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Theoretical Prediction of the Co−C Bond Strength in Cobalamins

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The homolytic Co−C bond dissociation energy (BDE) is central to the understanding of the function of vitamin B_{12}, an important coenzyme of many proteins. We investigate why earlier density functional (B3LYP) estimations of the BDE in methylcobalamin have given so poor results (91−117 kJ/mol) compared to the experimental estimate (155 ± 13 kJ/mol). Improving the basis set increases the discrepancy, as does a proper treatment of basis set superposition error (∼3 kJ/mol) and inclusion of zero-point energy corrections (−21 kJ/mol). On the other hand, relativistic (+6 kJ/mol), solvation (+7 kJ/mol in water), and thermal corrections (+6 kJ/mol) increase the BDE. However, neither of these corrections can explain the discrepancy. Instead, the problem seems to be the B3LYP density functional, which gives a corrected BDE of 78 kJ/mol, whereas the density functional Becke−Perdew-86 method and second-order perturbation theory (MP2) give BDEs of 134−139 kJ/mol. A comparison with other methods indicates that the error comes from the Hartree−Fock exchange (∼40 kJ/mol) and the LYP functional (∼15 kJ/mol). The problem is not restricted to methylcobalamin but seems to be general for homolytic metal−carbon BDEs of transition metals in tetra-pyrrole-like systems.

1. Introduction

Cobalamins are among the most complicated cofactors in biology.[1] The chemical structure of these vitamin B_{12} derivatives is shown in Figure 1. They consist of a corrin ring, which is similar to heme, but it is saturated at 10 atoms at the periphery of the ring and one of the methine linkages is missing. In the center of the corrin ring, a cobalt ion is bound to the four pyrrole nitrogen atoms. In the free coenzyme and in some proteins, the 5,6-dimethylbenzimidazole (DMB) group at the end of the long nucleotide tail coordinates to cobalt.[1−3] However, in many other enzymes, the imidazole ring of a histidine residue replaces DMB as the fifth ligand.[4−6] The sixth coordination site on the opposite side of the corrin ring may be occupied by either cyanide (vitamin B_{12}), a methyl group (methylcobalamin, MeCbl), or a 5′-deoxyadenosyl group (adenosylcobalamin, AdoCbl). This almost unique organometallic Co−C bond is the site of reactivity of the coenzyme. MeCbl and AdoCbl support rather different reactions: MeCbl acts as a methylation reagent by a heterolytic cleavage of the $Co^{III}-C$ bond to Co(I) and (formally) a CH_3^+ group, whereas AdoCbl acts as a radical generator through a homolytic cleavage of the Co−C bond to Co(II) and an adenosyl radical.[7]

An impressive amount of experimental research has been directed toward the understanding of how the Co−C bond is labilized and how the reactivities of the two coenzymes differ, but so far no consensus seems to have been reached.[7] Recently, quantum chemical calculations using density functional theory have been used to acquire insight into the reactivity of cobalamins.[8−14] For example, three studies have provided strong arguments against any catalytically significant trans steric effects.[8,9,14]

Density functional calculations, especially those performed with the B3LYP functional, have been successful in the study of models of proteins involving transition metals.[15,16] Typically, they reproduce bonds around the metal with an error of less than 0.07 Å,[17,18] and they give energies that are accurate to within ∼25 kJ/mol.[15,16] This is true also for cobalamin models, except the axial Co−N bond length, for which the extremely shallow potential explains the larger errors (0.12−0.15 Å; the errors are small in energy terms).[14] However, for the homolytic Co−C bond dissociation energy (BDE), the discrepancy between theory and experiments is larger than expected. The BDE for MeCbl in ethylene glycol has been determined by kinetic studies to be 155 ± 13 kJ/mol,[19,20] whereas B3LYP calculations give a much lower value, ranging from 91 to 117 kJ/mol, depending

