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Metal Coordination by Sterically Hindered Heterocyclic Ligands, Including 2-Vinylpyridine, Assessed by Investigation of Cobaloximes

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Structural and ^{1}H NMR data have been obtained for cobaloximes with the bulkiest substituted pyridines reported so far. We have isolated in noncoordinating solvents the complexes $CH_3Co(DH)_2L$ (methylcobaloxime, where DH = the monoanion of dimethylglyoxime) with L = sterically hindered N-donor ligands: quinoline, 4-CH_3quinoline, 2,4-$(CH_3)_2$pyridine, and 2-R-pyridine (R = CH_3, OCH_3, CH_2CH_3, $CH{=}CH_2$). We have found that the Co–N_{ax} bond is very long in the structurally characterized complexes. In particular, $CH_3Co(DH)_2$(4-CH_3quinoline) has a longer Co–N_{ax} bond (2.193(3) Å) than any reported for methylcobaloximes. The main cause of the long bonds is unambiguously identified as the steric bulk of L by the fairly linear relationship found for Co–N_{ax} distance vs CCA (calculated cone angle, CCA, a computed measure of bulk) over an extensive series of methylcobaloximes. The linear relationship improves if L basicity (quantified by pK_a) is taken into account. In anhydrous $CDCl_3$ at 25 °C, all complexes except the 2-aminopyridine adduct exhibit ^{1}H NMR spectra consistent with partial dissociation of L to form the methylcobaloxime dimer. ^{1}H NMR experiments at –20 °C allowed us to assess qualitatively the relative binding ability of L as follows: 2,4-$(CH_3)_2$pyridine > 4-CH_3quinoline ≈ quinoline ≈ 2-CH_3pyridine > 2-CH_3Opyridine > 2-CH_3CH_2pyridine > 2-$CH_2{=}CH$pyridine. The broadness of the ^{1}H NMR signals at 25 °C suggests a similar order for the ligand exchange rate. The lack of dissociation by 2-aminopyridine is attributed to an intramolecular hydrogen bond between the NH_2 group and an oxime O atom. The weaker than expected binding of 2-vinylpyridine relative to the Co–N_{ax} bond length is attributed to rotation of the 2-vinyl group required for this bulky ligand to bind to the metal center, a conclusion supported by pronounced changes in 2-vinylpyridine signals upon coordination.

Introduction

Few bonds in chemistry respond to changes in steric bulk by exhibiting a wide range of lengths. The Co−N_{ax} bond in B_{12} and in B_{12} models, however, is among those few bonds in chemistry that show a large variation in length,[1,2] and thus, the study of these compounds is of fundamental interest. Information gained from studying factors influencing bond length can be used in the design of metal-containing compounds with potential applications in therapeutic agents, in sensors, etc., as well as in attempts to understand B_{12} enzymology.[2]

The trans influence of the axial N-ligand of the B_{12} coenzyme in promoting Co−C bond homolysis in B_{12}-dependent enzymatic processes is a topic of considerable active research.[1,2] In particular, such investigations often focus on how variation in the length of the Co−N_{ax} bond affects this influence. Efforts aimed at assessing this parameter utilize B_{12} holoenzymes (most relevant, but also most difficult and uncertain), cobalamins (the class of molecules to which B_{12} coenzymes belong and the standard against which the lengthening in the holoenzyme must be assessed), and synthetic models (which allow the greatest degree of structural variation and hence the greatest opportunity to elucidate the fundamental factors influencing bond length).

As a consequence of the advances in the field, crystallography has provided well-defined parameters for the axial fragments in a large number of accurate cobalamin structures.[3] In contrast, state-of-the-art determination of enzyme

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structures does not allow similarly accurate characterization of protein-bound cobalamins. Thus, any comparison aimed at establishing which structural changes occur when cobalamin binds the protein is not straightforward. In addition, the dimethylbenzimidazole axial ligand linked to the corrin ring in cobalamins is sometimes displaced by an imidazole from histidine in protein-bound cobalamins. In fact, the reported lengths of the $Co-N_{imidazole}$ bond in base-off/His-on cobalamin bound to methylmalonyl-CoA mutase (2.53 Å)[4] and the $Co-N_{dimethylbenzimidazole}$ bond in diol dehydrase (2.50 Å)[5] may be very long compared to that of the isolated cobalamin (2.237(3) Å).[6] The validity of this lengthening is controversial, and the analysis of the length of the bond was further confused by conclusions reached in EXAFS studies.[7] Kratky et al., on the basis of EXAFS[8] and X-ray data,[9] concluded that the $Co-N_{ax}$ bond is most probably not much longer than the 2.09 Å reported for the isolated imidazolylmethylcobinamide (cobinamides are derived from cobalamins by removal of the dimethylbenzimidazole loop).[10]

Studies on the B_{12} model $[CH_3Co((DO)(DOH)pn)(1,2\text{-}Me_2Im)]^+$ [((DO)(DOH)pn) = N^2,$N^{2'}$-propane-1,3-diylbis-(2,3-butanedione-2-imine-3-oxime), 1,2-Me_2Im = 1,2-dimethylimidazole)] reveal a significant difference between the two $Co-N_{ax}-C$ angles (unsymmetric N_{ax} coordination) and a lengthening of the $Co-N_{ax}$ distance by ~0.06 Å with respect to that in the $[CH_3Co((DO)(DOH)pn)(1\text{-MeIm})]^+$ (1-MeIm = 1-methylimidazole) analogue, which has two similar $Co-N_{ax}-C$ angles (symmetric N_{ax} coordination).[11] The lengthening and the unsymmetric N_{ax} coordination, reflecting the lopsided nature of the bulkier ligands, will decrease the overlap of the ligand and metal orbitals. These considerations suggest that unsymmetric N_{ax} coordination could contribute to the lengthening of the $Co-N_{ax}$ bond in the protein-bound cobalamin with respect to that of free cobalamin. For example, the two $Co-N_{ax}-C$ angles, which are approximately equal in imidazolylmethylcobinamide (symmetric N_{ax} coordination), differ by more than 15° (unsymmetric N_{ax} coordination) in the base-off/His-on cobalamin bound to the proteins.[4,9]

Thus, both in models and in cobalamins, long bonds and unsymmetric N_{ax} coordination may occur but the $Co-N_{ax}$ bond is typically longer in cobalamins than in models. The latter observation, together with the clear relationship of increasing Co−C bond homolysis rate with increasing $Co-N_{ax}$ bond length in organocobalt B_{12} model cobaloximes ($RCo(DH)_2L$, where DH = the monoanion of dimethylglyoxime, L = axial ligand),[12] led to the hypothesis that control of this distance may be crucial in biological processes and that long bonds promote homolysis.[1] Deconvoluting the contributions to the lengthening of the $Co-N_{ax}$ bond requires the study of well-defined versatile B_{12} model series amenable to systematic variation by judicious increase in bulk.

