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Carbon−Cobalt Bond Distance and Bond Cleavage in One-Electron Reduced Methylcobalamin: A Failure of the Conventional DFT Method

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Geometry optimizations at the HF, B3LYP, and CASSCF levels of electronic structure theory have been performed for methylcobalamin (MeCbl) model compounds in both the Co(III) (MeCbl(III)) and Co(II) (MeCbl(II)) formal oxidation states. Since the HOMO−LUMO and C−Co $\sigma-\sigma^*$ MO gaps are significantly smaller in the MeCbl(II) compounds compared with MeCbl(III), a pseudo-Jahn Teller effect is possible. CASSCF calculations show that there is strong coupling between C−Co $\sigma-\sigma^*$ MOs for the MeCbl(II) models leading to strong state mixing with significant total charge density transfer (~0.4 e$^-$), mainly from the C−Co σ MO to C−Co σ^* MO (~0.3 e$^-$). CASSCF(9:7) calculations show that the strong state mixing leads to an increase in the C−Co bond length for MeCbl(II) model compounds from 1.969 Å (DFT and HF calculations) to 2.164 Å in the base-on MeCbl(II) model and from 1.938 Å to 2.144 Å in the base-off MeCbl(II) model. Concomitantly, the Co−N axial bond length increases from 2.121 Å (DFT) to 2.344 Å in the CASSCF calculation. This coupling interaction between states can be used to explain the much lower Co−C bond dissociation enthalpy and much faster bond cleavage rate for the one-electron reduced methylcobalamin radical anion compared to MeCbl(III). It may also be important for axial bond distances in other Co(II) compounds.

Introduction

The alkylcorrinoids, methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl), function as vitamin B_{12} cofactors (coenzymes) in a number of mammalian and prokaryotic enzyme systems. In these cofactors, the Co atom is coordinated to four in-plane nitrogen atoms from a reduced tetrapyrrole (corrin) ring structure as well as to upper (β) and lower (α) axial ligands. The upper ligand is a methyl group in methylcobalamin and a 5′-deoxyadenosyl group in adenosylcobalamin. The lower ligand is 5,6-dimethylbenzimidazole in both cobalamin coenzymes. These cobalamin molecules possess relatively weak cobalt−carbon bonds (ca. 30 kcal/mol) that are cleaved during the enzymatic process.[1] The mechanism of how the protein activates the C−Co bond in B_{12}-dependent enzymes is still an active area of research.[2] In this paper, we focus on electronic structure and modeling of methylcobalamin, MeCbl, species which are involved in methyl transferase reactions.

In methyl transferase reactions, the methyl group of MeCbl(III) is transferred by heterolytic fission of the Me-Co(III) bond of the corrinoid forming a Co(I) species. For example, in the methionine synthase enzymatic reaction, the pathway involves transfer of the Me group from the Me-Cbl(III) to the sulfur atom of the amino acid homocysteine (Hcy), thereby forming the amino acid methionine which contains the new Me-S bond. In the process, the cofactor is left in the Co(I), Cbl(I)$^-$, form for further recycling. The methylcobalamin radical anion, MeCbl$^-$, can be an intermediate or part of a transition state in possible mechanisms[3] for this reaction. We have recently explored a reductive cleavage mechanism for this process by electrochemical experiments and by DFT calculations.[4,5]

