Electronic Structure of the Coenzyme Vitamin B_{12} and Related Systems. 1. $Co(DH)_2(L)(R)$ Compounds (DH = Dimethylglyoxime; L = NH_3, py, 2-NH_2py, 5,6-Dimethylbenzimidazole; R = CH_3, *i*-C_3H_7, 5′-Deoxyadenosyl) as Model Systems for the Vitamin B_{12} Coenzyme

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In this study, part 1 of a series examining the electronic structure of the coenzyme vitamin B_{12} and related derivatives, we present a study of the electronic structure of $Co(DH)_2(L)(R)$ (DH = dimethylglyoxime; L = NH_3, py, 2-NH_2py, 5,6-dimethylbenzimidazole; R = CH_3, *i*-C_3H_7, 5′-deoxyadenosyl) as model systems for the vitamin B_{12} coenzyme. We have optimized 12 DH derivatives with varying degrees of steric bulkiness and σ donor capability of the axial ligands. Our goal was to determine which factors may contribute to structural changes in the equatorial ligand and in the Co–axial bonds and to validate the use of the model system in understanding the function of coenzyme B_{12}. In the model systems, we were able to demonstrate the effects upon the Co–axial bonds as a result of (a) puckering of the DH ligand, (b) trans-steric interactions, and (c) trans-electronic influence. By constraining the DH ligand to initially remain planar and then allowing full relaxation of the equatorial ligand, we were able to determine how puckering of the equatorial ligand alone affected the Co–axial bonds. We found that upon relaxation, the nitrogens of the glyoxime rings bend predominantly toward the nitrogen-bound axial ligand, while the carbons of the glyoxime rings could be displaced in either direction depending on the steric bulkiness of the axial ligands. The Co was displaced toward the alkyl group, where the amount of displacement depended upon the steric bulkiness of the axial ligands. Puckering of the equatorial ligand alone did not cause an elongation of the Co–C bond, even though there was a lengthening of the Co–N(ax) bond upon distortion of the DH ligand. To examine the trans-steric influence, we substituted the axial groups with bulky substituents. Bulky axial ligands induced conformation changes in the equatorial ligand with a slight elongation of the Co–alkyl bond. The Co–C(ax) bond length increased with an increase in the bulkiness of R as well as L. The longest Co–C(ax) and Co–N(ax) bonds were found in R = adenosyl and L = 2-NH_2py. To examine the trans-electronic influence upon the axial bond, we varied the basicity of L and the σ donor character of R. There was no structural evidence that the Co–alkyl bond weakened as a result of a decrease in the basicity of L. Comparison of overlap populations in the alkyl derivatives with planar equatorial ligands and fixed average Co–C and C–N(ax) bond lengths indicated little variation in the electronic contributions from the alkyl groups, even though they possessed different σ-donating strengths. Although the DH derivatives have provided useful information for modeling the alkyl–cobalt bond in the coenzyme, our results indicate that there is very little structural changes in the equatorial ligand that significantly influence the alkyl–cobalt bond.

Introduction

Vitamin B_{12} coenzyme, also known as 5′-deoxyadenosylcobalamin, is one of the few stable organometallic complexes found in nature. The cobalamin compound is a biologically important coenzyme which contains a structurally unique corrin ligand in the equatorial plane of a pseudooctahedral cobalt(III) complex. Two axial ligands, 5′-deoxyadenosyl and 5,6-dimethylbenzimidazole complete the octahedral coordination about the cobalt center. The corrin moiety, which could be viewed as a modified porphyrin ring, is thought to be more flexible than porphyrins; the resultant flexibility is a potential condition for the biological activity of the dependent enzymes.[1] Several enzymes, including homocysteine methyl transferase, methylmalonyl-CoA mutase, dioldehydratase, and glycerol dehydrase, are dependent on coenzyme B_{12}.[2] Typically, the vitamin B_{12} coenzyme mediated reactions are of the type shown in Figure 1. In these enzymatic reactions, homolytic cleavage of the stable alkyl–cobalt bond found in 5′-deoxyadenosylcobalamin is thought to be an essential step.[2-11]

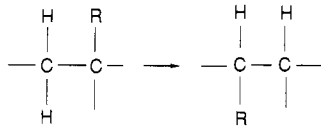

Figure 1. Typical vitamin B_{12} mediated reaction.

Enzymatic activity is dependent on the flexibility of the tetrapyrrole core, the Co–C bond dissociation energy, and the interaction between the coenzyme and the apoprotein. In the presence of the holoenzyme complex (coenzyme bound to the apoprotein), there is a reported 10^{13} increase in the rate of cleavage of the Co–adenosyl bond.[6b,10] In the absence of the enzyme, however, the 5′-deoxyadenosyl cofactor is very stable. This marked increase in the rate of dissociation can be attributed to the energy generated from the intrinsic cofactor–enzyme binding

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energy[10] or a triggering mechanism induced by the enzyme. In either case, conformational changes in the corrin ligand are thought to weaken the Co–C bond and therefore initiate the crucial formation of the adenosyl radical in the enzymatic process. The "butterfly" bending of the corrin ligand is the most frequently suggested conformational change in the equatorial ligand and is apparently induced by interactions with the apoenzyme.[8,10,12] A distortion of the corrin ring is thought to increase the steric interactions with the axial adenosyl ligand, thereby lengthening the Co–C bond or causing angular distortions about the bond.[9] The Co–C(adenosyl) bond can also weaken due to alteration of the position of the benzimidazole (benz) ligand or a change in the Co–N(benz) bond length in the coenzyme.[13,14] Changing the ligand trans to the Co–alkyl group is known to affect the Co–C bond dissociation energy.[8,15] Electronic effects induced by the trans-axial ligands, steric effects from cis-peripheral ligands on the macrocycle core, and steric crowding of bulky trans-axial ligands are thought to contribute significantly to the overall function of the coenzyme.[5,13,15–21] Structural changes in the enzyme and cofactor which trigger Co–C homolysis are of considerable interest in understanding the functions of the B_{12} dependent enzyme systems.

