Inorg. Chem. **2004**, *43*, 6628–6632

Inorganic Chemistry
Article

Structure–Energy Relations in Methylcobalamin with and without Bound Axial Base

Carme Rovira* and Xevi Biarnés

Centre de Recerca en Química Teòrica, Parc Científic de Barcelona, Josep Samitier 1-5,
08028 Barcelona, Spain

Karel Kunc

Laboratoire d'Optique des Solides, CNRS and Université P. et M. Curie, T13-C80, 4 pl. Jussieu,
75252 Paris-Cedex 05, France

Received February 13, 2004

The properties of the Co–C bond in methylcobalamin (MeCbl) are analyzed by means of first-principles molecular dynamics. The optimized structure is in very good agreement with experiments, reproducing the bent-up deformation of the corrin ring as well as the metal–ligand bond distances. The analysis of the binding energies, bond orders, and vibrational stretching frequencies shows that the axial base slightly weakens the Co–C bond (by 4%), while the alkyl ligand substantially reinforces the Co–axial base bond (by 90%). These findings support several experiments and provide insight into the conversion between the base-on and base-off forms of the MeCbl cofactor.

Introduction

The molecule of methylcobalamin (MeCbl) acts as cofactor of enzymes involved in many relevant biological reactions in which a methyl group is transferred from one substrate to another.[1] The MeCbl molecule (Figure 1a) is built from a cobalt−corrin macrocycle with several acetamide, propanamide, and methyl substituents. The central Co(III) atom is in an octahedral environment, with methyl and benzimidazole (BZM) in the axial positions. The latter is part of a nucleotide that is connected to the corrin ring via one of the propanamide corrin substituents. The first step of the reactions catalyzed by MeCbl-dependent enzymes is the heterolytic cleavage of the cobalt−carbon bond of the cofactor to yield a methyl cation and a five-coordinated Co^{I}Cbl species.[1]

It is known that in several methylcobalamin-dependent enzymes the cofactor adopts the so-called base-off form, in which the BZM is detached from the corrin ring (Figure 1a). In this case, a histidine residue from the protein might replace the BZM.[1] A recent study shows that the cofactor of methionine synthase interconverts between base-on and base-off forms during catalysis.[2] In some other enzymes, such as methyltransferases of corrinoid iron−sulfur acetogenic and methanogenic organisms, it is assumed that there is no axial base coordinated to the cobalt atom and the cofactor remains

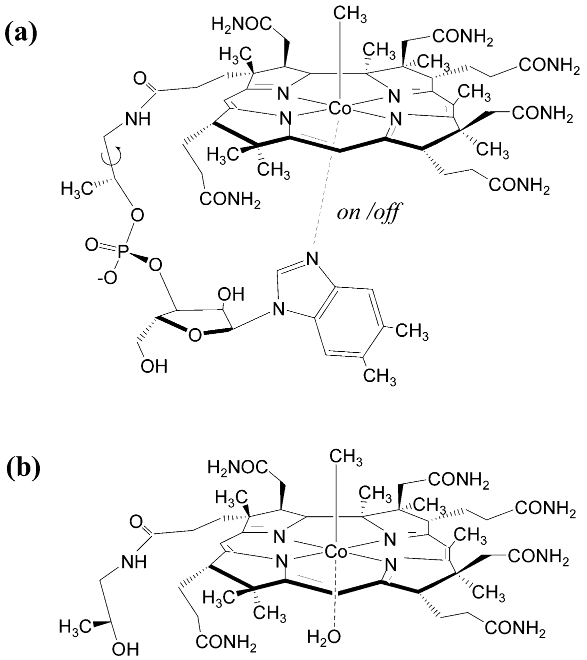

Figure 1. Structures of MeCbl (a) and MeCbi$^+$ (b). The distortion of the corrin ring is not displayed.

---

* Author to whom correspondence should be addressed. E-mail: crovira@pcb.ub.es.

[1] Ludwig, M. L.; Matthews, R. G. *Annu. Rev. Biochem.* **1997**, *66*, 269−313.

[2] Barandarian, V.; Ludwig, M. L.; Matthews, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 8156−8163.