There have been a very large number of publications using electronic structure calculations to model cobalamin compounds. Early Huckel calculations indicated the nature of the visible transitions,[6] and more recently, time-dependent density functional theory, TD-DFT, was used to assign the transitions for the coenzymes.[7] In addition to Huckel calculations, other semiempirical methods such as PM3 and PRDDO have also been tried (see citations in ref 8). Although these methods can be used to treat the structure of large molecular systems, like the complete methylcobalamin molecule (183 atoms, 506 e$^-$), they show incorrect molecular orbital (MO) energy results. More recently, properties for geometry-optimized alkyl-corrin model systems have been analyzed by DFT calculations. These studies include different alkyl axial substituents and their bond distances and dissociation enthalpies, BDE,[9,10] the effect of different functionals on BDE[11] and structure,[12] calculation of coenzyme models,[8] trans axial ligand effects on the Co−R bond,[13−16] vibrational frequency analysis,[17,18] the influence of electric field on the Co−C bond,[9,19] and the electronic properties of Co^{2+}-Cbl forms.[20] These DFT calculations were done, for the most part, with the Becke3LYP exchange correlation hybrid functional employing an effective core potential and a relevant basis set for the cobalt valence electrons. Only very recently has a multiconfigurational (MCSCF) study, with CASPT2, been used, and this was for a Cbl(I) model.[21] It was found that CASPT2 does better than DFT, but the latter gives reasonable results.

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Kozlowski has reviewed the quantum chemical modeling results on C−Co bond activation.[22] He points out that DFT calculations confirm the anomalous trans effect where the Co−C and Co−N_{ax} bond distances both lengthen or shorten together under the influence of the trans alkyl group as noted by De Ridder et al.[23] and Xu and Brown.[24] It has also been concluded by theoretical[9,13−15,20,25] and experimental[26] means that the axial N-base does not have a large effect on Co−C bond bond distance and thus on cleavage. An MO model which explains this anomalous effect was recently proposed in a study which used molecular dynamics within the Carr−Parrinello approach and the Becke−Perdew DFT-LSD theory,[27] and Kozlowski and co-workers have made a very detailed DFT MO analysis of this anomalous trans effect.[28]

However, the only electronic structure calculations for the one-electron reduced methylcobalamin, the radical anion, have been our recent studies.[4,5] The original electrochemical experimental results[29] and our more recent studies[4,5] show that in nonaqueous media, which simulates the protein environment, the one-electron reduction of MeCbl forming the radical anion $[MeCbl]^-$ enormously enhances the rate of dissociation of the Co−C bond. Martin and Finke[30] estimated that the Co−C bond dissociation enthalpy is weakened by 60% by the addition of one electron to Me-Cbl(III), which is consistent with our recent results.[4] On the other hand, our DFT theoretical calculations at the B3LYP/LAN2DZ level[4] show that there is no change in the Co−C bond distance for the radical anion, which suggests a problem with the DFT methodology.

For Me-Cbl(III) itself, these DFT calculations indicate that the first σ^* Co−C orbital is situated ∼2 eV above the π^* corrin ring LUMO and ∼5 eV above the HOMO and is actually the LUMO(4). Therefore, a one-electron addition should not go into a σ^* orbital but into the π^* corrin ring LUMO orbital. Such an addition should not greatly effect the stability of the Co−C bond according to the DFT calculations, and indeed, they show no change in this bond length for models of the $[MeCbl]^-$ radical anion. However, if there are interactions of electronic states, a single-configuration type of calculation will not represent the correct structure. This appears to be the case, and CASSCF calculations to presented herein show a dramatic lengthening of Co−C bond in the reduced species.

The failure of the DFT results to show this bond lengthening appears to be a consequence of the inadequacy of the DFT method if the electronic wave function is dependent on the nuclear coordinates.[31] In other words, when the Born−Oppenheimer approximation is not valid, the Kohn−Sham DFT theory may not give accurate results, because it does not account for the nonadiabatic coupling due to nondynamical (near-degeneracy) correlation effects. Various extensions of the conventional DFT method to multiconfigurational states have been proposed to treat this problemm and it is an active area of research.[32,33] However, herein we have used the CASSCF method to account for these nondynamical correlation effects. According to Bersuker,[34] for a near-degeneracy between ground and excited states, nonadiabatic coupling gives rise to a pseudo-Jahn−Teller (PJT) effect which can lead to significant changes in the bonding properties of radical ions as well as bond breaking properties. This situation is relevant for many open-shell systems, and the PJT effect has also been discussed for cation radicals.[35]