Numerous experimental studies have been carried out to determine the effect of changing the transition metal center,[22] substitution and rearrangement of peripheral ligands,[5] increasing the length of the alkyl group between the adenosyl and the cobalt center,[23] and altering the configuration of the tetrapyrrole macrocycle[5] on the function of the enzyme. These experimental studies are often very difficult to carry out, and very few derivatives of the cobalamin have been structurally characterized. As a consequence, model systems have been routinely employed to mimic the corrin equatorial ligand. Several model systems have been extensively studied,[6b,11,13–21,24–28] although one might question the appropriateness of even the more widely accepted models.[29] Current models of the vitamin B_{12} coenzyme complex include *trans*-bis(DH) (DH = dimethylglyoximato) derivatives (also known as cobaloximes), Costa's model,[30a] Schiff base complexes,[30b] and many of their derivatives. Experimental and theoretical studies using these model systems have examined the steric interactions which cause conformational changes in the equatorial ligand and the trans-axial ligand and electronic effects which alter the Co–C(ax) bond length, C–Co–N(eq) angle, and Co–C bond dissociation energy. Model systems have demonstrated the following: (1) Conformational changes in the equatorial ligands which mimic the corrin moiety are induced by bulky trans ligands. A bending of the equatorial ligand toward the alkyl ligand causes an increase in the Co–C(ax) bond length.[23,24] (2) An increase in the basicity of the trans-axial ligands results in an increase in the Co–C bond dissociation energy,[31] although there is no evidence that the Co–C(ax) bond length is affected.[24] (3) The Co–N(ax) bond tends to elongate with increasing σ-donating capacity of the trans-alkyl group.[24] From experimental studies using these various models one general conclusion has been reached: Conformational changes in the corrin macrocycle are probably induced in the presence of the enzyme, and these conformational changes weaken the Co–alkyl bond.

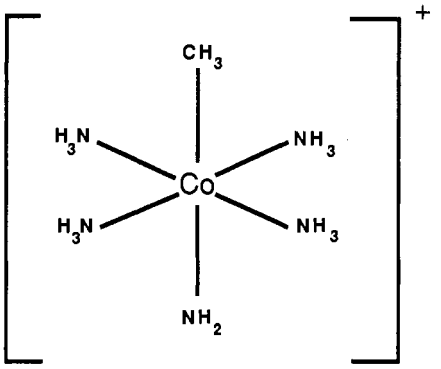

Figure 2. Model system used by Christianson and Lipscomb.[32]

In addition to the substantial experimental contributions, theoretical calculations[32–35] have focused on factors which enhance the Co–C homolysis. PRDDO calculations done by Christianson and Lipscomb[32] on the structure shown in Figure 2 suggest that electronic factors induced by the trans-axial ligand do not result in an increase in the Co–C bond length but rather than the Co–C bond lengthening is more likely due to steric interactions. The geometries of the equatorial ligands were altered in this study to mimic the ruffling of the corrin macrocycle. This study suggested that a deviation in the C–Co–N(eq) angle from 90° results in a weakening of the Co–C(ax) bond (as evidenced by the population analyses). A lengthening of the Co–alkyl bond has been directly related to a reduction in the bond dissociation energy.

Other theoretical work includes the extended Hückel (EH) and perturbation calculations by Mealli, Sabat, and Marzilli[33] on the structure shown in Figure 3. EH calculations were used to explore the Co–C homolysis in the vitamin B_{12} coenzyme, and it was suggested that a necessary component of the Co–C(ax) homolysis is a prior weakening of the Co–N(ax) bond. This bond could weaken as a result of conformational changes in the corrin macrocycle induced by the enzyme.

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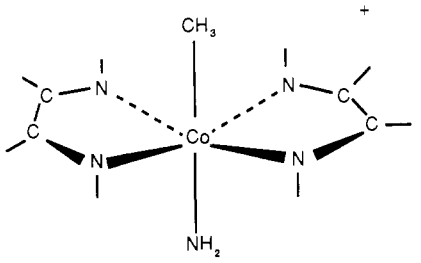

Figure 3. Model system used by Maelli, Sabat, and Marzilli.[33]

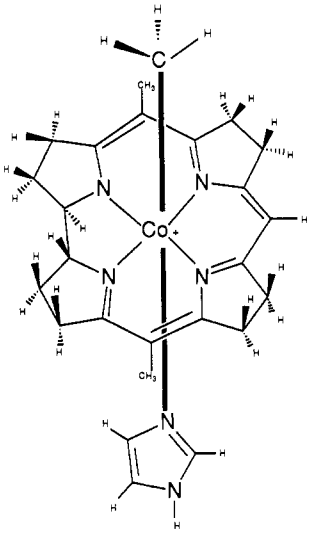

Figure 4. Model system used by Zhu and Kostic.[34]

Molecular orbital calculations done by Zhu and Kostic[34] on the model shown in Figure 4 also provide evidence of how structural deformations in Co(corrin)Im$(CH_3)^+$ influence the Co–C bond strength. Their findings, using the Fenske–Hall method, show that the tilt angle of the Co–C bond with respect to the corrin ring (N(eq)–Co–C) and distortion of the configuration at the C(alkyl)–H bond from a tetrahedral arrangement greatly affect the cobalt–alkyl bond. Although their model includes the corrin ligand, their study was limited to conformational changes about the cobalt–axial bonds and did not include structural changes in the equatorial ligand.

The above data pose several questions, one of which is the following: How reliable is the cobaloxime model in mimicking the cobalamin system?[29] Cobaloximes lack the conjugation of the π system about the corrin ligand that is available in the cobalamins and, furthermore, are considerably more flexible than the corrin ligand. Most importantly, can the model systems be used to predict the factors that are responsible for the Co–C(ax) bond homolysis in vitamin B_{12} coenzyme? To probe these questions, we have initiated a molecular orbital study of the electronic structure of coenzyme B_{12} and its derivatives. In the first paper of this series, we present an analysis of the factors which may contribute to structural changes in the equatorial ligand and the alkyl–cobalt bond, as a first step in assessing the viability of the well-characterized cobaloxime model systems in mimicking conformational changes in the coenzyme. In our approach we use the approximate molecular orbital methodology partial retention of diatomic differential overlap (PRDDO)[36,37] to optimize the ground-state structures of the cobaloxime derivatives. Part 1 includes geometry optimization studies on a variety of $Co(DH)_2(L)(R)$ (Figure 5) complexes (DH = dimethylglyoxime; L = NH_3, py, 2-NH_2py, 5,6-dimethylbenzimidazole; R = CH_3, i-C_3H_7, 5′-deoxyadenosyl) to determine the influence of the ligand trans to the alkyl group. We have chosen the cobaloxime system because it has been extensively reviewed and characterized experimentally. The different L and R groups in our model systems were chosen because of their different electron donor/acceptor abilities as well as varying steric requirements.