10.1021/ic049810s CCC: $27.50

in the base-off form (Figure 1a). Even though these variations do not inhibit catalysis or change significantly the reaction rates,[1,3] their functional role is not yet known. A recent study suggests that the binding of the axial base would stabilize the Co−methyl bond that develops in the transition state of the methyl transfer reaction in methionine synthase.[3] However, thermolysis measurements for adenosylcobalamin (AdoCbl), also using data for adenosylcobinamide (AdoCbi$^+$, Figure 1b), conclude that the trans axial base weakens the Co−C bond by 4.5 ± 2.7 kcal/mol.[4a] In fact, the trend that the Co−C bond strength increases in base-off complexes and cobinamides[4b] is a general observation that dates back to the work by Schrauzer and Grate[5a−b] on the synthesis of cobalamins with very weak Co−C bonds. It was demonstrated that the binding of the axial base induces the cleavage of the Co−C bond in neopentyl and benzylcobalamins.[5c]

The interest in elucidating the role of the axial base in AdoCbl and MeCbl has motivated a number of investigations. A popular hypothesis is that by controlling the identity of the lower axial ligand, enzymes can modulate the Co(II)/Co(I) reduction potential, which is particularly important with respect to the cofactor reactivation mechanism after accidental oxidation of the Co^{I}Cbl postheterolysis product to the Co(II) oxidation state.[6] However, several experimental[7] and theoretical studies[8−11] of cobalamins with a variety of axial ligands show that these changes do not influence significantly the properties of the Co−C bond. An interesting observation was made by Ridder et al.,[9] who first reported the phenomenon of simultaneous Co−C and Co−N bond lengthening/shortening in cobalamins, something that was later reported for numerous B_{12} compounds and models.[12]

Density functional theory has been used with succes to analyze the properties of the Co−axial ligand bonds in cobalamins using small models.[10,11] A recent study by Stich et al.[11] provides a simple orbital model to explain the interplay among both axial ligands. However, despite the amount of information available, a quantitative study of the mutual strength of the Co−axial ligand bonds in MeCbl has not been performed.

Here we report on the structure, energy, and dynamics of the cobalt−axial ligand bonds in MeCbl and methylcobinamide (MeCbi$^+$) (Figure 1), with special emphasis on the presence of only one or both axial ligands. Since the BZM axial ligand is connected to the corrin ring via one of the sidearms (Figure 1a), the use of the complete MeCbl molecule is crucial to describe the properties of the Co−N_{ax} bond.

Computational Details

Our calculations are performed on the full molecules of MeCbl and MeCbi$^+$ using first principles molecular dynamics within the Car−Parrinello approach.[13,16] A detailed description of the Car−Parrinello method can be found in several recent publications.[14] We used the generalized gradient-corrected approximation of the spin-dependent density functional theory (DFT-LSD), following the prescription of Becke and Perdew.[17] The Kohn−Sham orbitals were expanded in a plane wave basis set with the kinetic energy cutoff of 70 Ry. Earlier calculations on cobalt-based macrocycles[15] showed that this cutoff is sufficient to achieve a good convergence of energies and structural properties of cobalt complexes. The molecules were enclosed in orthorhombic cells of sizes 22 × 18 × 17 Å (MeCbl) and 18 × 15 × 16 Å (MeCbi$^+$). Periodic boundary conditions were used for the neutral MeCbl molecule, while for MeCbi$^+$ we used an isolated box. Only valence electrons were explicitly included in our computation, and their interaction with the ionic cores was described by norm-conserving, ab initio pseudopotentials generated by means of the scheme developed by Troullier and Martins.[18] The pseudopotential for Co was supplemented with nonlinear core corrections to improve its transferability with respect to spin state energies.[19]

Structure optimizations were performed by means of molecular dynamics with scaling of the nuclear velocities. A time step of 0.14 fs was used, and the fictitious mass of the Car−Parrinello Lagrangian was set to 1200 au. The initial structure of MeCbl was taken from its X-ray structure.[20] To quantify the effect of the BZM on the Co−C bond, a base-off structure was build by rotation of the corrin sidearm around the C−C bond that connects the propanamide and the PO_4^- group until the Co−BZM distance is very large (>8 Å). The internal structure of the corrin side chain was kept fixed during the geometry optimization of the base-off

---

(3) Dorweiler, J. S.; Finke, R. G.; Matthews, R. G. *J. Am. Chem. Soc.* **2003**, *42*, 14653−14662.