The approach of using bulky L is hampered by the low formation constants resulting from steric effects. An attempt to study in solution long $Co-N_{ax}$ fragments of some adducts of the B_{12} cobinamide model by EPR and visible spectroscopy was made in ethylene glycol solution by addition of a large excess of lopsided, bulky N-donor planar ligands.[13] However, no binding of ligands such as 2-picoline was observed,[13] although these adducts, which should have a particularly long bond, had been reported to form.[14] Because the more recent finding that 2-picoline did not bind could be attributed to the steric hindrance of the equatorial cobinamide macrocycle and its side chains, we directed our attention to the methylcobaloxime B_{12} model,[15] which has a less bulky equatorial moiety. Although some properties of cobaloximes are known to have a dependence on axial ligands linearly related to the dependence of cobalamins on axial ligands,[16] cobaloximes are somewhat electron-deficient compared to cobalamins and have higher axial ligand binding constants. Also, some examples of cobaloximes with bulky L (e.g., 2-picoline) are known.[17] Here we report the synthesis and characterization in solution of the methylcobaloximes with the following lopsided, bulky N-donor ligands: quinoline, 4-lepidine (4-methylquinoline), 2-picoline (2-methylpyridine), 2,4-lutidine (2,4-dimethylpyridine), 2-vinylpyridine, 2-methoxypyridine, and 2-ethylpyridine. The structural characterization by crystallography of the adducts with 4-lepidine, 2-picoline, 2-vinylpyridine, and 2-aminopyridine is presented. The last complex is a known compound, but our previous attempts to obtain single crystals for crystallographic experiments were not successful.

Experimental Section

Materials. $[CH_3Co(DH)_2]_2$[18] and $CH_3Co(DH)_2H_2O$[19] were prepared as previously reported. N-donor ligands (except 2-vinylpyridine, which was purchased from Lancaster), $S(CH_3)_2$, and

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anhydrous CH_2Cl_2 and heptane were obtained from Aldrich and used without further purification. Deuterated solvents were obtained from Isotech. For new compounds, the results of elemental analyses, performed by Atlantic Microlabs, Atlanta, GA, are tabulated in the Supporting Information.

Syntheses. $CH_3Co(DH)_2S(CH_3)_2$. A synthesis for this complex has been described previously.[19] In our alternative procedure, a solution of $CH_3Co(DH)_2H_2O$ (0.75 g, 2.33 mmol) in MeOH (10 mL) was treated with 3 equiv of $S(CH_3)_2$ (0.43 g, 6.99 mmol). The solution was then filtered before adding water (5 mL) and cooling the reaction mixture (−20 °C) in a beaker covered with Parafilm to prevent evaporation of $S(CH_3)_2$. After 10 days, orange crystals were collected by filtration and washed with cold water, yield 0.55 g (64%). Analytical data (C, H, N) for this known compound were satisfactory. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.07 (s, 3H, C*H*$_3$–Co), 1.80 (s, 6H, S(C*H*$_3$)$_2$), 2.22 (s, 12H, C*H*$_3$C=N), 17.96 (s, 1H, O−*H*−O).

$CH_3Co(DH)_2L$ (L = Quinoline, 4-Lepidine, 2,4-Lutidine, 2-Picoline). A solution of $CH_3Co(DH)_2S(CH_3)_2$ (0.1 g, 0.273 mmol) in CH_2Cl_2 (15 mL) was treated with 10 equiv of L. After filtration and the addition of heptane (2 mL), this solution was set aside in the hood for crystallization. Partial evaporation of the solution produced a dark red solid that was collected by filtration in yields over 50%. The complexes were generally not recrystallized because they were very hygroscopic. For L = 4-lepidine and 2-picoline, crystals suitable for X-ray analysis were obtained from the reaction mixture.

$CH_3Co(DH)_2L$ (L = 2-Vinylpyridine, 2-Ethylpyridine, 2-Methoxypyridine). The typical preparation carried out in a drybox involved treating a solution of $[CH_3Co(DH)_2]_2$ (0.15 g, 0.246 mmol) in dry CH_2Cl_2 (15 mL) with 10 equiv of L. The solution was filtered, and 1.5 mL of dry heptane was added. After partial evaporation of the solution, a dark red solid was collected by filtration in >50% yield. The complexes were not recrystallized because they were very hygroscopic. For L = 2-vinylpyridine, crystals suitable for X-ray analysis were obtained from the reaction mixture.

$CH_3Co(DH)_2$(2-aminopyridine). An alternative synthesis has been described previously.[17] Our synthesis was carried out in a drybox by treating a solution of $[CH_3Co(DH)_2]_2$ (0.15 g, 0.246 mmol) in dry CH_2Cl_2 (20 mL) with 2.5 equiv of 2-aminopyridine (0.12 g, 1.24 mmol). The solution was filtered and set aside for crystallization. Partial evaporation of the solvent produced an orange powder that was collected and washed with a minimum of CH_2Cl_2. Analytical data (C, H, N) for this known compound were satisfactory. Orange crystals suitable for X-ray analysis were obtained in the drybox through partial evaporation of a dry EtOH/cyclohexane (1:3) solution.

NMR Spectroscopy. ^{1}H NMR spectra referenced to Me_4Si (TMS) were recorded on Varian Mercury 300 (300 MHz) and Varian Unity 600 (600 MHz) spectrometers. Samples were prepared in anhydrous $CDCl_3$, unless otherwise stated. ^{1}H NMR data appear in Tables 3 and 4 and in Supporting Information.

X-ray Crystallography. The X-ray structural analyses were performed by the X-ray Crystallographic Laboratory at Emory University, Atlanta, GA. The crystals of $CH_3Co(DH)_2L$ (L = 4-lepidine, 2-picoline, 2-vinylpyridine, 2-aminopyridine) were coated with Paratone N oil, suspended in a small fiber loop, and placed in a cooled nitrogen gas stream at 100 K on a Bruker D8 SMART APEX CCD sealed-tube diffractometer with graphite-monochromated Mo Kα (0.710 73 Å) radiation. A hemisphere of data was collected by using a series of combinations of φ and ω scans with 10-s frame exposure and 0.3° frame width. Data collections, indexing, and initial cell refinements were all handled by using SMART[20] software. Frame integration and final cell refinements were carried out by using SAINT[20] software. The final cell parameters were determined by least-squares refinement on 8192 reflections for $CH_3Co(DH)_2L$ (L = 4-lepidine, 2-picoline, 2-vinylpyridine) and 2580 reflections for $CH_3Co(DH)_2$(2-aminopyridine). The SADABS[19] program was used to carry out absorption corrections. The structures were solved by direct methods and difference Fourier techniques (SHELXTL, V5.10).[20] Hydrogen atoms were placed at their expected chemical positions and included in the final cycles of least-squares refinement with isotropic thermal factors related to the atom ridden upon. The C−H distances were fixed at 0.93 Å (aromatic), 0.98 Å (methine), 0.97 Å (methylene), or 0.96 Å (methyl). All non-hydrogen atoms were refined anisotropically. Scattering factors and anomalous dispersion corrections are taken from ref 20. Structure solution, refinement, graphics and generation of publication materials were performed by using SHELXTL, V5.10 software. Crystal data and refinement parameters are presented in Table 1.

Cone Angle Calculations. All calculations were performed on a Pentium Pro PC. The calculation of the cone angles of the ligands N-coordinated to an isolated atom of cobalt at the fixed distance of 2.0 Å was carried out by a local program[21] according to Immirzi's algorithm,[22] as modified in ref 23. The input coordinate files of the Co−L groups were obtained by the Hyperchem 6.03[24] molecular modeling package using the AMBER force field.