Although the molecular details which will explain the enzymatic activation of the Co(III)−C bond for cleavage will ultimately depend on knowledge of protein structural interactions with R-cobalamins at the active site of the enzymes, it is important to explore the applicability of theoretical calculation models for the coenzymes themselves. We have examined the differences between CASSCF and DFT calculations for molecular models of the one-electron reduced state of methylcobalamin. We interpret the lengthening of the Co−C and Co−N_{ax} bonds in the CASSCF case and the fast Co−C bond cleavage in terms of "vibronic" coupling and the PJT effect.

Results and Discussion

Density Functional Calculations for Methylcobalamin Redox States. We recently performed calculations on Me-Cbl models for total energy as a function of Co−C bond distance as the bond is stretched. We used the B3LYP functional and the LAN2DZ basis set contained in the *Gaussian 03* code[36] to give a dissociation-energy type curve.[5] This was done for base-on and base-off models of positively charged $CH_3{-}Co(III)^+$ and likewise for the neutral reduced $CH_3{-}Co(II)$ models. For convenience, these curves are presented in the Supporting Information, Figure S1. The reduced complex is only Co(II) in a formal sense, since the added electron should go into the corrin ring π system. The optimized DFT geometry for all four species with this basis set shows nearly the same equilibrium C−Co bond distance of around 2.00 ± 0.01 Å.[5] As mentioned, this cannot be valid given the small BDE of the reduced species.[30,37]

The dissociation total energy barrier heights from single-point calculations for both the base-on and base-off $CH_3{-}Co(III)^+$ models were almost the same, ca. 2.8 eV. However, for the base-on $CH_3{-}Co(II)$ model, this dissociation energy was much lower, ca. 1.6 eV, and for the base-off species, even lower, ca. 1.1 eV. A calculation of the total energy with geometry optimization at each constrained C−Co bond length for the base-off $CH_3{-}Co(II)$ model gives the lowest energy barrier for C−Co bond breaking. This value of 0.7 eV is found at around 2.4 Å[5] (Figure S1). However, even with this barrier, a kinetic calculation for the rate of intramolecular electron transfer (ET) shows that fast bond cleavage is improbable. Furthermore, an intramolecular ET at an avoided crossing would involve mixing of the ground π^* orbital and the excited σ^* orbital to give a pseudo-degenerate system as the bond vibrates. To allow orbital overlap, we had originally proposed that there would have to be geometric contortion in the transition state.[4] However, this would not be necessary if the intramolecular ET is between orbitals of the same symmetry, and indeed, CASSCF results discussed below show that the intramolecular ET should be between σ and excited σ^* C−Co orbitals. For pseudodegenerate states, as discussed above, there can be a failure of the DFT method.[31]

We have also estimated the energy of our model compounds including solvent using the Onsager model, and we find that the barrier of the Co−C bond breaking does not change greatly with the simple Onsager model. Therefore, we do not expect a large effect on the 0.7 eV barrier by including the solvent. An electric field could also effect the barrier,[9,19] and our DFT calculations show (Figure S2) that this effect is much more pronounced for Co(II) than Co(III) species and more pronounced for the base-off species in both cases. However, a field of 2.7×10^7 V/cm (0.01 au) or 5.4×10^7 V/cm (0.02 au) is required to reduce the approximate DFT bond dissociation energy by 60% or 80%, respectively (Figure S2), and these field strengths are about an order of magnitude too high for realistic situations. We conclude that neither the Co−C bond distance nor the activation for bond breaking in the methycobalamin radical anion can be explained by our DFT calculations.