(4) (a) Hay, B. P.; Finke, R. G. *J. Am. Chem. Soc.* **1987**, *109*, 8012−8018. (b) Seravalli, J.; Brown, K. L.; Ragsdale, S. W. *J. Am. Chem. Soc.* **2001**, *123*, 1786−1787.

(5) (a) Grate, J. H.; Schrauzer, G. N. *J. Am. Chem. Soc.* **1979**, *101*, 4601−4611. (b) Schrauzer, G. N.; Grate, J. H. *J. Am. Chem. Soc.* **1981**, *103*, 541−546. (c) Tsou, T.-T.; Loots, M.; Halpern, J. *J. Am. Chem. Soc.* **1982**, *104*, 623−624.

(6) Banerjee, R. *Chem. Rev.* **2003**, *103*, 2083−2094.

(7) See for instance: Hirota, S.; Polson, S. M.; Puckett, J. M.; Moore, S. J.; Mitchell, M. B.; Marzilli, L. G. *Inorg. Chem.* **1996**, *35*, 5646−5653.

(8) Mealli, C.; Sabat, M.; Marzilli, L. *J. Am. Chem. Soc.* **1987**, *109*, 1593−1594.

(9) De Ridder, D. J. A.; Zangrando, E.; Bürgi, H.-B. *J. Mol. Struct.* **1996**, *374*, 63−83.

(10) (a) Dölker, N.; Maseras, F.; Lledós, A. *J. Phys. Chem. B* **2001**, *105*, 7564−7571. (b) Andruniow, T.; Zgierski, M. Z.; Kozlowski, P. M. *J. Am. Chem. Soc.* **2001**, *123*, 2679−2680. (c) Andruniow, T.; Zgierski, M. Z.; Kozlowski, P. M. *J. Phys. Chem.* **2000**, *104*, 10921−10927. (d) Jensen, K. P.; Sauer, S. P. A.; Liljefors, T.; Norrby, P.-O. *Organometallics* **2001**, *20*, 550−556. (e) Jensen, K.; Ryde, U. *THEOCHEM* **2002**, *585*, 239−255. (f) Kurmaev, E. Z.; Moewes, A.; Ouyang, L.; Randaccio, L.; Rulis, P.; Ching, W. Y. *Europhys. Lett.* **2003**, *62*, 582−567. (g) Jensen, K.; Ryde, U. *J. Phys. Chem A* **2003**, *107*, 7539−7545. (h) Dölker, N.; Maseras, F.; Lledós, A. *J. Phys. Chem. B* **2003**, *107*, 306−315.

(11) Stich, T. A.; Brooks, A. J.; Buan, N.; Brunold, T. C. *J. Am. Chem. Soc.* **2003**, *125*, 5897−5914..

(12) See for instance: Bresciani-Pahor, N.; Forcolin, M.; Marzilli, L. G.; Randaccio, L.; Summers, M.; Toscano, P. J. *Coord. Chem. Rev.* **1985**, *63*, 1−125.

(13) Car, R.; Parrinello M. *Phys. Rev. Lett.* **1985**, *55*, 2471.

(14) (a) Tse, J. S. *Annu. Rev. Phys. Chem.* **2003**, *53*, 24−290. (b) Marx, D.; Hutter, J. Ab initio molecular dynamics: Theory and implementation. In *Modern Methods and Algorithms of Quantum Chemistry*; Grotendorst, J., Ed.; John von Neumann Institute for Computing: Julich, Germany, 2000; pp 301−409.

(15) (a) Rovira, C.; Kunc, K.; Hutter, J.; Parrinello, M. *Inorg. Chem.* **2001**, *40*, 11−17. (b) Rovira, C.; Kunc, K.; Parrinello, M. *Inorg. Chem.* **2002**, *41*, 4810−4814.

(16) Computations were performed using the CPMD program. Copyright IBM Corp. 1990−2003. Copyright MPI für Festkörperforschung, Stuttgart, Germany, 1997−2001.

(17) (a) Becke, A. D. *J. Chem. Phys.* **1986**, *84*, 4524−4529. (b) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822−8824.

(18) Troullier, N.; Martins, J. L. *Phys. Rev. B* **1991**, *43*, 1993−2006.

(19) Louie, G.; Froyen, S.; Cohen, M. L. *Phys. Rev. B* **1982**, *26*, 1738−1742.

(20) Randaccio, L.; Furlan, M.; Geremia, S.; Slouf, M.; Srnova, I. *Inorg. Chem.* **2000**, *39*, 3403−3413.