Results and Discussion

Syntheses. Methylcobaloximes are generally synthesized from $CH_3Co(DH)_2H_2O$ by substitution of water in the presence of an excess of L (L = N-donor neutral ligand) in methanol solution[25] or in CH_2Cl_2 suspension.[17] Similar attempts to obtain derivatives with L = quinoline, 4-lepidine, 2-picoline, 2,4-lutidine, 2-vinylpyridine, 2-ethylpyridine, or 2-methoxypyridine were unsuccessful, because these ligands are weaker than water. However, complexes with L = quinoline, 4-lepidine, 2-picoline, and 2,4-lutidine could be synthesized easily from $CH_3Co(DH)_2S(CH_3)_2$ in noncoordinating CH_2Cl_2/heptane solution. Indeed, although $S(CH_3)_2$ is a stronger ligand than water,[26] its high volatility causes rapid escape from solution and promotes the substitution reaction, as previously described.[19,26] In turn, $CH_3Co(DH)_2S$-

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Table 1. Selected Crystal Data and Structure Refinements for $CH_3Co(DH)_2L$ (L = 4-Lepidine, 2-Picoline, 2-Vinylpyridine, 2-Aminopyridine)

param	4-lepidine	2-picoline	2-vinylpyridine	2-aminopyridine
empirical formula	$C_{19}H_{26}CoN_5O_4$	$C_{15}H_{24}CoN_5O_4$	$C_{16}H_{24}CoN_5O_4$	$C_{14}H_{23}CoN_6O_4$
fw	447.38	397.32	409.33	398.31
wavelength, Å	0.710 73	0.710 73	0.710 73	0.710 73
cryst system	triclinic	triclinic	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a, Å	8.2978(13)	9.0887(13)	8.879(3)	9.1131(12)
b, Å	8.9555(14)	9.2319(13)	9.144(3)	9.3076(12)
c, Å	14.710(2)	11.9708(17)	12.123(4)	11.4675(15)
α, deg	85.548(3)	86.525(3)	91.552(6)	86.492(3)
β, deg	78.537(3)	88.950(3)	91.931(7)	88.428(3)
γ, deg	67.784(3)	61.918(3)	116.729(5)	61.207(3)
V, Å^3	991.8(3)	884.5(2)	877.7(5)	850.83(19)
Z	2	2	2	2
d(calcd), Mg/m^3	1.498	1.492	1.549	1.555
μ, mm^{-1}	0.902	1.001	1.011	1.042
F(000)	468	416	428	416
cryst dimens, mm	0.23 × 0.075 × 0.070	0.29 × 0.14 × 0.10	0.41 × 0.33 × 0.02	0.22 × 0.08 × 0.06
N indep reflcns, R(int)	6555, R(int) = 0.0509	5777, R(int) = 0.0287	5686, R(int) = 0.0598	5615, R(int) = 0.0329
R1 ($I > 2\sigma(I)$)	0.0710	0.0616	0.0834	0.0802
wR2 ($I > 2\sigma(I)$)	0.1116	0.1285	0.1930	0.1454
R1	0.1483	0.1103	0.1690	0.1146
wR2	0.1291	0.1406	0.2256	0.1575

$(CH_3)_2$ was obtained from $CH_3Co(DH)_2H_2O$ by substitution of H_2O with $S(CH_3)_2$ at low temperature. For weaker L (L = 2-vinylpyridine, 2-methoxypyridine, and 2-ethylpyridine), the $[CH_3Co(DH)_2]_2$ dimer was used as starting reagent, and the reactions were performed in a drybox by using anhydrous CH_2Cl_2 and heptane. In $[CH_3Co(DH)_2]_2$ the oxime oxygen of one methylcobaloxime moiety axially binds the Co of the other moiety, and as previously reported, even very weak ligands can disrupt this bond to form adducts.[18] This method was also used for L = 2-aminopyridine, even though this is a relatively strong ligand (see below).

All the complexes (except that with L = 2-aminopyridine) are water sensitive, both in solution and in the solid state. Thus, if they are dissolved in chloroform not previously dried, the aqua complex precipitates immediately. In particular, the low carbon content found in the elemental analyses of $CH_3Co(DH)_2$(2-ethylpyridine) and $CH_3Co(DH)_2$-(2-vinylpyridine) could be explained by their water sensitivity in the solid state. Indeed, the ^{1}H NMR spectrum at 300 MHz in DMSO-d_6 (to prevent the precipitation of aqua derivative) of a 2-month-old sample of $CH_3Co(DH)_2$(2-ethylpyridine) showed complete replacement of L by H_2O. A 4-day-old sample of the same complex already showed a L/Co ratio significantly less than 1. $CH_3Co(DH)_2$(2-vinylpyridine) behaved similarly. The 2-aminopyridine complex exhibited no water sensitivity, probably because of stabilization due to hydrogen bonding between a 2-amino group hydrogen and the nearby oxime oxygen.[17]

X-ray Structures. ORTEP drawings and numbering schemes for the four $CH_3Co(DH)_2L$ complexes, where L = 4-lepidine, 2-picoline, 2-vinylpyridine, and 2-aminopyridine, are given in Figures 1 and 2. Selected bond lengths and angles and the displacements, *d*, of Co out of the equatorial coordination plane (toward L) for these complexes are reported in Table 2, together with those of some other methyl- and isopropylcobaloximes containing planar N-ligands.

For the four complexes, the equatorial moiety is very similar, and bond lengths and angles do not differ significantly from those reported for cobaloximes bearing other L ligands.[27,28] The axial ligands adopt the so-called orientation A,[15] i.e., the plane containing L nearly bisects the oxime O−H−O bridges, which is typical for cobaloximes with L = a planar N-donor ligand, such as pyridine or Me_3Bzm (Me_3Bzm = 1,5,6-trimethylbenzimidazole). The Co−CH_3 distances, which range from 1.986(4) to 1.995(3) Å for L = 4-lepidine, 2-picoline, and 2-aminopyridine, do not differ within experimental error from those reported for other methylcobaloximes with N-containing ligands, some of which are listed in Table 2. The increase in bulk of the L ligand (from L = H_2O to L = PPh_3) has been shown to increase the trans Co−C distance by about 0.1 Å when R is a bulky group, such as adamantyl, whereas little lengthening of the Co−C bond distance occurs in the corresponding methyl derivatives (<0.04 Å).[15,29] Therefore, for the complexes in Table 2, it is not surprising that the Co−C distances do not change significantly when R = methyl but increase slightly with the bulk of L when R = isopropyl. We cannot explain the value of 1.953(5) Å for the Co−CH_3 bond in $CH_3Co(DH)_2$(2-vinylpyridine). The significant shortness of this bond length is unprecedented for a Co−CH_3 bond in methylcobaloximes. This value is very close to the range (1.945(5)−1.958(8) Å) reported for a series of vinyl- and chlorovinylcobaloximes,[30] even though the methyl carbon is sp^3 hybridized and the vinyl carbon is sp^2 hybridized.