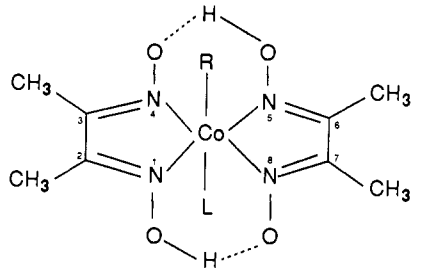

Figure 5. Model system used in this study: $Co(DH)_2(L)(R)$ (DH = dimethylglyoxime; L = NH_3, py, 2-NH_2py, 5,6-dimethylbenzimidazole; R = CH_3, i-C_3H_7, 5′-deoxyadenosyl).

Methodology

The method of partial retention of diatomic differential overlap (PRDDO)[36,37] was used to obtain geometries and energies for the 12 structures analyzed in this study. PRDDO is an approximate molecular orbital method which closely reproduces minimal basis set ab initio calculations. This method has been very successful in predicting metal–ligand bond lengths in transition metal complexes and determining conformational preferences in numerous organometallic systems.[38–40] More recently, the PRDDO methodology has been expanded so that calculations on 1000 orbital molecules have become routine. PRDDO allows us to carry out a systematic assessment of substituent effects in large organometallic complexes which would be computationally prohibitive at the ab initio level.

With the exception of the description of the 4s/4p orbitals, the basis set on the cobalt center was taken from previously optimized Slater orbital basis sets for Co(I).[41] We chose to vary the 4s/4p exponent (with the constraint that 4s = 4p) in an effort to better describe the metal–ligand bond lengths. To determine the optimal cobalt basis set and to optimize the 4s/4p orbital exponent, we chose several structures which have been characterized experimentally (Tables 1 and 2) and calculated the Co–N(eq) and Co–C/N(ax) ligand bond lengths as a function of the 4s/4p orbital exponent. We chose the cobalt basis set and the 4s/4p exponent value from calculations where the geometries most closely reproduced experimental geometrical parameters. In our final basis set, the valence 4s/4p exponents were set equal to 1.70. In Tables 1 and 2, we compare experimental versus PRDDO geometries for four *trans*-bis(DH) (DH = dimethylglyoximato) derivatives. The PRDDO values listed for the DH equatorial ligand were averaged for the four structures in Table 1, and the experimental values were taken from the average structural data presented in a thorough review of the cobaloxime derivatives.[24] We found that PRDDO geometries were very similar to the experimental bond distances and angles with an average error of 0.05 Å and 1.0°, respectively.

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Table 1. Comparison of Experimental and PRDDO Geometries (Equatorial Parameters) (Å, deg) in Cobaloximes with Ranges Listed in Parentheses

param	expt[a,b]	PRDDO[a]
Co–N	1.890 (0.136)	1.950 (0.054)
C–C	1.462 (0.112)	1.477 (0.017)
C–N	1.301 (0.170)	1.297 (0.016)
N–O	1.349 (0.130)	1.331 (0.028)
C–CH_3	1.501 (0.140)	1.488 (0.013)
N–Co–N	81.38 (4.3)	82.3 (1.8)

[a] Averages values from the geometries of the following: R = CN, L = pyridine (py); R = CH_3, L = py; R = i-C_3H_7, L = py; R = i-C_3H_7, L = 2-aminopyridine (2-NH_2py). [b] References 11, 42, 45, and 49.

Table 2. Comparison of Experimental and PRDDO Geometries (Axial Distances in Å) in Cobaloximes

	param	expt[a]	PRDDO
R = CN	Co–C	1.94	1.96
L = py	Co–N	2.00	2.03
R = CH_3	Co–C	2.00	1.95
L = py	Co–N	2.06	2.04
R = i-C_3H_7	Co–C	2.08	1.99
L = py	Co–N	2.10	2.07
R = i-C_3H_7	Co–C	2.10	2.01
L = 2-NH_2py	Co–N	2.19	2.07

[a] References 11, 42, 45, and 49.

In optimizations of large organometallic systems, it is often tempting to rely on symmetry to greatly reduce computational expenditures. For the systems we chose to study in this preliminary work, virtually no symmetry existed; therefore, nearly complete relaxation was allowed for all structures. In all optimizations, it was assumed that C–H bond distances were equivalent in the equatorial ligand. In the optimization of the axial ligands, all C–H bond distances were assumed to be equivalent. Optimization of the pyridine and 2-aminopyridine assumed that these ligands remained planar. For those structures where py or 2-NH_2py were thoroughly optimized, there were insignificant changes in the geometry of the ligand. The internal ring parameters of the pyridine changed by less than 1° for the bond angles and less than 0.005 Å for the bond distances. We therefore optimized the 5,6-dimethylbenzimidazole (benz) ligand alone and then incorporated the optimized fragment into our model systems. The geometry of the 5,6-dimethylbenzimidazole was then constrained within the model structure, with relaxation only at the Co–N bond. We included the Co–dimethylbenzimidazole translational and rotational degrees of freedom. The 5′-deoxyadenosyl fragment was also optimized prior to incorporation into the actual DH models. We constrained the internal ring parameters of the ribose and adenine rings, but allowed free rotation about the ribose–adenine bond and the ribose–CH_2 bond. We included all geometric degrees of freedom about the Co–C axial bond. We began with 12 structures, using the DH equatorial ligand and substituting the axial ligands with R = CH_3, i-C_3H_7, and 5′-deoxyadenosyl and L = NH_3, py, 2-NH_2py, and 5,6-dimethylbenzimidazole. Because conformational changes in the equatorial ligand are thought to induce significant changes in the Co–alkyl bond in the cobalamin complex, we optimized the geometries of our complexes constraining the DH moiety to be planar. We also optimized each structure allowing the full relaxation of the equatorial ligands. These structures are referred to as the planar and puckered forms, respectively, and the effects of the relaxation of the equatorial ligands from the planar to the puckered forms will be discussed in detail below. Displacement of the Co from the equatorial plane was determined by calculating the distance of the Co atom from the least-squares best plane defined by the four equatorial nitrogens. To determine the amount of bending of the glyoxime rings from the equatorial plane, we measured the intersection angle between the two glyoxime planes. The glyoxime planes were defined by (N_1,C_2,C_3,N_4) and (N_5,C_6,C_7,N_8). The final energies and geometries of planar versus puckered conformations were compared in an effort to understand the energetic cost/gain in distorting the Co–N(eq) plane.