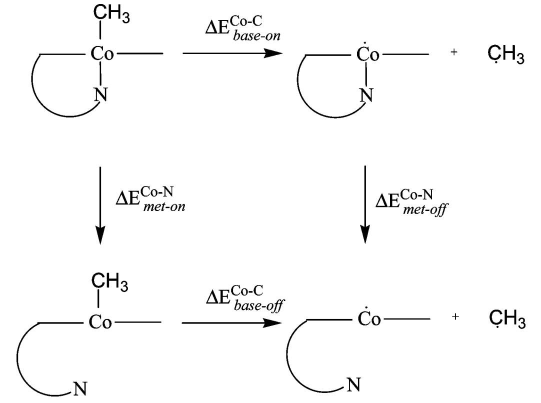

Figure 2. Schematic diagram of the species considered in the calculation of binding energies.

Table 1. Main Parameters Defining the Computed Structure of MeCbl, in Comparison with the X-ray Structure (Data in Parentheses)[20,a]

param	value	param	value
Co−C	1.99 (1.98)	∠C−Co−N_{ax}	(175.1)
Co−N_{ax}	2.15 (2.16)	∠N_c−Co−N_{ax}	87.3−95.2 (85.7−94.8)
Co−N_c	1.87, 1.93 (1.88, 1.89, 1.93, 1.97)	∠C−Co−N_c	88.1−92.2 (86.3−94.8)
N_c−C	1.34−1.45 (1.32−1.49)	δ(N_c−C_1−C_2−N_c)	40.8 (41.7)
		α	13.3 (13.6)
C_1−C_2	1.55 (1.42)		

[a] Distances are given in Å, and angles are in deg.

form. As X-ray structures of methylcobinamides are not available, the initial structure of MeCbi$^+$ was constructed from the optimized structure of MeCbl. Binding energies (Δ*E*) were obtained by subtracting the energy of the molecules from that of the optimized isolated fragments. In the case of the Co−N_{ax} bond ($\Delta E_{\text{met-on}}{}^{\text{Co-N}}$ or $\Delta E_{\text{met-off}}{}^{\text{Co-N}}$, depending on wether the CH_3 ligand is present or not), the binding energy was computed from the difference between the energy of the base-on and base-off forms. Figure 2 illustrates the coordination state of each species used in the calculation of binding energies. The cleavage of the Co−C/Co−N_{ax} bonds was considered as homolytic/heterolytic to compare with the experimental information available.[21−23] The calculations were done in the lowest energy spin state of each molecule: singlet for MeCbl and MeCbi$^+$ (both base-on and base-off) and radical doublet ($S = 1/2$) for the met-off systems.

Harmonic ligand stretch frequencies were computed from the diagonalization of the Hessian matrix obtained by finite differences (a step size of 0.02 Å was employed for the atomic displacements). Bond orders were computed after projection of Kohn−Sham orbitals into a minimum basis set of atomic states (we project on the pseudoatomic 1s orbital of H, (2s, 2p) of C, N, and O, and (3d, 4s, 4p) of Co). Finite temperature molecular dynamics simulations of MeCbl used a time step of 0.12 fs, and the fictitious mass of the Car−Parrinello Lagrangian was set to 900 au. The molecule was allowed to evolve for a total time of 2 ps at an average temperature of 270 K. Only the last picosecond was used for the analysis.

Results and Discussion

The most relevant structural parameters obtained from the calculations of MeCbl are summarized in Table 1. The computed structure is in good agreement with experiment. In particular, the Co−N_{ax} bond distance is well reproduced for the first time using DFT. The distortion of the corrin ring, measured as the N_c−C_1−C_2−N_c dihedral angle (N_c = corrin nitrogen atom; C_1 and C_2 are the carbon atoms connecting the two closest pyrrole rings) amounts to 40.8°, in good agreement with the experimental value of 41.7°. In the case of an isolated corrin[15a] this distortion was found to be less pronounced (35.6°). Another structural parameter often used to describe the corrin distortion is the axial base induced "bent-up" conformation of the corrin ring[5a,24] (α angle in Chart 1). The distortion of the computed structure (13.3°) matches perfectly the experimental value (13.6°).