In contrast to the insensitivity of the Co−CH_3 distances, the Co−N_{ax} distances are very long (with respect to the pyridine and imidazole cobaloximes) and are greatly affected by the introduction of a pyridine ortho substituent or by the presence of a condensed ring; similar trends have been described for *i*-$C_3H_7Co(DH)_2$(2-aminopyridine)[17] and in some

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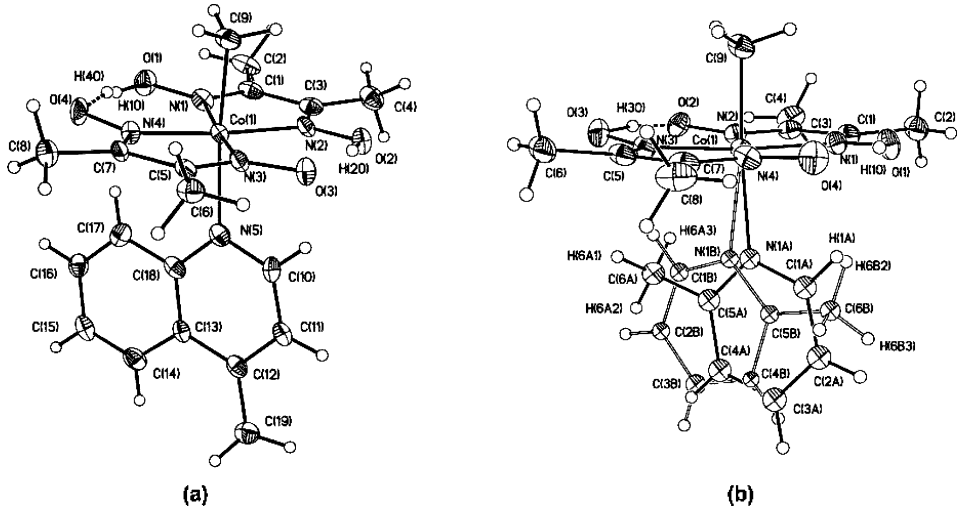

Figure 1. ORTEP drawings for (a) $CH_3Co(DH)_2$(4-lepidine) and (b) $CH_3Co(DH)_2$(2-picoline), in which the conformations with occupancy factors 0.72 and 0.28 are represented with black and gray bonds, respectively. In (a) both positions (half-occupancy each) of the disordered oxime H bridge are shown.

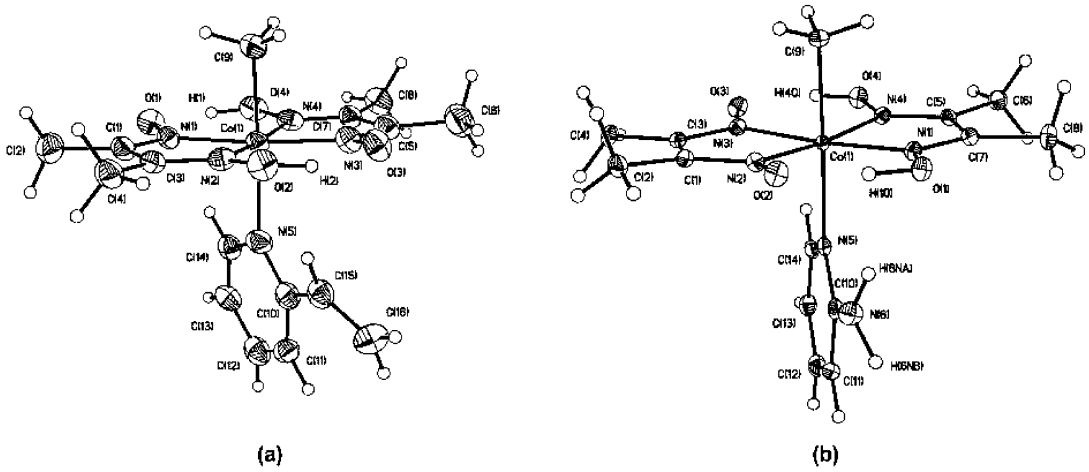

Figure 2. ORTEP drawings for (a) $CH_3Co(DH)_2$(2-vinylpyridine) and (b) $CH_3Co(DH)_2$(2-aminopyridine).

Table 2. Selected Bond Lengths (Å), Angles (deg), and Calculated Cone Angles (CCA) for $CH_3Co(DH)_2L$ and i-$C_3H_7Co(DH)_2L$ (Displacement of Co Out of the Equatorial Coordination Plane, d (Å), toward L)

L	Co−C_{ax}	Co−N_{ax}	α_1[a]	α_2[a]	d (Å)	CCA	ref
			$R_{ax} = CH_3$				
imidazole	1.985(3)	2.019(3)	129.7(1)	124.8(1)	0.03	95.5	28
Me_3Bzm	1.989(2)	2.060(2)	133.6(1)	121.5(2)	0.06	101.2	32
pyridine	1.998(5)	2.068(3)	122.3(3)	119.7(4)	0.04	101.1	27
1,2-Me_2Im	2.001(2)	2.086(1)	134.9(1)	119.1(1)	0.06	108.6	31
2-aminopyridine	1.986(4)	2.121(3)	128.2(3)	115.5(2)	0.09	110.7	this work
2-picoline[b]	1.988(3)	2.142(4)	128.6(3)	113.4(3)	0.09	112.8	this work
2-vinylpyridine	1.953(5)	2.143(4)	131.3(4)	113.0(3)	0.08	113.8	this work
4-lepidine	1.995(3)	2.193(3)	130.3(2)	113.9(2)	0.09	113.9	this work
			$R_{ax} = i$-C_3H_7				
Me_3Bzm	2.076(2)	2.097(2)	134.4(1)	120.9(2)	0.06	101.2	32
pyridine	2.085(3)	2.099(2)	121.2(2)	120.8(2)	0.02	101.1	27
1,2-Me_2Im	2.096(3)	2.121(2)	134.0(2)	120.4(2)	0.04	108.6	31
2-aminopyridine	2.097(6)	2.194(4)	129.7(4)	115.7(3)	0.04	110.7	17

[a] See Figure 3a for definition of α_1 and α_2 angles. [b] Data referring to orientation of coordinated 2-picoline with occupancy factor 0.72 (see Figure 1b).

$RCo(DH)_2L$ complexes with L = 1,2-Me_2Im[31] and Me_3Bzm[32] (see also Table 2). As already observed for other lopsided ligands,[31,32] the α_1 and α_2 angles (Figure 3a) around the axial N donor differ noticeably (∼13−18°) in $CH_3Co(DH)_2L$, where L = 4-lepidine, 2-picoline, 2-vinylpyridine, and 2-aminopyridine, whereas these angles are similar in imidazole and pyridine cobaloximes (Table 2 and Figure 3a). As mentioned above, a protein-induced unsymmetric N-

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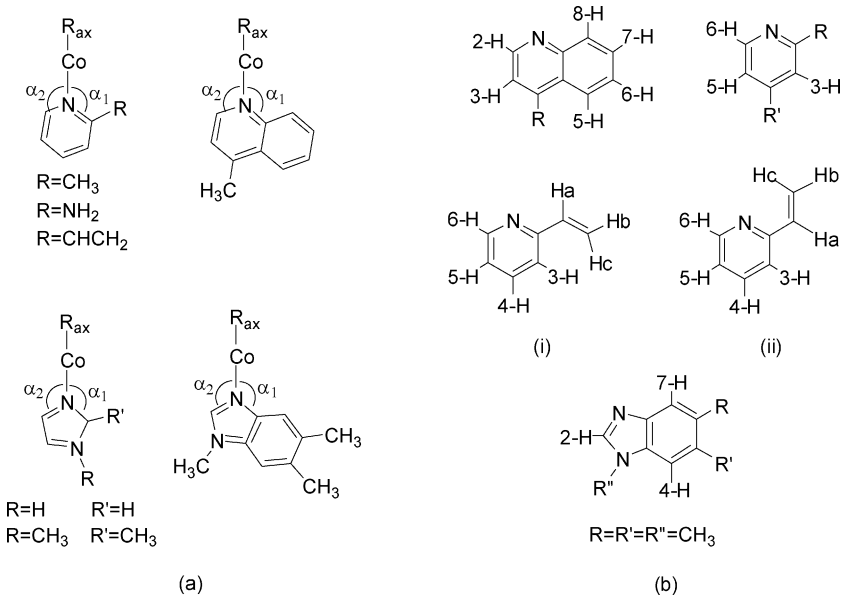

Figure 3. (a) α_1 and α_2 angles for the L ligands in $R_{ax}Co(DH)_2L$ complexes with $R_{ax} = CH_3$ and i-C_3H_7. (b) Numbering scheme of the L H atoms in the $CH_3Co(DH)_2L$ complexes reported in this work.