Results and Discussion

Changes in the Co–C bond may be brought about by three contributing factors: cis-steric interactions, trans-steric interactions, and trans-electronic influence. This cis- and trans-steric influence both involve interactions between the axial and equatorial ligands. *In the cis interactions, distortions in the corrin macrocycle or equatorial ligand toward the trans-alkyl(ax) ligand result in a lengthening of the Co–alkyl bond.* The cis-steric influence is associated with bulky substituents (e.g. the propanamide and ethanamide peripheral ligands) on the corrin macrocycle interacting with the axial ligands. These nonbonded interactions possibly account for the longer Co–alkyl bond lengths observed in the cobalamin complexes. Furthermore, the corrin ligand is thought to pucker toward the Co–alkyl group in the holoenzyme increasing the cis-steric interactions and weakening the alkyl bond. Because cis-steric interactions are associated with bulky equatorial substituent effects, they cannot be modeled directly by the DH system.

Table 3. Energetics of Puckered versus Planar Geometries of Cobaloximes

	ΔE (kcal/mol)[a]		
	NH_3	py	benz[b]
CH_3	2.8	6.2	4.8
i-C_3H_7	6.6	4.7	1.6
ade[c]	5.6	5.8	0.4

[a] $\Delta E = E_{planar} - E_{puckered}$. [b] benz = 5,6-dimethylbenzimidazole. [c] ade = adenosyl.

The trans-steric influence occurs when the bulkiness of an axial ligand induces an elongation or weakening of the trans metal–ligand bond. In many model systems that have been characterized, the trans-axial ligand is known to induce bending or puckering in the equatorial ligand. This puckering or bending then affects the ligand trans to the bulky substituent by weakening or elongating the metal–ligand bond. Both the cis- and trans-steric influences involve nonbonded interactions between the axial ligand and the equatorial plane and, therefore, collectively influence the axial bond.

The trans-electronic influence is associated with how a change in basicity of the axial base affects the Co–alkyl bond distance and/or bond dissociation energy (trans effect) and how changes in the σ donor character of the alkyl group affects the Co–N(ax) bond distance. As indicated previously, an increase in the basicity of the trans-axial ligands results in an increase in the Co–C bond dissociation energy, although there is no evidence that the Co–C(ax) bond length is affected. Experimental studies indicate that an increase in the σ donor character of the alkyl ligand results in an increase in the Co–N(ax) bond distance.

To systematically study these effects, we first present a detailed analysis of how puckering of the equatorial ligand induces conformational changes in both the equatorial and axial ligands. We then discuss the trans-influence in the fully relaxed species by studying how various L groups affect a given Co–R distance and, similarly, how various R groups affect a given Co–L distance, and we demonstrate that the steric bulkiness of the axial ligands induce changes in the axial bond lengths. Finally, we show that trans-electronic influence has a minimal effect on the Co–axial bonds.

Effects of Equatorial Ligand Puckering. Energetics. Table 3 compares the differences in the total energies of the puckered and the planar conformations for the cobaloxime alkyl derivatives. We have omitted the 2-NH_2py systems because the amino group is involved in hydrogen bonding with the equatorial ligand, a characteristic that is not shared by the other nitrogen base derivatives. In all instances the puckered form is energetically favored since it represents a more completely optimized structure. The calculated relaxation energies vary from 0.4 kcal/mol (R = adenosyl, L = benz) to 6.6 kcal/mol (R = i-C_3H_7, L = NH_3). In general, if both axial ligands are bulky, the relaxation energies are small. For example, when R = adenosyl and L = benz, the relaxation energy is only 0.4 kcal/mol. A similar effect is seen when both axial ligands are small, as in R = CH_3 and L = NH_3,