Chart 1

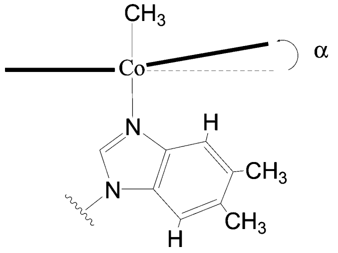

Table 2. Binding Energies (Δ*E*, in kcal/mol) and Bond Lengths (Å) Computed for the Co−C and Co−N_{ax} Bonds in MeCbl[a]

	calcd		exptl	
	dist	Δ*E*	dist	BDE
base-on				
Co−C	1.99	−31.7	1.98	−36, −37 ± 3[b]
Co−N_{ax}	2.15	−7.5	2.16	<−8[c]
base-off				
Co−C	1.98	−33.1	–	−41 ± 3.2[d]
met-off				
Co−N_{ax}	2.17	−1.37	–	–

[a] The experimental data correspond to bond lengths and bond dissociation energies (BDE). [b] Data from ref 22. [c] Estimated BDE for AdoCbl, given as an upper limit, from ref 23. [d] Value obtained by applying the enthalpy increase base-on/ base-off for AdoCbl reported in ref 4a to MeCbl.

As a way to have a glimpse of the temperature fluctuation of the Co−axial ligand bond distances, as well as the mobility of the corrin side chains, a molecular dynamics simulation of the MeCbl cofactor in its base-on form was performed. The time evolution of the two axial distances obtained from the simulation is depicted in Figure S1 of the Supporting Information. The Co−C bond distance oscillates between 1.9 and 2.15 Å and mainly reflects the Co−C bond stretch. In contrast, the Co−N_{ax} bond distance, fluctuating between 2.15 and 2.35 Å, displays a complex anharmonic behavior. It is likely that the tension on the Co−N_{ax} bond transmitted through the corrin sidearm affects to the dynamics of the bond. The propanamide and acetamide corrin side chains appear to be very mobile, with the terminal amide groups adopting several conformations during the dynamics. This conformational flexibility of the amide groups could help to anchor the cofactor in the protein by forming suitable hydrogen bonds with the protein residues.

---

(21) (a) Martin, B. D.; Finke, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 2419−2420. (b) Martin, B. D.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 585−592. (c) Hung, R. R.; Grabowski, J. J. *J. Am. Chem. Soc.* **1999**, *121*, 1359−1364.

(22) Hay, B. P.; Finke, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 4820−4829.

(23) Sirovatka, J. M.; Finke, R. G. *J. Am. Chem. Soc.* **1997**, *119*, 3057−3067.

(24) Lanhert, P. G. *Proc. R. Soc. London, Ser. A* **1968**, *303*, 43.

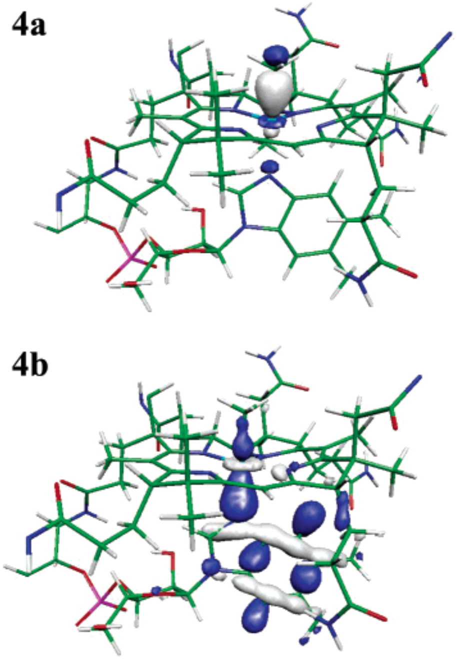

Figure 3. Isosurface plots of the two occupied orbitals that mainly contribute to the Co−C and Co−N_{ax} bonds in MeCbl.

The data of Table 2 show that the binding energy of the Co−C bond (−32 kcal/mol) is in reasonable agreement with the experimental values of −36 and −37 kcal/mol.[21] It should be taken into account that the strength of the Co−C bond in cobalamins is in general underestimated by DFT, even though the trends are well reproduced.[10] Moreover, solvent effects are not included in the calculations, which could partly account for the difference between the computed and experimental values. The computed Co−C bond strength in MeCbl is very similar to the one obtained using small models,[10g] indicating that the strength of the Co−C bond is not influenced by the corrin side chains. This is not the case for the Co−BZM bond strength, as our computed value (7.5 kcal/mol) is larger than the one reported in the pioneering work of Dölker et al. using small models lacking all the corrin substituents.[10a] In this study, the bond between Co and BZM ligand was found to be quite weak (−2.2 kcal/mol) and long (2.29 Å). Therefore, including the corrin side chains in the model appears to be crucial to reproduce the properties of the Co−BZM bond.