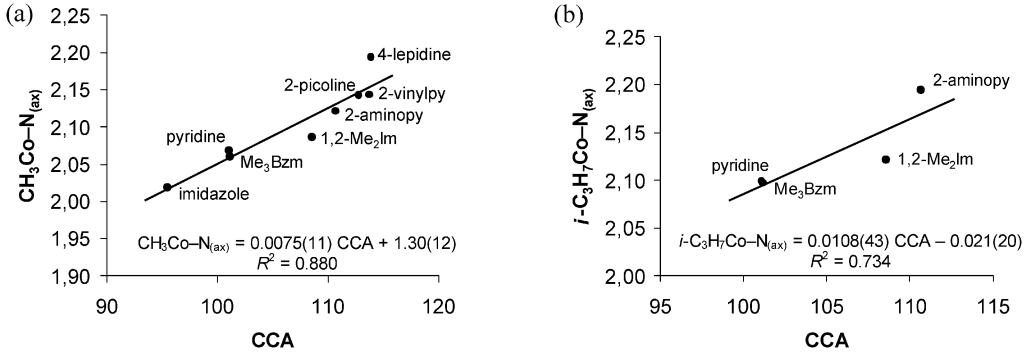

Figure 4. Plot of (a) the CH_3Co-N_{ax} bond length (Å) vs CCA (deg) and (b) the i-$C_3H_7Co-N_{ax}$ (Å) bond length vs CCA (deg) for the complexes reported in Table 2 (2-vinylpy = 2-vinylpyridine, 2-aminopy = 2-aminopyridine). The fitting equation and R^2 values are reported.

coordination of the histidine imidazole may contribute to the lengthening in the $Co-N_{ax}$ in base-off/His-on B_{12} enzymes,[4,9] although there is some controversy about the values. Our more precise values in Table 2 do not show a significant relationship between $Co-N_{ax}$ distance and the magnitude of the difference in $Co-N_{ax}-C$ bond angles, suggesting that the effect of unsymmetric N-coordination may be small. More data, however, are needed before a definitive conclusion can be reached.

Plots of the CH_3Co-N_{ax} and of i-$C_3H_7Co-N_{ax}$ distances against the L pK_a's do not exhibit a linear trend (R^2 values of 0.208 and 0.085, respectively). In contrast, inspection of Table 2 clearly shows that the $Co-N_{ax}$ distances increase with increasing bulk of the neutral L ligand for both the methyl and isopropyl series. In fact, when the $Co-N_{ax}$ distances in methyl derivatives (spanning ~0.2 Å) are plotted against the calculated cone angles (CCA) of L (see Experimental Section), the fairly linear relationship ($R^2 = 0.880$) of Figure 4a is obtained. However, the linear relationship of $Co-N_{ax}$ distances vs CCA and a measure of basicity, pK_a, of the ligands yields $R^2 = 0.914$ for the following equation:

$$Co-N_{ax} = 0.0070(10)(CCA) - 0.011(8)(pK_a) + 1.42(14)$$

The slight but significant improvement in R^2 suggests that an increase in the basicity of L shortens the $Co-N_{ax}$ bond slightly.

Similar results were obtained for the less numerous isopropyl series, for which the linear relationship between the $Co-N_{ax}$ distance and the CCA gives $R^2 = 0.734$ (Figure 4b). The fit improved to $R^2 = 0.873$ when the contribution of basicity was included with the following equation:

$$Co-N_{ax} = 0.0108(43)(CCA) - 0.021(20)(pK_a) + 1.12(38)$$

This good fit indicates that the main influence on the lengthening of the $Co-N_{ax}$ bond is bulk (parametrized by using CCA) and that basicity (parametrized by using pK_a) has a slight but detectable contribution opposing the influence of the bulk and tending to shorten the $Co-N_{ax}$ bond. Finally, when the $Co-N_{ax}$ distance in isopropyl complexes is plotted against those in the corresponding methyl complexes, the good linear relationship ($R^2 = 0.966$) of Figure 5 is obtained. The slope of the line (1.65), significantly larger than unity, is clear evidence that the steric trans influence exerted by the bulkier isopropyl group is greater than that of the methyl group. Because significantly smaller d values in the isopropyl derivatives than those in the methyl analogues (Table 2) are

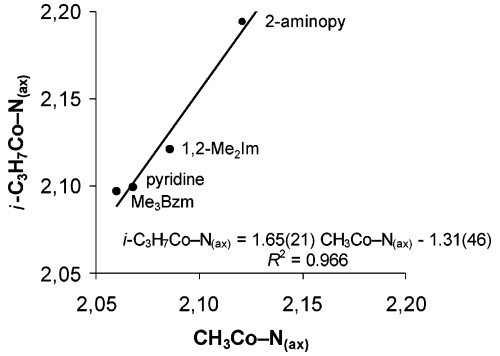

Figure 5. Plot of *i*-$C_3H_7Co-N_{ax}$ (Å) bond length vs CH_3Co-N_{ax} (Å) bond length. The fitting equation and R^2 values are reported.

observed, the latter comparison can be interpreted in terms of the greater bulk of isopropyl vs methyl. For the same L ligand, the bulk of isopropyl causes a decrease of the displacement of Co toward L in isopropylcobaloximes as compared with methylcobaloximes. Consequently, a further lengthening of the $Co-N_{ax}$ bond (in addition to lengthening due to the electronic trans influence) occurs to alleviate the steric interactions between L and the equatorial ligands. The observation that the $Co-N_{ax}$ distance (2.193(3) Å) in $CH_3Co(DH)_2$(4-lepidine) is essentially equal to that found for *i*-$C_3H_7Co(DH)_2$(2-aminopyridine) (2.194(4) Å)[17] suggests that the lengthening of the axial Co−N bond due to the bulk of L (steric cis influence), greater in $CH_3Co(DH)_2$(4-lepidine) than in $CH_3Co(DH)_2$(2-aminopyridine), is "fortuitously" compensated by the lengthening due to the electronic trans influence of the *i*-C_3H_7 group being greater than that of the CH_3 group.

^{1}H NMR Spectroscopy. We focus on the ^{1}H NMR spectra of $CH_3Co(DH)_2L$ with weakly bound bulky L (Supporting Information and top seven entries in Tables 3 and 4), recorded in anhydrous $CDCl_3$ to avoid substitution of L by water. These compounds show common features and are compared to three compounds with tightly bound L (bottom three entries in Tables 3 and 4). The spectrum of $CH_3Co(DH)_2$(2-ethylpyridine) (Figure 6A(a),B(a),C(a)) is shown as an example of the room temperature spectrum of the seven compounds. At room temperature, most of the signals are broad and partially overlapped owing to the equilibrium.

$$[CH_3Co(DH)_2]_2 + 2L \leftrightarrows 2CH_3Co(DH)_2L$$

Although the 25.0 °C spectra provide some qualitative rate information not readily available at lower temperature (see below), we first discuss the results at −20.0 °C, a temperature at which the sharper signals allow us to determine the chemical shifts accurately (Tables 3 and 4; also see Figure 6A(b),B(b),C(b) for spectra of the representative compound, $CH_3Co(DH)_2$(2-ethylpyridine)). The singlet due to the equatorial methyls of $CH_3Co(DH)_2L$ (2.06−2.14 ppm range) and the four singlets arising from the equatorial methyls of the dimer are well resolved. Also the signals arising from the oxime O−H−O bridge and from the axial methyl both in $CH_3Co(DH)_2L$ (18.20−18.46 and 0.78−0.93 ppm, respectively) and in the dimer are sharp. The simple spectra of $CH_3Co(DH)_2L$ indicate that the L rotates rapidly around the Co−N bond. This finding is consistent with previous studies indicating that the rotation barriers are low.[33] However, it seems likely that the planar L ligand will spend more of its time in the most energetically favorable orientation.