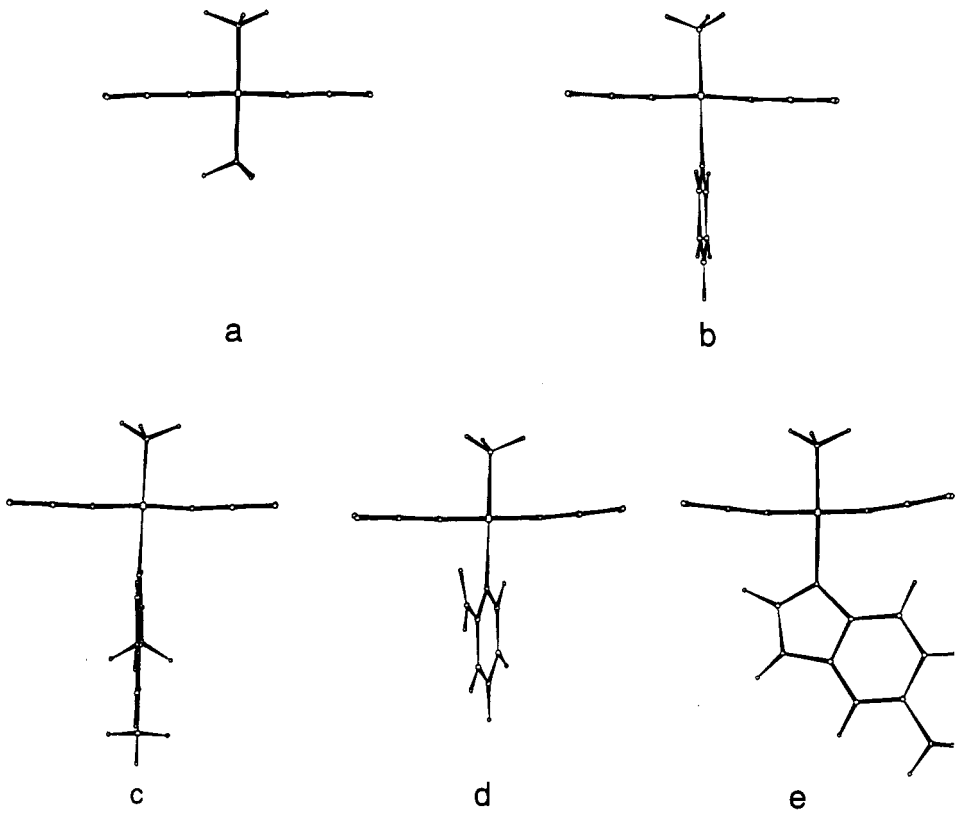

Figure 6. Stick plots of $Co(DH)_2(L)(R)$, where $R = CH_3$: (a) $L = NH_3$; (b) L = pyridine; (c) L = 5,6-dimethylbenzimidazole; (d) L = 2-aminopyridine; (e) L = 5,6-dimethylbenzimidazole rotated 90° to eclipse glyoxime rings for induced steric hinderance (see text).

where the relaxation energy is only 2.8 kcal/mol. However, axial ligands of markedly different size result in chemically important relaxation energies. For instance, when R = adenosyl and L = NH_3 the calculated ΔE is 5.6 kcal/mol. The notable trend in relaxation energies illustrates that conformational changes in the equatorial ligands can result in significant energetic effects, even in this simple model system. In the actual biological system, in which steric effects can be *induced*, one can anticipate even greater energetic consequences.

Conformational Changes in the Equatorial Ligand. Comparison of the geometrical parameters of the DH ligand upon relaxation from the planar to the puckered forms of all 12 structures showed that on the average, there was only a very slight increase in the Co–N(eq) bond distance, from 1.92 to 1.94 (±0.01) Å, and essentially no change in the other parameters. In both the puckered and planar conformations, the glyoxime rings remained planar (the dihedral angle N_1–C_2–C_3–N_4 is zero). There was a small, but measurable, change in the dihedral angles defined by Co–N_1–C_2–C_3 and Co–N_5–C_6–C_7 and the deviation from planarity was typically asymmetrical. For example, in $R = CH_3$, $L = NH_3$, the dihedrals Co–N_1–C_2–C_3 and Co–N_5–C_6–C_7 were 1.9 and 4.4°, respectively. For R = adenosyl, $L = NH_3$, the same dihedral angles were 0.6 and 2.3°. Asymmetry in the glyoxime rings is associated with a slightly nonlinear R–Co–L angle, which has been seen experimentally as well as in our optimized structures. For example, experimentally the R–Co–L bond angle in $Co(DH)_2(i\text{-}C_3H_7)(py)$ is found to be 175° compared to our calculated value of 177°.[42] From Figures 6–8, which depict plots of the puckered derivatives for all 12 structures, several more noticeable conformational changes which result from puckering become evident.[43] These changes include displacement of the Co from the equatorial plane, bending of the glyoxime rings from the plane, and, most importantly, changes in the Co–axial bond lengths.

Our calculations essentially reproduced the experimental trends in the axial bond distances, yet the direction of the distortion of the equatorial ligands, as measured by the bending of the equatorial nitrogens, did not always agree with experiment. For example for $R = CH_3$, L = py, we have calculated that the cobalt was displaced toward the alkyl group 0.037 Å from the nitrogen equatorial plane (Table 5) and that the intersection angle between the two glyxoime rings was 1.4° with the glyoxime rings bending in a tilted fashion (Table 6, Figure 6b). In the crystal structure, the cobalt was displaced toward the pyridine by 0.029 Å and the intersection angle between the glyoxime rings was 1.7°.[44,45] The general trend seen experimentally in a wide variety of these complexes is a small displacement of the cobalt toward R; however, displacements in the opposite direction do occur, especially when R is a bulky group such as adamantyl or in some cases isopropyl[24] (we would expect adenosyl to behave similarly). In any case, our calculated distortions from planarity, as displayed in Figures 6–8, are intuitively reasonable and consistent with experiment when the axial ligands are bulky and when steric effects are artificially induced, as described below. These are the most important situations from the perspective of modeling the actual biochemical system.

There is some evidence to suggest that, in the absence of steric effects and other effects due to the crystal environment, our calculated distortions are reasonable. For instance, it has been argued[46] that structural distortions from idealized coordination geometries can be related to the differences in bond polarities of the metal–ligand bonds. Consider the Co(III) complex CoX_5Y.

(42) Marilli, L. G.; Tosano, P. J.; Randacio. L.; Bresciani-Pahor, N.; Calligaris, M. *J. Am. Chem. Soc.* **1979**, *101*, 6754.

(43) The hydrogens and the bridging O–H groups have been omitted from the equatorial ligand for simplicity so that the tilting or bending of the DH ligand can be more easily discerned.

(44) We have used the coordinates from the crystal structure to calculate the displacement and intersection angle to ensure we are comparing similar parameters.

(45) Attia, W. M.; Zangrando, E.; Randaccio, L.; Antonlini, L.; Lopez, C. *Acta Crystallogr.* **1989**, *C45*, 1500.

(46) Elian, M.; Hoffmann, R. *Inorg. Chem.* **1975**, *14*, 1058.