The data of Table 2 show that the axial base slightly weakens the Co−C bond: the Co−C binding energy is 1.7 kcal/mol smaller for the base-on than for the base-off form. It could be argued that, for a system of this size, this small energy difference is at the limits of our accuracy. Nevertheless, as it will be seen later on, the analysis of other bond properties (e.g. bond order and vibrational stretch frequency) gives support to this conclusion. The binding energy of the Co−N_{ax} bond shows a different trend, being larger for MeCbl than for the "met-off" form. In this case the change is more pronounced (6.1 kcal/mol). Therefore, we observe an opposite effect of the two axial ligands: the alkyl ligand strengthens the bond of the axial base, while the axial base weakens the bond with the alkyl ligand. This situation is somewhat different from what is found in other biologically relevant metal−macrocycles containing a M{d^6} cation in an octahedral environment. In the hemeproteins myoglobin and hemoglobin, for instance, the synergy between the two heme axial ligands (O_2 and His) is well docummented.[25]

Table 3. Binding Energies (kcal/mol) and Bond Lengths (Å) Computed for the Co−C and Co−N_{ax} Bonds in Methylcobinamide[a]

	calcd		exptl	
	dist	ΔE	dist	BDE
base-on				
Co−C	1.98	−33.0	−	-34 ± 1.8[b]
Co−O_{ax}	2.42	−1.9	−	−
base-off				
Co−C	1.98	−31.7	−	−
met-off				
Co−O_{ax}	2.43	−0.9	−	

[a] The experimental data correspond to bond lengths and bond dissociation energies (BDE). [b] Data for AdoCbi$^+$, from ref 4a.

The opposite effect of the two axial ligands can be rationalized with a simple orbital picture. There are two occupied orbitals that mainly contribute to the Co−C and Co−N_{ax} bonds in MeCbl (Figure 3). The lowest energy orbital (**4b**) is a σ^{CH_3}−d_{z^2}−σ^{BZM} bonding orbital, being mostly weighted on σ^{BZM} (this orbital is the no. 41 below the HOMO). The second orbital (**4a**) lies higher in energy than **4b** (it is the no. 22 below the HOMO), and it is only bonding with respect to the Co−C bond. Additional calculations show that a slight elongation of the Co−C bond (by 0.15 Å) raises the energy of both orbitals (0.1 eV in **4b** and 0.3 eV in **4a**), thus weakening the Co−N bond.[26] In contrast, elongation of the Co−N_{ax} bond by the same amount raises the energy of **4b** (by 0.3 eV) but lowers that of **4a**, although to a lesser extent (−0.1 eV). Since the energy of the two orbitals vary in opposite directions, the effect of stretching the Co−N_{ax} bond is less pronounced than in the previous case. This simple argument, already introduced by Mealli et al. in 1987, explains why the alkyl ligand influences significantly the bond of the axial base,[8] while the axial base has a minor effect on the Co−C bond. A very similar model is proposed by Stich et al. in a recent TD-DFT analysis of cobalamins.[11] Our study using the complete MeCbl molecule provides quantitative support to these previously proposed orbital models.

Analogous calculations for MeCbi$^+$ show that the Co−C bond is somewhat stronger (−33.0 kcal/mol) than in MeCbl (−31.7 kcal/mol), and the coordinated water is very weakly bound (−1.9 kcal/mol). Similarly to what is found for MeCbl, the Co−C bond strength changes slighly upon axial base binding (it increases by 1.3 kcal/mol) and the Co−water bond is much weaker when the methyl ligand is not present.

The fact that the binding energy of the Co−C bond changes relatively little upon detaching the axial base (by

---

(25) (a) Traylor, T. G.; Vijay, S. *Biochemistry* **1992**, *31*, 2847. (b) Rovira, C.; Kunc, K.; Hutter, J.; Ballone, P.; Parrinello, M. *J. Phys. Chem. A* **1997**, *101*, 8914−8925.