Table 3. ^{1}H NMR Chemical Shifts for the $CH_3Co(DH)_2$ Moiety of Complexes with Various L Ligands (600 MHz, Anhydrous $CDCl_3$, δ in ppm from TMS)

L	CH_3–Co (s, 3H)	CH_3–C=N (s, 12H)	O−*H*−O (s, 2H)
quinoline[a]	0.93	2.07	18.46
4-lepidine[a]	0.90	2.06	18.45
2-picoline[a]	0.81	2.14	18.28
2,4-lutidine[a]	0.78	2.13	18.28
2-vinylpyridine[a]	0.83	2.11	18.20
2-methoxypyridine[a]	0.79	2.10	18.33
2-ethylpyridine[a]	0.82	2.13	18.27
2-aminopyridine[b,c]	0.85	2.14	17.79
pyridine[b,d]	0.82	2.13	18.29
Me_3Bzm[b,e]	0.83	2.10	18.58

[a] Spectrum obtained at −20 °C. [b] Spectrum obtained at room temperature. [c] Spectrum obtained at 300 MHz. [d] Reference 42. [e] Reference 32.

Some of the NMR shifts can be understood by recognizing that the plane of L is in orientation A in the lowest energy position of L, as shown in Figures 1 and 2. In orientation A, the magnetic anisotropy of L should cause shielding of equatorial methyl groups and deshielding of the O−H−O groups. The equatorial methyl singlet is slightly upfield (0.03−0.08 ppm) for methylcobaloximes with L = quinoline and 4-lepidine in comparison with that in complexes with L = 2-subtituted pyridines. The O−H−O singlet is slightly downfield in methylcobaloximes with L = quinoline and 4-lepidine (0.12−0.26 ppm) in comparison with that in $CH_3Co(DH)_2L$ with L = 2-substituted pyridines. These upfield/downfield shifts could be explained by postulating that the quinoline-type ligands spend more time in orientation A in comparison with 2-substituted pyridines. Also, quinoline-type ligands are probably more anisotropic than 2-substituted pyridines. Another interesting shift difference is found for the axial methyl resonances of $CH_3Co(DH)_2L$; the shifts for the complexes with the quinoline-type ligands are 0.10−0.22 ppm downfield from those for the complexes with 2-substituted pyridines.

The axial methyl signal shifts upfield with greater basicity when L = 4-substituted pyridines; comparison of the shifts of a series of such compounds (data not shown) to those observed here (Table 3) reveals that for bulky L the shifts are more downfield than would be expected from the basicity of L. This finding is consistent with the expected weaker electron donation of the bulky L resulting from the longer $Co-N_{ax}$ bond. The relatively greater downfield shift of the resonances of the axial methyl of $CH_3Co(DH)_2L$ with L = quinoline and 4-lepidine thus reflects both the lower basicity and the relatively high bulk of these ligands.

Because at −20.0 °C we can observe and assign signals of the free and the bound ligand (cf. Figure 3b for L numbering scheme), the shift changes upon coordination

(33) (a) Marzilli, L. G.; Summers, M. F.; Zangrando, E.; Bresciani-Pahor, N.; Randaccio, L. *J. Am. Chem. Soc.* **1986**, 4830−4838 and references therein. (b) Geremia, S.; Calligaris, M.; Randaccio, L. *Eur. J. Inorg. Chem.* **1999**, 1981−1992.

Table 4. ^{1}H NMR Chemical Shifts for L in Various $CH_3Co(DH)_2L$ (600 MHz, Anhydrous $CDCl_3$, δ in ppm from TMS)[a]

L	2-*H*	3-*H*	4-*H*	5-*H*	6-*H*	7-*H*	8-*H*	C*H*$_3$
quinoline[b]	9.22 (d)	7.40 (t)	8.18 (d)	7.79 (d)	7.55 (t)	7.79 (t)	8.73 (d)	
4-lepidine[b]	9.06 (d)	7.23 (d)		7.93 (d)	7.56 (t)	7.78 (t)	8.69 (d)	2.66 (s)

L	6-*H*	5-*H*	R = 4-*H*	3-*H*	R = C*H*$_3$		
2-picoline[b]	8.74 (d)	7.09 (t)	7.54 (t)	7.08 (d)	2.52 (s)		
					R = C*H*$_3$	R′ = C*H*$_3$	
2,4-lutidine[b]	8.56 (d)	6.89 (d)	-	6.89 (s)	2.47 (s)	2.23 (s)	
					vinyl *H*a	*H*b	*H*c
2-vinylpyridine[b]	8.77 (d)	7.16 (t)	7.65 (t)	7.46 (d)	7.40 (dd)	5.55 (d)	5.60 (d)
					R = OC*H*$_3$		
2-methoxypyridine[b]	8.43 (d)	6.91 (t)	7.68 (t)	6.66 (d)	3.80 (s)		
					R = C*H*$_2$CH$_3$	CH$_2$C*H*$_3$	
2-ethylpyridine[b]	8.74 (d)	7.16 (t)	7.60 (t)	7.10 (d)	2.80 (q)	1.27 (t)	
					R = N*H*$_2$		
2-aminopyridine[c,d]	8.13 (d)	6.45 (t)	7.27 (t)	6.29 (d)	5.59 (bs)		

L	6-*H*, 2-*H*	5-*H*, 3-*H*	4-*H*
pyridine[c,e]	8.63 (d)	7.32 (m)	7.73 (m)

L	7-*H*	4-*H*	2-*H*	R = C*H*$_3$	R′ = C*H*$_3$	R″ = C*H*$_3$
Me$_3$Bzm[c,f]	7.56 (s)	7.16 (s)	7.79 (s)	2.38 (s)	2.40 (s)	3.8 (s)

[a] See Figure 3b for the numbering scheme of the L protons; dd = doublet of doublets. [b] Spectrum obtained at −20 °C. [c] Spectrum obtained at room temperature. [d] Spectrum obtained at 300 MHz. [e] Reference 42. [f] Reference 32.