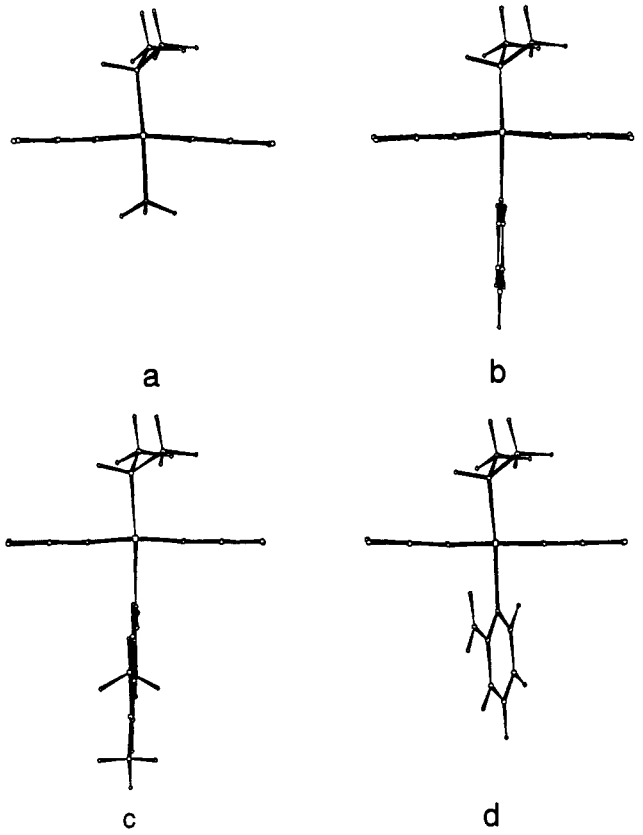

Figure 7. Stick plots of $Co(DH)_2(L)(R)$, where R = i-C_3H_7: (a) L = NH_3; (b) L = pyridine; (c) L = 5,6-dimethylbenzimidazole; (d) L = 2-aminopyridine.

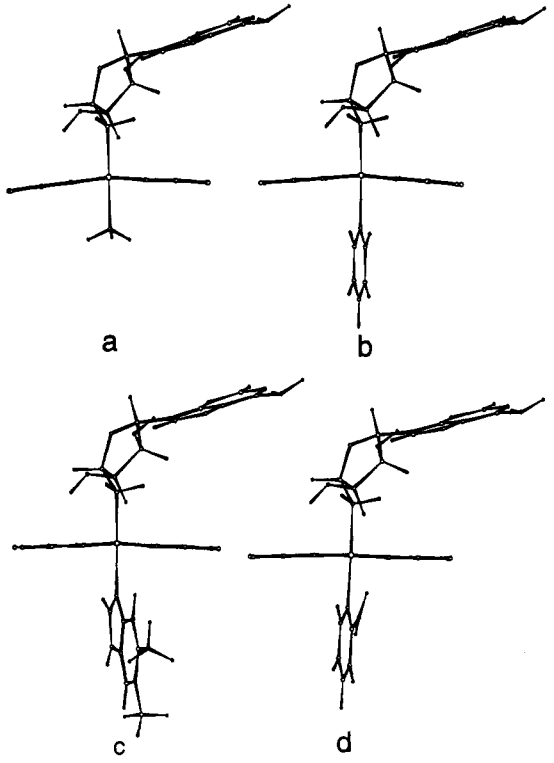

Figure 8. Stick plots of $Co(DH)_2(L)(R)$, where R = 5′-deoxyadenosyl: (a) L = NH_3; (b) L = pyridine; (c) L = 5,6-dimethylbenzimidazole; (d) L = 2-aminopyridine.

If all bonds to the metal are purely covalent, then an octahedral geometry clearly results. If the Co–Y bond is 100% ionic while the Co–X interaction is nonpolar, then square-pyramidal CoX_5^+ will form, with the metal displaced above the base plane (or, equivalently, toward the axial L group). In an intermediate case such as we have here, distortions from pure octahedral coordination toward a square pyramid will occur, and the Co will be displaced toward the ligand with the *least* polar bond: the axial R group. We have confirmed these qualitative ideas in a simple model system by completely optimizing $Co(NH_3)_5F^{2+}$ with PRDDO and at a higher theoretical level with the density functional program DMOL.[47] Both methods yield distorted octahedrons with the cobalt displaced toward the NH_3 trans to the more electronegative F. The average N(ax)–Co–N(eq) bond angles were 91.7° (PRDDO) and 94.7° (DMOL).

Table 4. Axial Bond Distances (Å) for Puckered/Planar Cobaloxime Derivatives

	param	NH_3	py	benz	2-NH_2py
CH_3	Co–C	1.95/1.95	1.95/1.94	1.95/1.95	1.95/1.94
	Co–N	2.01/2.01	2.04/2.03	2.04/2.03	2.06/2.05
i-C_3H_7	Co–C	1.97/2.02	1.99/2.02	2.01/2.02	2.01/2.01
	Co–N	2.02/2.01	2.07/2.01	2.07/2.04	2.07/2.10
ade	Co–C	1.99/2.01	2.02/2.01	2.01/2.01	2.02/2.01
	Co–N	2.03/2.00	2.07/2.03	2.06/2.02	2.09/2.07

Table 5. Distance (Å) That Cobalt Is Displaced from the Nitrogen Equatorial Plane toward the Alkyl Group

	NH_3	py	benz	2-NH_2py
CH_3	0.048	0.037	0.021	0.002
i-C_3H_7	0.063	0.058	0.048	0.016
ade	0.079	0.069	0.053	0.042

Table 6. Intersection Angle (deg) between the Glyoxime Planes

	NH_3	py	benz	2-NH_2py
CH_3	0.3	1.4	6.3	6.6
i-C_3H_7	3.7	1.4	1.9	2.6
ade	8.4	8.4	7.5	2.2

Changes in the Axial Bonds. In Table 4 we present the Co–C and Co–N axial bond distances for the puckered versus the planar conformations for all 12 derivatives. In most cases, the structural effects upon puckering are clear. For the methyl derivatives, puckering of the DH ligand results in very little change in either of the axial bond distances. In the sterically demanding isopropyl and adenosyl derivatives, the Co–N bond distance lengthens upon puckering, because the puckering is in the direction of L. An exception is when L = 2-NH_2py, where hydrogen bonding, which occurs in both forms, probably has a mediating effect. The Co–R distances change very little when both axial substituents are bulky (e.g., L = benz or 2-NH_2py) but generally shorten in the puckered form when L is less sterically demanding (e.g., L = NH_3 or py).