(26) In the extreme case of the homolytic cleavage of the Co−C bond, the weakening of the Co−BZM bond simply reflects the change in oxidation state of the Co center from +2 in the met-off form to +3 in MeCbl. As the extra electron on the Co center in the met-off form localizes in the Co{dz^2}-derived molecular orbital (that is antibonding with respect to the Co−N_{ax} bond), the Co−N_{ax} bond weakens with respect to MeCbl.

Table 4. Bond Orders and Vibrational Frequencies (cm^{-1}) Computed for the Co−C and Co−N$_{ax}$ Bonds in Methylcobalamin

	calcd		exptl
	bond order	freq	freq
base-on			
Co−C	0.70	509	500−505[a]
Co−N$_{ax}$	0.24	437	−
base-off			
Co−C	0.72	600	−
met-off			
Co−N$_{ax}$	0.21	89	

[a] Data from refs 11 and 28.

≈4%) makes it difficult to elucidate whether the axial base strengthens or weakens the Co−C bond. For this reason, other properties such as the vibrational frequency and bond order were analyzed. The values obtained are summarized in Tables 3 and 4.

The computed Co−C stretching frequency (509 cm^{-1}) is in good agreement with the experimental value of 500−505 cm^{-1}.[11,28] The most interesting aspect is that the Co−C stretching is smaller in MeCbl than in its base-off form.[28] In contrast, the Co−N$_{ax}$ frequency is larger in MeCbl than in the met-off form (in this case, the change is more pronounced, as it was the change in binding energy), reflecting an increase in Co−N$_{ax}$ bond strength upon CH$_3$ binding. Analysis of the bond orders give further support to this trend. The Co−C bond order increases in the base-off form and the Co−N$_{ax}$ bond order decreases for the met-off form, even though the magnitude of the changes is small.

In conclusion, the analysis of the axial ligand binding energies, bond orders, and vibrational frequencies evidences an opposite effect of the axial ligands in MeCbl: the CH$_3$ ligand significantly reinforces (by 90%) the bond with the axial base, while the axial base slightly weakens (by 4%) the Co−C bond. This is in agreement with experimental studies showing that the Co−C bond is stronger for the base-off form[4,5] and suggest that interconversion between base-on and base-off forms of the cofactor in MeCbl-dependent enzymes will have little effect on the strength of the Co−C bond. It is likely that the same arguments discussed here apply to AdoCbl and cobaloxim models as well. Further investigations in this direction are planned.

Acknowledgment. This work was supported by the DGI-Spain and the Generalitat de Catalunya (Projects BQU2002-04587-CO02 and 2001SGR-00044). Computer resources were provided by the IDRIS (Orsay, France) institute and the CEPBA-IBM Research Institute (CIRI) (Barcelona, Spain). C.R. is grateful for the financial support from the Ramón y Cajal program of the Spanish Ministry of Science and Technology and the ICREA foundation. We thank E. Canadell for a careful reading of the manuscript and one of the reviewers for his very insightful comments.

Supporting Information Available: Optimized structures of the molecules investigated as well as a graphic of the evolution of the Co−C and Co−N$_{ax}$ distances in the CPMD simulation. This material is available free of charge via the Internet at http://pubs.acs.org.

IC049810S

---

(27) Previous calculations on models of MeCbl and AdoCbl found a similar Co−C binding energy in both cases.[10a]

(28) Puckett, J. M., Jr.; Mitchell, M. B.; Hirota, S.; Marzilli, L. G. *Inorg. Chem.* **1996**, *35*, 4656−4662. (b) Nie, S.; Marzilli, P. A.; Marzilli, L. G.; Yu, N.-T. *J. Chem. Soc., Chem. Commun.* **1990**, 770−771.

(29) It should be noted that vibrational frequencies obtained by finite differences obtained within the harmonic approximation are in general higher than experimental values and only trends are expected to be correct. For this reason, we consider the agreement in the Co−C stretch frequency as fortuitous. On another hand, the Co−N$_{ax}$ frequency is largely overestimated in the calculations. It has been demonstrated experimentally that the identity of the lower axial ligand has essentially no effect on the Co−C stretching frequency in MeCbl derivatives.[28a,30]

(30) Dong, S.; Padmakumar, R.; Banerjee, R., Spiro, T. G. *Inorg. Chim. Acta* **1998**, *270*, 392−398.