($\Delta\delta$) can be determined (Supporting Information). For all L, the ortho proton signal undergoes a downfield shift (positive $\Delta\delta$ ranging from 0.21 to 0.31 ppm). The $\Delta\delta$'s for the 8-H signals of quinoline and 4-lepidine are large, 0.65 and 0.62 ppm, respectively. Interestingly, a large $\Delta\delta$ (+0.41) was also observed for the 7-H resonance in $CH_3Co(DH)_2$-(Me$_3$Bzm)[31] (Supporting Information). For coordinated L, 8-H in quinoline-type ligands and 7-H in Me$_3$Bzm are similarly situated close to the equatorial DH moiety of the complex. Some signals of the ortho substituents are also influenced by coordination (Supporting Information); e.g., the CH_3 signal of 2-ethylpyridine is shifted downfield by 0.21 ppm. In particular, the behavior of the vinyl group resonances in 2-vinylpyridine is noteworthy, because the vinyl Ha signal shifts downfield by 0.61 ppm, while the Hc signal moves upfield ($\Delta\delta = -0.59$ ppm). Furthermore, the downfield shift of the Ha signal is not concordant with the slight upfield shift (−0.01 to −0.09 ppm range) exhibited by the signals of a similarly positioned H in other L (ortho CH_3 in 2-picoline and 2,4-lutidine, ethyl CH_2 in 2-ethylpyridine). Also, $\Delta\delta$ for the 3-H resonance in 2-vinylpyridine is downfield (+0.12 ppm) but upfield for other 2-substituted pyridines (−0.04 to −0.08 ppm). Previous calculations[34] and NMR studies[35] showed that the preferred conformation of free 2-vinylpyridine is ii rather than i (cf. Figure 3b). The change in the preferred conformation upon coordination caused by steric repulsion with the equatorial moiety of the complex probably accounts for the large $\Delta\delta$ of the Ha and Hc resonances and for the opposite shift trends exhibited by the Ha and 3-H resonances in comparison to other 2-substituted pyridines.

Although there is an ortho substituent on L, the peaks of the 2-aminopyridine complex are sharp in the spectrum at room temperature, and there is no evidence for free L in solution. This difference in behavior compared to the seven compounds just discussed above can be attributed to the stabilization of axial binding caused by the intramolecular hydrogen bond between the NH_2 group and an oxime O.[17] This hydrogen bond could also be the cause of the relatively upfield oxime O−H−O signal (17.79 ppm) compared to the values observed (18.20−18.58 ppm) for other $CH_3Co(DH)_2L$ complexes (Table 3).

At room temperature (Supporting Information), two broad signals are observed for the axial methyls of $CH_3Co(DH)_2L$ (0.80−0.90 ppm) and $[CH_3Co(DH)_2]_2$ (0.62 ppm). A very broad signal between 1.80 and 2.49 ppm arises from the superimposition of the resonances of the equivalent equatorial methyls of $CH_3Co(DH)_2L$ and the nonequivalent equatorial methyls of $[CH_3Co(DH)_2]_2$.[18] In the very downfield region, the spectra show one broad singlet for the two equivalent O−H−O protons of the adduct (18.10−18.70 ppm) and two broad resonances due to the nonequivalent O−H−O protons of the dimer (13.32 and 18.79 ppm).[18] For L = ortho-substituted pyridines (L = 2-picoline, 2,4-lutidine, 2-ethylpyridine, 2-methoxypyridine, 2-vinylpyridine), the signals due to the ortho groups are also quite broad and the splitting of the multiplets is no longer resolved. Some signals due to the aromatic protons of L are very broad and allow us to separate the seven compounds studied here into two general groups. The signal for the ortho proton at 25.0 °C appears as one quite broad singlet for adducts in the first group (2-vinylpyridine, 2-ethylpyridine, 2-methoxypyridine), while the ortho proton gives rise to two broad singlets for adducts in the second group (2-picoline, 2,4-lutidine, 4-lepidine, quinoline). For the quinoline complex, an additional broad aromatic signal (8-H at 8.75) was also observable. Thus, ligands in

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(35) (a) Sugiura, M.; Takao, N.; Fujiwara, H. *Magn. Reson. Chem.* **1988**, *26*, 1051−1057. (b) Rowbotham, J. B.; Schaefer, T. *Can. J. Chem.* **1974**, *52*, 136−142.

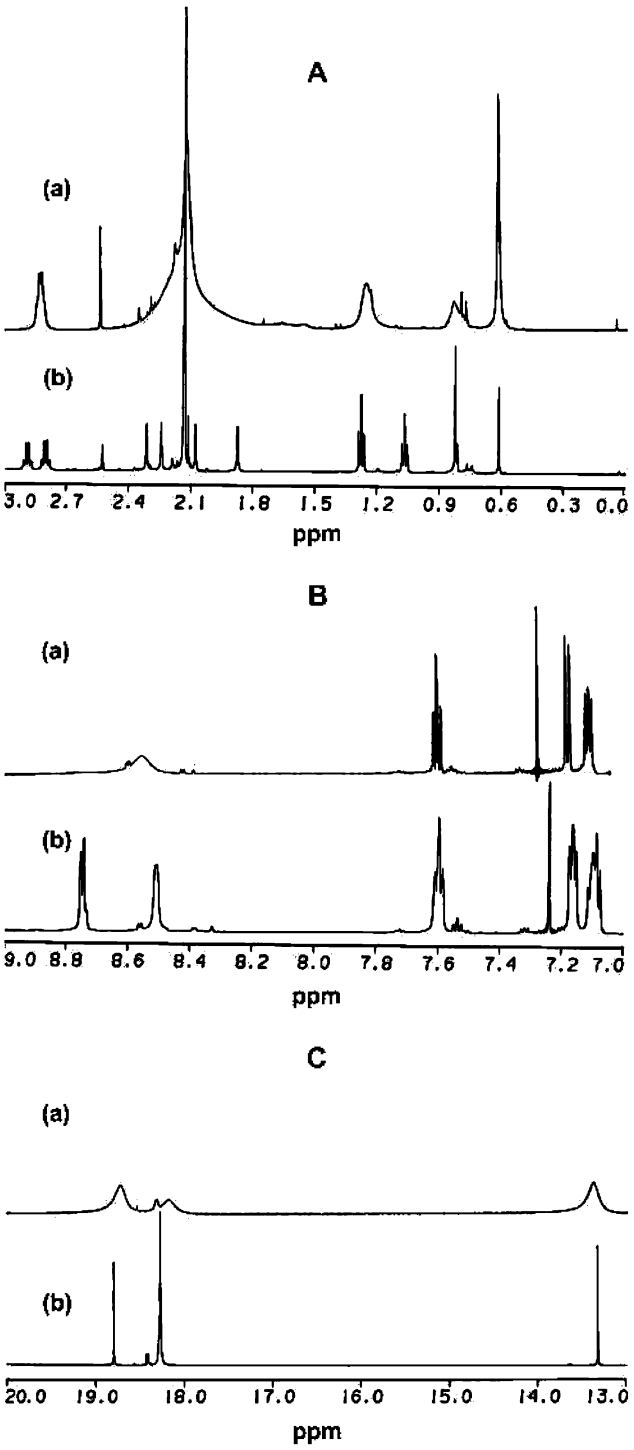

Figure 6. ^{1}H NMR spectra recorded at 600 MHz for $CH_3Co(DH)_2$(2-ethylpyridine) (A, 0.0−3.0 ppm range; B, 7.0−9.0 ppm range; C, 13.0−20.0 ppm range) at (a) 25.0 °C and (b) −20.0 °C.

the second group undergo moderately slow exchange at 25.0 °C compared to the relatively faster exchange for ligands in the first group, which show only one broad signal due to the coalescence of the individual signals.

Brown and co-workers have used ^{1}H NMR spectroscopy to study adduct formation from the methylcobaloxime dimer with various ligands (L = pyridine, trimethylamine, isonitrile, trimethyl phosphite, etc.) in anhydrous CD_2Cl_2.[36] In every case, adduct formation was practically complete at a 1:1 L:Co ratio, except for L = diphenyl sulfoxide, which exhibited a detectable amount of dimer and free ligand. We found that all the ligands examined here were particularly weak, as all the complexes show partial dissociation of the ligand in dry chloroform solution with formation of dimer.