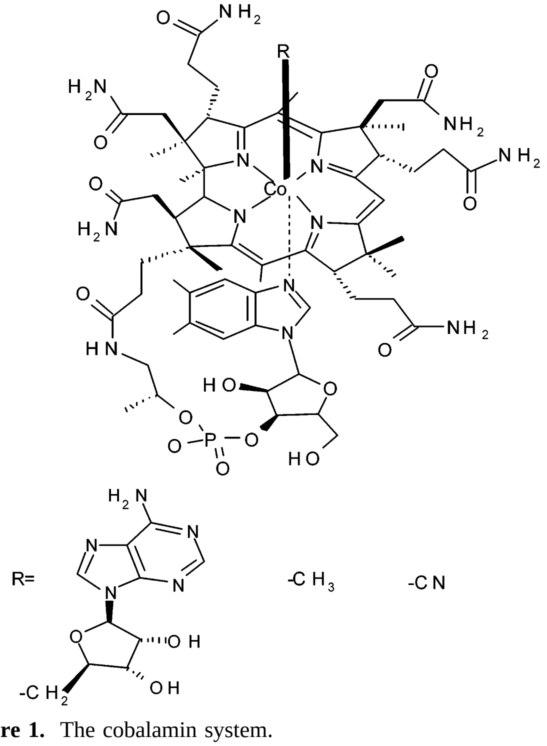

Figure 1. The cobalamin system.

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on the details of the calculations.[9,12,14] Thus, there is a discrepancy of 40−60 kJ/mol between theory and experiments. This is much larger than the expected error in the B3LYP method[15,16] and it makes it harder to interpret the calculations. Considering the importance of this energy for the reactions of cobalamin enzymes, it would be highly desirable to gain a deeper understanding of this discrepancy.

In this paper, we perform a systematic investigation of possible errors in the calculations, including variations in the basis set and theoretical method, and taking into account relativistic effects, basis set superposition error, zero-point energies, thermal effects, and solvation. We show that the calculated Co−C BDE depends strongly on the method and basis sets used and that the discrepancy is probably caused by problems with the B3LYP method. By studying several different density functional methods and various model systems, we get some insight into the cause and generality of the problem.

2. Methods

In all calculations in this paper, MeCbl is modeled by a corrin ring without any side chains (Cor), a central Co(III) ion, imidazole (Im) as one axial ligand, and a methyl group (Me) as the second axial ligand ($Co^{III}CorImMe$). This is the same model that was used in the earlier calculations.[8−14] Calculations have also been performed on a model where the Im ligand has been replaced with DMB or where the Me group has been replaced by a ribosyl (Rib) group. We do not expect that the side chains of the corrin ring will affect the BDE, but this remains to be demonstrated; for heme models, the effect of the side groups is minimal.[21]

The homolytic Co−C BDE is the energy of the reaction

$$Co^{III}CorImMe^{+} \rightarrow Co^{II}CorIm^{+\bullet} + Me^{\bullet} \qquad (1)$$

Several different theoretical methods were used to calculate this energy: the Hartree−Fock method (HF), second-order Møller−Plesset perturbation theory (MP2), and density functional calculations with the local-density approximation (S−VWN) and the gradient-corrected Becke−Lee−Yang−Parr (BLYP), Becke−Perdew 1986 (BP86), and Becke−Perdew−Wang 1991 (BPW91) methods, both as pure functional and as hybrid functionals in combination with HF exchange: B1LYP, B3LYP, B3P86, and B3PW91.[22−29] Energies were calculated on geometries optimized by the relevant method.

All calculations were performed with the Turbomole suite of software, version 5.3.[30,31] For the open-shell species on the right-hand side of eq 1, the unrestricted formalism was used for the density functional calculations, whereas the restricted open-shell formalism was employed for the HF and MP2 methods. Geometry optimizations were carried out in redundant internal coordinates; they were considered to be converged when the energy changed by less than 10^{-6} Hartree (2.6 J/mol) and the maximum norm of the internal gradient was less than 10^{-3} a.u.

Six different basis sets were used in the calculations. They are described in Table 1. Basis set 1 is the triple-ζ 6−311+G-(2d,2p) basis set, which includes diffuse functions on heavy atoms and two polarization functions on all atoms.[32−35] For cobalt, we have used the DZ basis set of Schäfer et al.,[36] enhanced with several functions (see Table 1). This basis set was used in our earlier calculations for accurate single-point energies.[14] Basis set 2 employs the same basis for non-cobalt atoms but the TZVPP basis set of Schäfer et al.[37] This basis (6s4p3d1f) is slightly smaller and less flexible than the enhanced DZpdf basis set (9s7p4d2f). Basis set 3 is the TZV basis for all atoms, that is, it is triple-ζ, but does not contain any polarization functions.[37] Basis set 4 is the 6-31G(d)basis set[38−40] combined with the DZpdf basis set[14] for cobalt. It was used in our earlier geometry optimizations. Basis set 5 uses TZV for cobalt and 6-31G(d) for other atoms. It was employed in one of the earlier studies.[12] Finally, basis set 6 was LANL2DZ, which applies a double-ζ D95 basis for non-cobalt atoms and an effective core potential to describe the cobalt core electrons.[41−44]