Induced Conformational Changes. In the actual enzyme system, the corrin ring bends toward the alkyl group in the coenzyme, but we have found that, in the DH model system, the direction that the DH ligand bends is strongly dependent on the steric bulkiness of the axial groups. Initially it was thought that a planar axial nitrogen ligand could not induce the conformational changes in the DH model that are predicted in the corrin system.[48] If, however, the planar axial ligand is oriented into a more sterically hindered conformation with respect to the equatorial plane similar to that in N^2,$N^{2'}$-propanediylbis(2,3-butadione 2-imine 3-oxime) generated by Gerli et al.,[48] there is a marked change in the puckering angle of the equatorial ligand as well as an increase in the Co–N(ax) bond distances. Computationally, it is very easy to mimic changes in the orientation of the axial ligands by a simple rotation about the Co–N(ax) bond. In the R = CH_3, L = benz structure (Figure 6e), we rotated the 5,6-dimethyl-

(47) DMOL is a product of Biosym Technologies, Inc. The calculation was done by employing a Janak–Moruzzi–Williams local correlation and a double numerical plus polarization basis set. Frozen cores (1s for N and F; 1s, 2s, and 2p for Co) were employed.
(48) Gerli, A.; Sabat, M. Marzilli, L. G. *J. Am. Chem. Soc.* **1992**, *114*, 6711.
(49) Bigotto, A.; Zangrando, E.; Randaccio, L. *J. Chem. Soc., Dalton Trans.* **1976**, *96*.

Table 7. Axial Bond Distances (Å) for Puckered Cobaloxime Alkyl Derivatives

	param	NH_3	py	benz	2-NH_2py
CH_3	Co–C	1.95	1.95	1.95	1.95
	Co–N	2.01	2.04	2.04	2.06
i-C_3H_7	Co–C	1.97	1.99	2.01	2.01
	Co–N	2.02	2.07	2.07	2.07
ade	Co–C	1.99	2.02	2.01	2.02
	Co–N	2.03	2.07	2.06	2.09

Table 8. Overlap Populations for Planar Cobaloxime Alkyl Derivatives

	param	NH_3	py	benz
CH_3	Co–C	0.48	0.48	0.46
	Co–N	0.22	0.26	0.28
i-C_3H_7	Co–C	0.46	0.46	0.46
	Co–N	0.23	0.26	0.28
ade	Co–C	0.46	0.46	0.46
	Co–N	0.22	0.26	0.28

benzimidazole group by 90° so that it eclipsed the glyoxime rings. We forced the L group to maintain this orientation but optimized all other degrees of freedom. Our results indicated that the constrained orientation of the benzimidazole was energetically less favored by 10 kcal/mol. In addition, there was a significant lengthening of the Co–N(ax) bond from 2.04 to 2.10 Å. In agreement with Gerli's model, there was no marked change in the Co–C bond length (1.95 Å); however, as in Gerli's system, the nitrogens of the equatorial ligand were distorted toward the alkyl group and the intersection angle defined by the glyoxime rings was now 14°. Figure 6e illustrates the calculated geometry. These results confirm that the planar axial nitrogen ligand can induce puckering of the equatorial ligand, but these changes do not necessarily coincide with a change in the Co–C(ax) bond length.

Trans-Influence. We divide our discussion of trans-influence into those due to steric factors and those resulting from electronic effects. Steric effects are discussed in the context of the fully optimized structures, while electronic effects are evaluated using idealized geometries for which the steric effects can be effectively eliminated.

Steric Effects. Steric effects of the trans-axial ligands can be determined from the change in the Co–C(ax) and Co–N(ax) bond distances as a result of varying R and L. From our previous discussion comparing puckered versus planar conformations, it is apparent that changes in the equatorial ligand are induced by the steric interactions with the axial substituents. The displacement of the Co from the equatorial plane and the bending of the glyoxime rings is strongly dependent upon the steric bulkiness of the axial groups.

In Table 5 we present the displacement of the Co from the equatorial plane. For a given L, an increase in the bulkiness of the R group results in an increase in the displacement of the Co from the plane (the steric bulkiness of the R group increases in the order CH_3 < *i*-C_3H_7 < adenosyl). The equatorial nitrogens tend to bend toward the nitrogen bound axial ligand, and therefore, the Co appears to be displaced toward the alkyl group. This displacement is greatest in R = adenosyl, where the displacement of the Co ranges from 0.08 to 0.04 Å depending on the steric bulkiness of L. If we compare structures with the same R while varying L, we find that the displacement of the Co from the plane decreases with an increase in the steric bulkiness of L.

The interaction angles between the glyoxime rings (Table 6) is also dependent upon the steric bulkiness of the axial ligands, although the trends are somewhat less clear. For R = CH_3 and L = NH_3, the intersection angle is essentially zero. If, however, we increase the steric bulkiness of one of the axial ligands, particularly when R = adenosyl, the intersection angles become large. When both axial ligands are bulky, one would expect little change from planarity, and indeed, for R = adenosyl and L = 2-NH_2py, the intersection angle is reduced to 2.2°.

In our optimized structures as well as in the experimentally characterized derivatives, the bond angles H(C)–C–Co deviate significantly from 109° of sp^3 hybrid orbitals. We see that, with an increase in the bulkiness of the axial ligands, these bond angles increase with values of 112° for H–Co–Co in R = CH_3, 115° for C–C–Co in R = *i*-C_3H_7, and 126° for C–C–Co in R = adenosyl. From Table 7, we find that there is an obvious lengthening of the axial bond length as we increase the bulkiness of either R or L. For example, the Co–C bond distance increases from 1.99 Å in the R = adenosyl, L = NH_3 complex to a distance of 2.02 Å in the R = adenosyl, L = 2-NH_2py derivative. Similarly, the Co–N distances increases from 2.01 Å in the L = NH_3, R = CH_3 derivative to a distance of 2.03 Å in the L = NH_3, R = adenosyl system. The axial bond distances are longest in those derivatives where both axial ligands are sterically bulky.

Electronic Effects. Trans-electronic influence has been demonstrated in experimental models by changes in the bond dissociation energies of the Co–alkyl group. Measurements of the bond dissociation energy for a series of DH models showed that an increase in the basicity of the N(ax) ligand resulted in an increase in the Co–C bond dissociation energy.[31] Structural data do not support this trend, however.[24] For the N(ax) ligands considered in this study, the basicity increases in the following order: py < benz < 2-NH_2py < NH_3. The deviation in the Co–C(ax) bond length for a given R group (Table 7) is small, and there is no evidence of a trend existing between the basicity of the L group and the change in the Co–C(ax) bond. The basicity of L does not appear to induce a trans-electronic influence changing the Co–C(ax) bond length. Even though we have not determined the trans *effect* as a result of increased basicity of L, an increase in the basicity of L may stabilize the Co(III) complex thereby increasing the bond dissociation energy.