Table 5. Integration Ratio of the Ortho Proton ^{1}H NMR Signal of Bound L to That of Free L in $CH_3Co(DH)_2L$ Solutions in Anhydrous $CDCl_3$[a]

L	signal	ratio
2,4-lutidine	6-*H*	9.9
4-lepidine	2-*H*	4.8
quinoline	2-*H*	4.4
2-picoline	6-*H*	3.6
2-methoxypyridine	6-*H*	1.7
2-ethylpyridine	6-*H*	1.0
2-vinylpyridine	6-*H*	0.4

[a] −20.0 °C, 600 MHz. See Figure 3b for the numbering scheme of the L protons.

The sharpened signals at −20.0 °C for all seven adducts indicate that the exchange is slower. This sharpening allowed us not only to determine accurate shifts as discussed above but also to integrate some signals of the free and bound ligands, particularly those due to the ortho protons. The integration ratio between the signals of the ortho proton of the coordinated ligand and of the free ligand provides a qualitative assessment of the order of L binding ability toward methylcobaloxime. This ratio ranges from 9.9 for L = 2,4-lutidine to 0.4 for L = 2-vinylpyridine (Table 5) according to the following sequence: 2,4-lutidine > 4-lepidine ≈ quinoline ≈ 2-picoline > 2-methoxypyridine > 2-ethylpyridine > 2-vinylpyridine. This sequence follows the deduced exchange rate trend (weaker ligands exchange faster) at 25.0 °C.

The very weak binding of 2-vinylpyridine is striking. This weakness was not expected, given that the Co−N bond length for $CH_3Co(DH)_2$(2-vinylpyridine) is not the longest we found. However, when the 2-vinylpyridine ligand is released and becomes free, rotation of the vinyl group allows the free ligand to assume a more energetically favored conformation (ii in Figure 3b). The driving force for 2-vinylpyridine to adopt this more favorable conformation would favor dissociation to form the dimer, an equilibrium process. In addition, vinyl group rotation should affect reaction rate. Because the emphasis of our study was the synthesis of compounds with interesting structural features, we did not perform a kinetic study. Previous work with alkylcobaloximes in noncoordinating solvents establishes that the mechanism of the ligand exchange reaction is SN_1-LIM.[37,38] The rate-determining step (RDS) is dissociation of L from $RCo(DH)_2L$ to form a five-coordinate $RCo(DH)_2$ intermediate. Competition experiments have shown that the putative five-coordinate intermediate reacts very quickly and relatively nonselectively with the entering ligand in the fast

(36) Brown, T. L.; Ludwick, L. M.; Stewart, R. S. *J. Am. Chem. Soc.* **1972**, *94*, 384 and references therein.
(37) Trogler, W. C.; Stewart, R. C.; Marzilli, L. G. *J. Am. Chem. Soc.* **1974**, *96*, 3697−3699.
(38) Stewart, R. C.; Marzilli, L. G. *J. Am. Chem. Soc.* **1978**, *100*, 817−822.

subsequent association step.[38,39] This subsequent step does not affect the overall rate. Thus, it is quite reasonable to postulate that the rotation of the 2-vinyl group during the RDS will enhance the rate of the dissociation step. However, the rate of the association step of the 2-vinylpyridine ligand to the five-coordinate intermediate should remain fast. This step should not be significantly affected by the requirement that the 2-vinyl group rotate away from the lone pair in order for the 2-vinylpyridine to coordinate in conformation i of Figure 3b. This conformation is found in the solid (Figure 2a), and NMR data are consistent with this conformation in solution.

Summary, Perspective, and Conclusions

In noncoordinating solvents, we isolated and characterized the methylcobaloxime adducts with bulky N-donor ligands: quinoline, 4-lepidine, 2,4-lutidine, 2-picoline, 2-vinylpyridine, 2-ethylpyridine, and 2-methoxypyridine. These complexes do not form in the presence of coordinating solvents such as water, even in trace amounts. This behavior appears to parallel that of alkylcobinamides,[13,40] although no evidence exists that alkylcobinamides form such adducts in noncoordinating solvents. In the 4-lepidine, 2-picoline, 2-vinylpyridine, and 2-aminopyridine methylcobaloxime adducts, the Co−N_{ax} bond is very long. The 2.193(3) Å Co−N_{ax} bond in the 4-lepidine adduct is the longest observed in methylcobaloximes. A fairly linear relationship was found between the Co−N_{ax} bond length and the CCA of the L ligands for a series of methyl- and isopropylcobaloximes. The relationship improves when the contribution of basicity (as quantified by pK_a) was introduced into the relationship. We conclude that the lengthening of the Co−N_{ax} bond is caused mainly by the steric hindrance of the ligands, measured by the CCA parameter. An interesting issue requiring future study is the possible influence of the unsymmetrical nature of the two Co−N_{ax}−C bond angles on the Co−N_{ax} bond length. The data in this study are insufficient to deconvolute the effects of steric repulsion and of unsymmetrical Co−N_{ax}−C bond angles on the Co−N_{ax} bond length.

Because well-established relationships exist between the structural and spectroscopic properties of cobaloximes and those of cobalamins and cobinamides,[3b,15,41] our fundamental inorganic chemistry results have direct bearing on the larger less well-defined B_{12} systems. Beyond the relevance to B_{12}, the versatility of the cobaloxime system helped us to establish a scale of steric parameters, specifically the CCA scale; use of the resulting scale could be extended to complexes with metal centers other than cobalt. In anhydrous $CDCl_3$ at 25 °C, all the complexes but the 2-aminopyridine adduct exhibit ^{1}H NMR spectra consistent with partial dissociation of L to form the methylcobaloxime dimer. ^{1}H NMR experiments at −20 °C allowed us to assess qualitatively the relative binding ability of L as follows: 2,4-lutidine > 4-lepidine ≈ quinoline ≈ 2-picoline > 2-methoxypyridine > 2-ethylpyridine > 2-vinylpyridine. The broadness of the ^{1}H NMR signals at 25 °C suggests a similar order for the exchange rate. The lack of dissociation by 2-aminopyridine is attributed to intramolecular hydrogen bonding. The weaker than expected binding of 2-vinylpyridine relative to the Co−N_{ax} bond length is attributed to rotation of the 2-vinyl group required for this bulky ligand to bind to the metal center, a conclusion supported by pronounced changes in 2-vinylpyridine signals upon coordination. Our results with 2-vinylpyridine show the possible role of a conformational change on binding. This change in conformation could be exploited in the design of systems with novel properties; for example, the conformational change could be linked to changes in fluorescent properties. A ligand with fluorescent properties dependent on conformation could be used for sensing metals or for incorporation into a metal-containing drug to detect binding of the agent to a biomolecule such as a protein.

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Supporting Information Available: Tables of elemental analyses, of ^{1}H NMR chemical shifts at 25 °C, of $\Delta\delta$, and of X-ray crystallographic files, in CIF format, for $CH_3Co(DH)_2$(4-lepidine), $CH_3Co(DH)_2$(2-picoline), $CH_3Co(DH)_2$(2-vinylpyridine), and $CH_3Co(DH)_2$(2-aminopyridine). This material is available free of charge via the Internet at http://pubs.acs.org.

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