.[7] Because of the hindered rotation, the Co−C bond dissociation energy (BDE) is found to be significantly smaller than is expected on the basis of its pK_a.[8]

2-Fluorocycloalkylcobaloxime also shows the presence of two sets of dmgH signals in a 1:1 ratio due to hindered rotation of the 2-fluorocyclohexyl ligand around the Co−C bond.[9]

We have recently observed the nonequivalence of dmgH methyl in dicobaloximes of the type $PyCo(dmgH)_2$-[*ortho* (and *meta*)-xylylene]-$Co(dmgH)_2Py$.[10] This is the first example where the cobalt-bound CH_2 behaves as diastereotopic and appears as a doublet of doublets at the freezing (lower) temperature. The nonequivalence could arise by hindered rotation of the Co−C and/or C−Ph bond, but it was attributed to Co−C bond restriction, although no evidence was given in its support.

The crystal structures of benzyl cobaloximes show that the benzyl group always lies over one of the dioxime wings (Supporting Information). The same was observed in $2\text{-}NO_2\text{-}C_6H_3\text{-}[CH_2Co(dmgH)_2Py]_2$.[10b] This poses another question: whether the π-interaction between the benzyl group and the dioxime ring current[4d,5] contributes to the nonequivalence of the dmgH methyl in some way (Scheme 1).

A study of 2-substituted benzyl cobaloximes could, therefore, throw further light on this question. The ^{1}H NMR spectrum of

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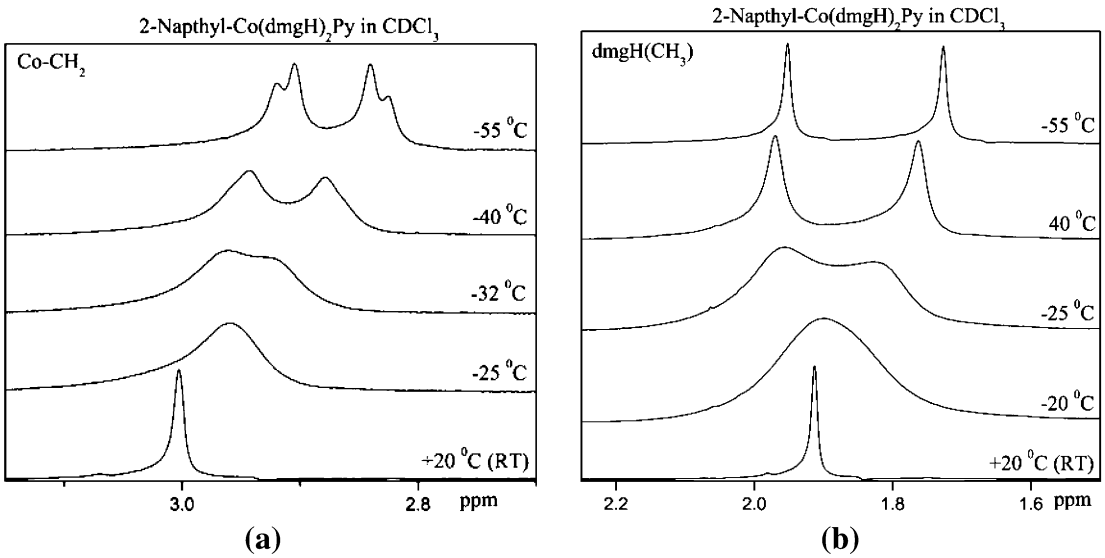

Figure 1. Variable-temperature ^{1}H NMR spectra of the (a) CH_2-Co and (b) dmgH (CH_3) in 2-naphthylCo(dmgH)$_2$Py.

benzyl cobaloxime, $PhCH_2Co(dmgH)_2Py$, in $CDCl_3$ shows a 12H singlet for the dmgH protons at 1.95 ppm even at −55 °C,[10] but it appears as two singlets (1:1) in 2-Br-$C_6H_4CH_2Co(dmgH)_2Py$ at −50 °C (Supporting Information). Also, the cobalt-bound CH_2 splits at −14 °C and appears as a doublet of doublets at lower temperature. The nonequivalence is quite striking especially because there is no chiral group attached to the cobalt center.

To rationalize the results we have considered the following possibilities.

(1) *Rotation about the Co−C bond is slowed while rotation about the C−Ph bond is still fast* (Supporting Information). (a) If the C−Ph bond is aligned along a mirror plane as in Scheme 1 or at right angles along the other mirror plane, or the alignment is averaged along one of these planes by rapid oscillation, then the methyl signals will be split into two signals of equal intensity. Since rotation about the C−Ph bond is rapid, the CH_2 protons will remain equivalent. (b) If the C−Ph bond is aligned off a mirror plane to make the CH_2 protons inequivalent, then four methyl signals of equal intensity should be observed. If the benzyl group preferentially lies over one of the dioxime wings and not over O−H···O, two out of four isomers will be absent and the remaining two isomers are superimposable. Therefore, only two sets of dmgH signal should be observed.