A Vibronic Mechanism for Bond Elongation and Reductive Co−C Cleavage in Reduced Alkylcobalamins. We have examined calculational models and found that DFT, Hartree−

Fock (HF), and CASSCF with suitable basis sets all give virtually the same structure for Me-Cbl(III) model compounds (Table S1, Supporting Information). It is, however, only the one-electron reduced species where the PJT effect could be pronounced. This is because the DFT calculated ground and first excited states of the open-shell one-electron reduced alkylcobalamins show that the SOMO−LUMO energy differences for the Co(II) models are about one-half of the values for the R−Cbl(III) model compounds. This means they are lower than about 1.5 eV for most R−Cbl(II) model compounds.[38] According to the literature,[35] compounds with such HOMO−LUMO differences can be subject to strong electron state mixing interactions. Therefore, DFT calculations with such differences may not give the correct "ground state," since there can be mixing of filled and unoccupied orbitals. The result of such orbital mixing is a fractional population of the orbitals, including a number of the antibonding "unoccupied" orbitals. The population increase of the antibonding orbitals and the population decrease of the bonding orbital will lead to the "weakening" of a certain bonds, depending on which orbitals are involved in the mixing. The force constant of particular vibrational modes that couples the ground and excited states is lowered in the ground state so that the deformation of the compound can take place more easily along the specific coordinates. The theory of such an effect is well-developed for highly symmetric compounds, and the PJT effect has been used to predict and rationalize the symmetry of molecular systems.[34] Because the CASSCF calculation is a multiconfigurational method, it can implicitly include this coupling, since it contains the excited-state derivative "vibronic" coupling contributions $\langle \Psi_o | \partial V_{ne} / \partial Q | \Psi_* \rangle$ from the PJT effect.[39]

We used the *NWChem* electronic structure package for MCSCF geometry optimization of the reduced methylcobalamin models[40] on the Rachel supercomputer at the Pittsburgh Supercomputer Center. In this CASSCF calculation, a 6-31G** basis set was used for the Co atom and 6-31G for all other atoms with an active space with nine electrons and seven orbitals (CAS:9,7). The model had cobalt in a complete corrin ring system but with all side chains replaced by hydrogens and with imidazole as the axial base. The results of the CASSCF calculation show the equilibrium Co−C bond distance is now 2.164 Å for base-on and 2.144 Å for base-off models and the bond length of the Co−N_{ax} is 2.344 Å for the base-on model of the reduced species. The variation in Co−C bond distance is from 1.969 Å in DFT to 2.164 Å in CASSCF for the base-on model and from 1.938 Å to 2.144 Å for the base-off Me-Cbl-(II) model. The Co−N_{ax} bond distance shifts from 2.121 Å evaluated by DFT to 2.344 Å in CASSCF in the base-on model. The other bond distances in the corrin ring are similar to those obtained by using the DFT and HF geometry optimization.

The C−Co bond lengthening of about 0.2 Å correlates with a much lower BDE of the reduced species. The DFT bond dissociation curve shows that the bond is on the verge of breaking at around 2.4 Å (Figure S1). Strong orbital coupling would lead to an avoided crossing along the bond reaction coordinate between the bound ground state and the dissociated excited state leading to a much lower dissociation barrier than in Figure S1.

Figure 1 shows a comparison of the MOs from the DFT and CASSCF calculations for the Me-Cbl(II) base-on model, using the same basis set in both as described above. In this figure, the α and β open-shell orbitals of the same MO number have nearly the same surface contours. The figure shows that the DFT LUMO(+3) C−Co σ* orbital has become the LUMO in the MCSCF calculations. The SOMO is still the corrin π* orbital, and the DFT π* LUMO has become π* LUMO(+1) orbital in the CASSCF calculations. The other change to note is that the DFT HOMO(−4) C−Co σ orbital has now moved to the HOMO(−1) (for both the base-on or base-off cases).