TABLE 1: The Basis Sets Employed in the Calculations

no.	Co	other atoms	references	# basis functions in $Co^{III}CorImMe$
1	DZspd2f[a]	6-311+G(2d,2p)	32-36	1099
2	TZVPP	6-311+G(2d,2p)	32-35,37	1076
3	TZV	TZV	37	520
4	DZpdf[b]	6-31G(d)	14,36,38-40	518
5	TZV	6-31G(d)	37,38-40	492
6	LANL2DZ	Dunning 95	41-44	339

[a] The DZpdf basis set[b] with an additional *s* function (0.0145941), and with two *f* functions (exponents 2.8 and 0.8) replacing that of DZpdf. [b] The DZ basis set of Schäfer et al. (621111111/3311111/3111/2),[36] augmented with one *f* (exponent 1.62), one *d* (0.1357), and two *p* functions (0.141308 and 0.043402).

Solvation effects were estimated using the conductor polarized continuum method (CPCM),[45−48] as implemented in Gaussian 98[49] (using the B3LYP method and basis set 4). Nonelectrostatic terms (cavitation, exchange, and dispersion) were included in the total energy. Calculations were performed at a dielectric constant of both 4 (similar to what may be expected in a protein[50,51]) and 78.4 (water solution). Probe parameters appropriate for water were used in both calculations. To get a better description of the cavity surface and charges induced by the solute, a smaller than default area of each surface element was used (tsare = 0.4 Å^2). Default radii were used for the atoms.

Basis set superposition errors and relaxation effects were corrected for by the extended counterpoise method:

$$\begin{aligned} BDE = -E(CMe,opt) + E(CX,CMe) + E(XMe,CMe) - \\ E(C,CMe) - E(Me,CMe) + E(C,opt) + E(Me,opt) \quad (2) \end{aligned}$$

Here, $E(x,y)$ denotes the energy of model x at the geometry y. The model is either $Co^{III}CorImMe$ (CMe), $Co^{II}CorIm$ (C), or a methyl radical (Me). X indicates that the basis functions, but not the atoms, of this part of the CMe model were included in the calculation. The geometry may either be fully optimized (opt) or kept at the optimized structure of $Co^{III}CorImMe$. The first three terms on the right-hand side of eq 2 constitute the standard formula for the counterpoise correction. To this, we have added four terms describing how the binding energy changes when the geometry of the $Co^{II}CorIm$ and Me moieties are allowed to relax.

Zero-point corrections and thermal effects were extracted from the vibrational frequencies, calculated with B3LYP and basis set 5 (DZpdf/6-31G*) using the Gaussian 98 software.[49] Thermodynamic corrections at 298 K and 1 atm were calculated with an ideal-gas approximation.[52] Relativistic corrections (scalar terms only)[31] to B3LYP energies were calculated by Turbomole with the various basis sets.

3. Results and Discussion

3.1 Basis Set Dependence. The aim of this article is to explain the discrepancy between calculated (91−117 kJ/mol[9,12,14]) and experimental (155 ± 13 kJ/mol[9,20]) homolytic Co−C BDE for MeCbl and to develop an accurate and

TABLE 2: BDEs (kJ/mol) Obtained with the Various Basis Sets, with or without Relativistic Corrections

basis set no.	BDE	relativistic correction	BDE with relativistic corrections
1	90.7	6.5	97.2
2	89.1	5.8	94.9
3	86.1	6.4	92.5
4	102.2	6.4	108.6
5	109.1	6.3	115.4
6	89.6		

appropriate procedure for calculating this central property of cobalamin chemistry. First, we investigated how the theoretical BDE varies with various basis sets, using the same theoretical method, B3LYP. Previous calculations with the same model have used basis sets number 5 (117 kJ/ mol[12]), 1 (on a geometry optimized with basis set 4; 91 kJ/mol[14]), and LANL2DZ on cobalt, 6-31G* on atoms bound to cobalt, and STO-3G on other atoms (99 kJ/ mol).[9]

BDEs calculated with the various basis sets are listed in Table 2. All are obtained by single-point calculations on geometries optimized by basis set 4 (DZpdf/6-31G*). It can be seen that the BDE varies between 86 (TZP) and 109 kJ/mol (TZP/6-31G*). Our result with the latter basis set is somewhat lower than that reported before (117 kJ/mol).[12] The reason for this difference is probably that different implementations of the B3LYP functional have been used and that we did not optimize the structures with this basis set.[31]

The result obtained with the largest basis set (1) is 91 kJ/mol. Thus, the BDE depends quite strongly on the basis set, and it tends to *decrease* as the basis set is improved. The largest theoretical BDE obtained before (117 kJ/mol[12]) seems to be an artifact of an unbalanced basis set, with a triple-ζ basis without any polarization functions on cobalt but a double-ζ basis with polarization functions on the other atoms. Both these differences tend to overestimate the σ-donation from methyl to cobalt, rendering the bond too strong.