(2) *Rotation about the Co−C bond is fast while rotation about the C−Ph bond is slowed*. For a phenyl substituted in the 2- or 3-position, slow rotation about the C−Ph bond results in the CH_2 protons being inequivalent provided that the plane of the phenyl ring is not aligned with the mirror plane running through the CH_2 group. In the structure in Scheme 1, the phenyl group is at right angles to the plane. The result is that the C−Ph bond induces chirality through atropisomerism. The chirality will do exactly the same as the presence of a chiral atom in Me(CN)-$CHCo(dmgH)_2Py$ and $MeCo(dmgH)_2NH(Me)CH_2Ph$. No barrier to rotation about the Co−C bond is required, but rotamer preference is. The rotamers give inequivalent CH_2 protons and two dmgH methyl signals (Supporting Information Figure S2). However, for this to happen, CH_2 must split before dmgH in order to induce atropisomerism, thus making dmgH inequivalent.

(3) *Rotation about both the Co−C and the C−Ph bond are slowed*. The presence of 2- or 3-substitution on the phenyl ring removes all the symmetry from the molecule. The CH_2 protons are inequivalent and the four methyl groups also become inequivalent. Thus four nonsuperimposable isomers will give four sets of dmgH signals. But in view of the π-interaction as stated in (1), two isomers will not be seen. Hence, only two isomers are possible and will produce two sets of signals.

Let us consider the low-temperature ^{1}H NMR spectra of 2-Br-$C_6H_4CH_2Co(dmgH)_2Py$. The $Co-CH_2$ resonance splits much before the dmgH methyl resonance, which points to slow rotation of the C−Ph bond. 2-$MeC_6H_4CH_2Co(dmgH)_2Py$ shows an opposite trend: two signals (1:1) for dmgH are observed at −20 °C, while CH_2 becomes nonequivalent below −45 °C. That means the Co−C bond rotation is hindered at −20 °C while the C−Ph bond is still rotating at this temperature. A similar trend is observed in the naphthyl cobaloxime: CH_2 splits at −30 °C and dmgH at −23 °C (Figure 1). Since the benzyl group orients over one dioxime wing, can the hindered rotation be partly due to an interaction of aromatic ring π-electrons with the dioxime ring current? Distances of 3.122 Å (C−H···π) and 3.564 Å (π···π) in 2-$MeC_6H_4CH_2Co(dmgH)_2Py$ and 3.133 (3.298) Å (C−H···π) and 3.534 Å (π···π) in 2-naphthyl-CH_2-$Co(dmgH)_2Py$ certainly support this argument (Figure 2).[11] The substituent at the 2-position always orients away from the dioxime and hence cannot have a direct interaction with the dioxime moiety. However it changes the electron density in the benzyl group and hence affects the magnitude of the π···π interaction. It also points out that the C−Ph is only flipping and not fully rotating (360°). Had this been the case, then the C−Ph bond would always be hindered.

The ^{1}H NMR study of 2-Br-$C_6H_4CH_2Co(dmgH)(dpgH)Py$ is much more interesting. The dmgH methyl is a singlet even at −55 °C, but CH_2 starts splitting at −12 °C. The presence of a singlet seems surprising! The case study falls into category 3,

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(11) Crystal data for 2-$MeC_6H_4CH_2Co(dmgH)_2Py$ (CCDC 282006): $C_{21}H_{28}CoN_5O_4$, M_r = 473.14, crystal size 0.27 × 0.22 × 0.18 mm; triclinic; space group $P\bar{1}$; a = 8.147(5) Å, b = 10.658(5) Å, c = 13.759(5) Å; α = 77.278(5)°, β = 76.152(5)°, γ = 70.892(5)°; V = 1082.9(9) Å^3; Z = 2; ρ = 1.452 Mg m^{-3}; T = 293(2) K; reflections measured/unique 2367/2194. Final R = 0.0592 (R_w = 0.1754). Crystal data for 2-naphthyl-$CH_2Co(dmgH)_2Py$ (CCDC 602782): $C_{24}H_{28}Co_1N_5O_4$, M_r = 509.44, crystal size 0.38 × 0.29 × 0.24 mm; triclinic; space group $P\bar{1}$; a = 10.0739(14) Å, b = 11.3738(16) Å, c = 12.1513(17) Å; α = 110.607(2)°, β = 100.011(2)°, γ = 109.289(2)°; V = 1161.8(3) Å^3; Z = 2; ρ = 1.456 Mg m^{-3}; T = 100(2) K; reflections measured/unique 7699/5512. Final R = 0.0897 (R_w = 0.2085).