The mixing of orbitals can be evaluated by comparing the amount of electron density transferred from one occupied orbital to another unoccupied orbital, e.g., by analyzing the population numbers of the MOs involved in the orbital mixing. In our case, the most important contribution comes from the coupling interactions of the HOMO(−1) σ and LUMO σ* giving 0.290 e^- population in the CASSCF LUMO for the base-on compound and about 0.305 e^- for the base-off compound. There is an important but lower contribution of the coupling interaction between the HOMO(−2) and LUMO(1) with about 0.09 e^- transferred for both base-on and base-off systems. The total charge transferred is ca. 0.4 e^-. Other molecular orbital couplings may take place but would require an even larger active space model, which would require enough memory for 1.5×10^3 matrixes, which was beyond our capability. However, our calculations do show some minor mixing contributions from the LUMO(2), which does not effect the axial bond lengths.

As indicated, the MCSCF HOMO(−1) C−Co σ to LUMO C−Co σ* coupling gives the most important contribution which leads to a shifting of the minimum of the total energy along the Co−C coordinate. Simultaneously, the Co−N bond increases, mainly under the influence of the anomalous trans effect of the shifting methyl group. We conclude that it is orbital couplings in the MCSCF calculations which lead to an increase in both the Co−C and the Co−N_{ax} bond distances.

We examined the effect of the number of electrons and orbitals in the active space. As the number of electrons goes from five to seven to nine in the CASSCF calculation, there is a dramatic increase in bond length. In fact, using only five electrons and five orbitals (CAS:5,5) gives results close to the DFT values. For the reduced MeCbl compounds, there is soft behavior, and the Co−N and Co−C axial bond lengths are very sensitive to the active space configuration. For example, for CAS:7,6 the calculation gives 2.053 Å for the Co−C and 2.33 Å for the Co−N_{ax} bond distances. It was observed that for CAS:9,7 the increase in Co−C bond distance comes by including the HOMO(−4) DFT orbital, which becomes HOMO(−1) in CASSCF. This fact suggests that the main contribution to the mechanism of Co−C elongation and bond breaking for the MeCbl radical anion comes from intramolecular charge transfer between the HOMO(−1) σ orbital and the LUMO σ* CASSCF orbitals.

This shift in the DFT ground-state equilibrium configuration, i.e., the distortion in the axial bond distances, can be viewed in terms of the relaxability theory described by Salem.[41] The change in energy to second order along the normal coordinate Q for the stretching mode of C−Co will include a "vibronic" coupling term which couples an excited state and ground state by a derivative potential-energy operator, i.e., there is a term in $\langle \Psi_o | \partial V_{ne} / \partial Q | \Psi_* \rangle^2 / (E_* - E_0)$ which can be summed over all such electronic interactions. This term is a negative contribution to the force constant that comes from the transition density discussed by Bader and MacDougall.[42] In our case, this transition density would come from the relaxation of charge density which accompanies the displacement of the Co and C nuclei. As long as the direct products of the excited-state and ground-state electronic wave functions have the same irreducible representation as the potential energy operator, i.e., the same symmetry as the mixing mode, this term will be finite and can