Although basicity may not affect the axial alkyl bond length, experiment suggests that the σ donor ability of the alkyl ligand may induce a trans-electronic influence by lengthening the Co–N(ax) bond. As the σ donor ability increases, the Co–N bond distance should also increase.[24] The σ donor ability of the R groups is *i*-C_3H_7 > adenosyl > CH_3. The stronger σ donors are, coincidentally, the bulkier ligands. Experimentally it is impossible to isolate the steric and electronic influence in these systems. However, we can calculate overlap populations to assess differences in the degrees of metal–ligand interaction. Comparisons of overlap populations become meaningful only if we fix the Co–C and Co–N distances at an average value (1.99 and 2.02 Å, respectively) and force the DH ligand to remain planar. The latter restriction eliminates steric effects due to the different degrees of equatorial ligand puckering in each system. The calculated overlap populations are listed in Table 8. Our calculations suggest that for a given L the Co–C interaction is slightly stronger for the R = CH_3 derivatives than for the isopropyl or adenosyl derivatives. Because the isopropyl and adenosyl ligands are presumably stronger σ donors, one might except larger overlap populations when compared to the methyl derivatives. However, it must be remembered that the adenosyl and isopropyl ligands exhibit significant distortion from true sp^3 hybridization due to steric interactions with the equatorial ligand (the C–C–Co angle in the isopropyl and adenosyl structures are 115 and 126°, respectively). These steric considerations force rehybridization about the Co–C–C bonds and reduce the Co–C overlap populations. This is clearly demonstrated by a model calculation for R = adenosyl and L = NH_3 in which the bond angles about the cobalt–carbon adenosyl ligand were forced to be tetrahedral. The Co–C overlap population increased from 0.46 to 0.52, compared to a value of 0.48 calculated for the methyl derivative. A similar argument has been made in the context of Fenske–Hall molecular orbital theory.[34] From our results, there appears to be no measurable trans-electronic influence when comparing overlap

populations with fixed bond lengths. Steric factors appear to dictate conformational changes in the Co–C(ax) bond.

Conclusions

We have optimized 12 DH derivatives with axial ligands of varying steric bulkiness and electronic characteristics. Our goal was to determine which factors may contribute to structural changes in the equatorial ligand and, most importantly, changes in the Co–axial bonds. This is of primary importance in suggesting models that may lead to an understanding of the function of coenzyme B_{12}.

By forcing the DH ligand to remain planar and then allowing complete relaxation of the equatorial ligand to the puckered form, we were able to isolate structural changes in the axial bonds which resulted from the distortion of the equatorial ligand. We have found that relaxation of the equatorial ligand results in distortions in the Co–axial bonds, bending of the glyoxime rings, and displacement of the Co from the nitrogen equatorial plane. In the alkyl systems, puckering of the DH ligand did not appreciably influence the Co–C(ax) bond distances. However, in almost all of the derivatives we have characterized, the Co–N(ax) bonds were elongated upon puckering. In most instances, the equatorial nitrogens bent toward the nitrogen bound axial ligand (corresponding to a displacement of Co toward the alkyl group), yet depending on the steric bulkiness of the alkyl group, the glyoxime rings tilted toward or away from the alkyl group. The relaxation energy generated from the distortion of the equatorial ligand from planarity was significant, lending credibility to the notion that steric interactions in these system can significantly affect the energetics of bond homolysis. The trans-steric influence were assessed by varying the bulkiness of R for a given L and, similarly, by varying the bulkiness of L for a given R. In the alkyl systems, an increase in the bulkiness of R resulted in longer Co–C(ax) bonds and a lengthening of the Co–N(ax) bond. Depending on the steric bulkiness of both axial groups, the equatorial ligand puckered and the cobalt was displaced from the equatorial nitrogen plane. For those derivatives with the same R, an increase in the steric bulkiness of L not only resulted in an increase in the Co–N(ax) bond length but also resulted in a slight increase in the Co–C(ax) bond length, confirming previous experimental findings. The Co–C(ax) and Co–N(ax) bond lengths were longest in the derivatives in which both ligands were bulky. To examine the effects of induced steric intractions on the Co–C(ax) bond, we changed the orientation of the benzimidazole ligand by 90° in the R = CH_3 derivative. Even though there was a significant change in the puckering of the equatorial ligand, a lengthening of the Co–N(ax) bond, and an increase in energy of 10 kcal/mol, there was no measurable effect on the Co–C(ax) bond distance. These results are very similar to those found by Gerli et al.[48] for $N^2,N^{2'}$-propanediylbis(2,3-butadione 2-imine 3-oxime).

Our results support experimental evidence that an increase in the basicity of the nitrogen-bound ligand has no structural effect on the Co–C(ax) bond. Similarly, changes in the σ donor character of the alkyl group did not appreciably influence the Co–C(ax) bond. The structural characteristics of these systems are dictated primarily by steric interactions.

Although the DH derivatives have experimentally provided very useful information for modeling the alkyl–cobalt bond of coenzyme B_{12}, the DH model system has provided limited information about conformational changes in the equatorial ligand. Conformational changes are small in the equatorial ligand in the DH model, and they exclude cis-steric interactions with peripheral ligands. In part 2 of this study, we will substitute the DH equatorial ligands with the unsubstituted corrin ring. The study will continue to examine the conformational changes in the axial and equatorial ligands resulting from steric interactions and trans-electronic influence. We hope that this study will complement the existing model studies and provide more information about the changes occurring in the corrin ring.

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Supplementary Material Available: Tables of Cartesian coordinates for both the puckered and planar conformations of $Co(DH)_2(L)(R)$ (DH = dimethylglyoxime; L = NH_3, py, 2-NH_2py, 5,6-dimethylbenzimidazole; R = CH_3, i-C_3H_7, 5′-deoxyadenosyl) (37 pages). Ordering information is given on any current masthead page.