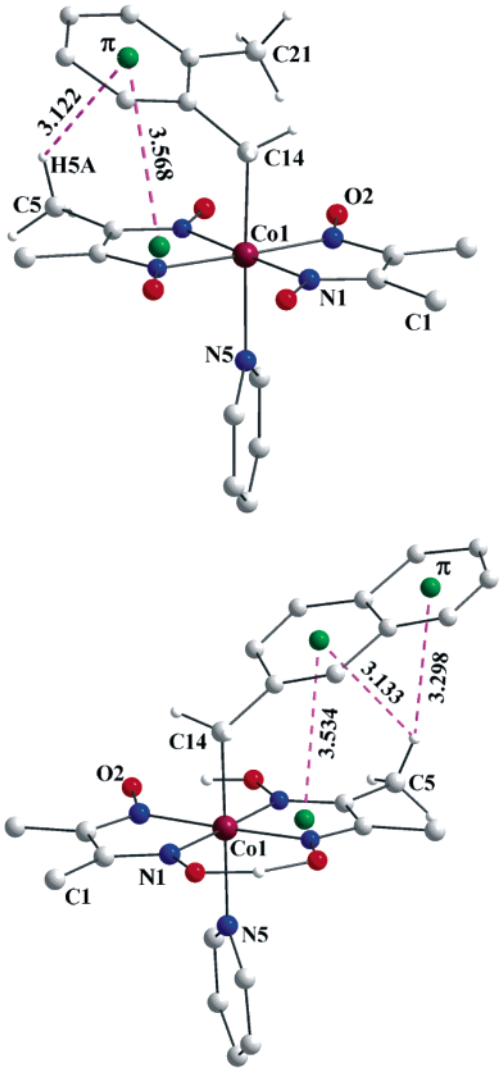

Figure 2. Crystal structure of 2-Me-C_6H_4-$CH_2Co(dmgH)_2Py$ and 2-naphthyl-$Co(dmgH)_2Py$.

where both C−Ph and Co−C bonds are restricted. At a temperature below −12 °C the C−Ph bond is restricted and the atropisomerism induced due to inequivalent CH_2 should result in four nonequivalent isomers; thus four sets of dmgH (1:1:1:1) peaks should appear. The appearance of a singlet means that only one isomer is present, and this is possible only if the Co−C bond is partially or fully restricted (Supporting Information Figure S3).

Interestingly, the nonequivalence in dmgH and CH_2 is not observed in $PhCH_2SO_2Co(dmgH)_2Py$ even at −55 °C. The benzyl group is oriented perpendicular to the dioxime plane and is too far away as observed in the crystal structure of 4-CNC_6H_4-$CH_2SO_2Co(dpgH)_2Py$.[12]

Conclusive evidence of the π-interaction with the dioxime ring current comes from the study in the pyrazine-bridged dicobaloximes.[13] For example the pyrazine-bridged alkyl complex attains the staggered conformation, whereas the benzyl analogue acquires the eclipsed conformation. The same types of π-interaction between the axial and equatorial ligands have been reported by Randaccio et al.[14] in $RCo(DBPh_2)_2B$ and Styne et al.[15] in $LFe^{II}(DBPh_2)_2L'$, where this interaction defines the ligand's orientation.

The weak interactions between axial and equatorial ligands cause restriction of Co−C and/or C−Ph bond rotation and seem to be responsible for the nonequivalence of dmgH methyl and CH_2 protons. It also looks as if such weak interactions (adenine to side chain methyl in the case of AdoCbl) might cause the stabilization of adenine during Co−C bond rupture and thus differentiates it from MeCbl. If the weak π-interaction is important, as the preliminary results show, the nonequivalence of the dmgH or CH_2 groups will occur irrespective of the nature of dioxime, and the extent of nonequivalence will depend on the ring current and puckering in the dioxime. To see the generality of this behavior, one must study more systems such as $ArCH_2Co(dioxime)_2Py$ [dioxime = gH, dpgH, dmestgH]. One must also study cobaloximes that have an axial organic group with a nonaromatic cyclic ring. These studies are currently underway.

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Supporting Information Available: ^1H NMR table, variable-temperature NMR, and supporting figures of restricted rotation and CIF files (also see CCDC numbers 282006, 602782). This material is available free of charge via the Internet at http://pubs.acs.org.

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