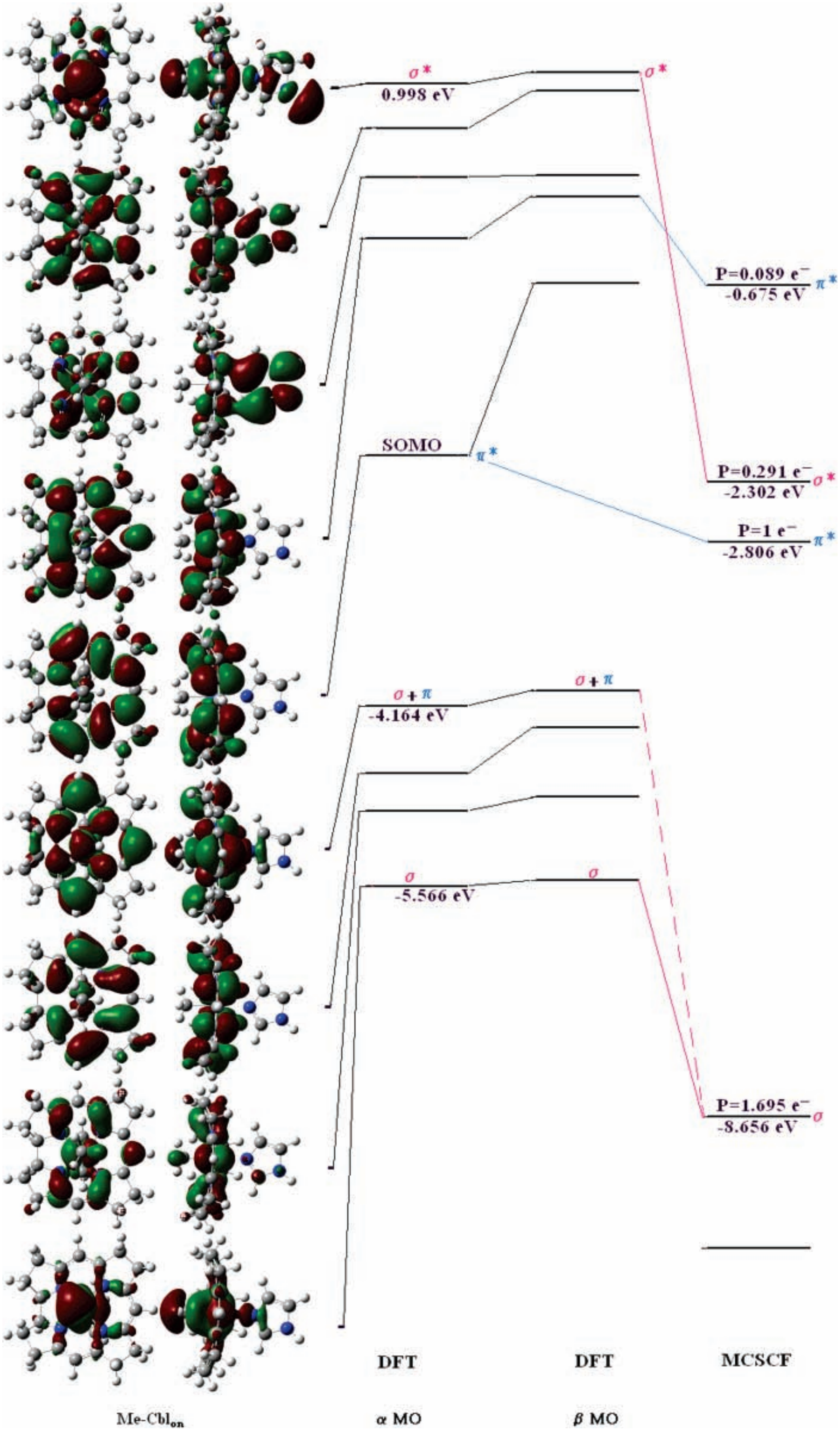

Figure 1. Comparison of DFT orbitals and energies (left) with the corresponding CASSCF orbitals and energies (right) for a base-on Me-Cbl(II) model. Calculations are geometry optimized with the B3LYP hybrid functional for DFT and CASSCF for MCSCF both with basis sets 6-31G** for Co and 6-31G for all other atoms. See text for other details.

reduce the curvature leading to a reduced force constant for the C−Co bond.[43] The magntitude of this PJT effect will depend on the energy gap, $E_* - E_0$, and on the overlap of the wave functions, $\Psi_o\Psi_*$, which is related to the above transition density. Thus, even for gaps of more than 1 eV, the distortion of the bond length can be dramatic.

We envisage that, as the bond stretches, the bond breaking step at the avoided crossing takes place by intramolecular ET from the HOMO(−1) C−Co σ orbital to its antibonding σ^* orbital. This bond breaking in methylcobalamin after one-electron transfer is preceded by an increase in both the Co−N_{ax} and Co−C_{ax} bonds under the influence of electronic state interactions. We previously addressed the question of whether the Co−C bond breaking in reduced alkylcobalamins[4,5] is a concerted or stepwise mechanism. Our calculations show that the SOMO of the reduced species has a strong π^* nature either from DFT or CASSCF calculations. Thus, charge transfer should go into this π^* orbital reorganizing the electronic structure which leads to mixing of $\sigma-\sigma^*$ orbitals of the C−Co bond. If an electron was immediately transferred to the σ^* molecular orbital, it would lead to the concerted mechanism, while if the electron goes into π^* SOMO, the coupling interactions increase both the Co−N$_{ax}$ and Co−C bond distances, making the bonds very weak. Moreover, the Co−N$_{ax}$ distance from the CASSCF calculation is significantly larger than the Co−C bond distance, about 0.2 Å larger, and thus, this bond should break first in the process that leads to Cbl(I)$^-$. We conclude, as before, that Co−C bond reductive cleavage in alkylcobalamines is rather a stepwise reaction than a concerted one. The point at which bond breaking occurs involves further displacement along the bond coordinate and may also involve the additional effect of a conical intersection. In addition, bond breaking will depend on factors such as the temperature, solvent, and electric field.

Conclusion

The strong state mixing effect in the reduced methylcobalamin shows that the minimum of the DFT energy surface in the Co^{3+}-Cbl parent becomes rather a saddle point than a minimum energy for “MeCbl(II)” species, and the real minimum, as shown by the CASSCF treatment, for the latter species corresponds to a geometry configuration with longer Co−C and Co−N$_{ax}$ bond lengths due to the PJT effect.The methylcobalamin radical anion when formed electrochemically undergoes rapid Co−C bond cleavage; however, in the methionine synthase (MS) reaction, if the mechanism involves charge transfer from the homocysteine thiolate to MeCbl, the same elementary steps would occur. An SET mechanism would give a true one-electron, [MeCbl]$^-$, intermediate, while an S$_N$2 mechanism would involve charge transfer in the transition state. Thus, on charge transfer, the histidine axial base in MS should dissociate first following a coupling of thiol radical and Me radical producing methionine and the Co(I), Cbl(I)$^-$, leaving species. In a DFT study of a model of this reaction,[44] a very similar stepwise process was proposed for an S$_N$2 mechanism on the basis of the DFT calculations. However, the true nature of the transition state should include the PJT effect, and it would seem that the Bader approach of reactivity based on charge density[42] should be applicable to such an S$_N$2 reaction.[45,46] In such a process, electronic state coupling should lead to a significant weakening of the Co−C and Co−N$_{ax}$ bonds as the charge is transferred from the thiolate. Finally, it is suggested that, in considering the electronic structure of Co(II) compounds with axial ligands, a major contribution to axial bond lengthening could come from $\sigma-\sigma^*$ orbital “vibronic” coupling. In fact, X-ray crystallographic evidence for this effect for a cobalamin model compound has been given for the axial ligands bond lengthening in a Co(II) macrocyclic complex.[47] Our CASSCF calculation does not completely treat the dynamical (short-range) electron correlation effect, which means that a full-multiconfigurational, full-valence type electronic structure calculation should be considered for “chemical accuracy” in such systems.

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Supporting Information Available: Table S1 of comparison of experimental structure coordinates with calculations on MeCbl(III) by different methods. Figure S1 for the dissociation energy vs C−Co bond distance for various Me-Cbl(III) and Me-Cbl(II) models and Figure S2 of the influence of electric field on these models. This material is available free of charge via the Internet at http://pubs.acs.org.

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(37) We estimated from our experimental data that the bond dissociation enthalpy of methylcobalamin is 31 ± 2 and that of its radical anion is 12 ± 2 kcal/mol (see ref 4).

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