Thus, we see that a triple-ζ basis set and *f* functions on cobalt are necessary to obtain an accurate value for the BDE. However, we also see that the basis set does not explain the discrepancy between theory and experiments; on the contrary, improvement of the basis set increases the discrepancy.

3.2 Relativistic Corrections. Next, we investigated the effect of relativistic corrections on the BDE. Scalar relativistic corrections (mass−velocity and Darwin terms, but no spin−orbit coupling) were calculated with Turbomole using the B3LYP method and basis sets 1−5. The results are also included in Table 2. It can be seen that the relativistic corrections do not vary with the basis set; they are +6 kJ/mol for all basis sets. Thus, they tend to increase the calculated BDE but not very much; the best estimate of the BDE is 97 kJ/mol, still 58 kJ/mol lower than the experimental value.

3.3 Basis Set Superposition Error and Relaxation Effects. Up to now, the BDE has been calculated simply by subtracting the energy of the Co^{II}CorIm complex and the methyl radicals from that of the Co^{III}CorImMe complex, all calculated at their optimized geometries. Thus, we have used the first and the two last terms in the more general eq 2. Such an energy includes relaxation effects, but it may contain significant basis set superposition error. By calculating the other terms in eq 2, we get an estimate of this error.

This was done with basis set 1. With this basis set, the superposition error is quite small, −3 kJ/mol, and of course decreases the BDE. With smaller basis sets, larger errors can be expected (e.g., 4 kJ/mol higher with basis set 3), but this is partly included in the basis set correction.

TABLE 3: Solvation Energies and the Solvation Correction to the BDE

species	solvation energy (kJ/mol) $\epsilon = 4$	solvation energy (kJ/mol) $\epsilon = 78.4$
Co^{III}CorImMe	-90.9	-140.6
Co^{II}CorIm	-90.9	-140.7
Me	4.9	7.0
BDE	5.0	7.1

On the other hand, relaxation effects are large and positive, 47 kJ/mol. Thus, it is not wise to calculate the BDE by a simple counterpoise calculation (terms 1−3 in eq 2) or by single-point calculations of the Co^{II}CorIm complex and the methyl radical at the geometry of the Co^{III}CorImMe complex. The main effect (32 kJ/mol) comes from the methyl radical, which changes its geometry from tetrahedral when bound to cobalt to trigonal planar in the radical, but also the Co^{II}CorIm complex relaxes by 15 kJ/mol.

3.4 Solvation Effects. The experimental measurements were performed in ethylene glycol solution (test measurements with AdoCbl have shown that the BDE in water solution is almost the same[53,54]), whereas the calculations are in a vacuum. Therefore, solvation effects may be one reason for the discrepancy between the results. To test this, we performed two calculations of the BDE in which the effect of a surrounding solvent is simulated by the polarizable continuum model (CPCM), using two different values of the dielectric constant, 4 and 78. The latter is representative for water solution, whereas all calculations together (including the vacuum calculation) give a feeling of what effects can be expected in other solvents, including the active site of an enzyme (a protein usually is assumed to have an effective dielectric constant of 2−16[50,51]).

The results in Table 3 show that solvation effects are small. The solvation energy of Co^{III}CorImMe and Co^{II}CorIm is similar, indicating that these two species have similar charge distributions and solvent-accessible surfaces. The methyl radical has a small, positive solvation energy and it provides all the differential solvation energy. Together, solvation effects increase the BDE by 5−7 kJ/mol, depending on the dielectric constant. Thus, solvent effects are small, which could be expected, because the reaction does not involve any charge separation. In fact, almost all the effect comes from the cavitation, dispersion, and repulsion energies; if these nonelectrostatic terms are ignored, the BDE increases by only 1 kJ/mol. If the solvation effects are instead calculated by the COSMO model implemented in Turbomole, the BDE *decreases* by 1 kJ/mol (only electrostatic terms).

3.5 Zero-Point Energies and Thermodynamic Corrections. The experimental BDE is an enthalpy, obtained at 120−141°C, whereas we have calculated pure (internal) energies. Two types of corrections are needed to convert the calculated energies to enthalpies, thermal corrections and zero-point energies. Both can be obtained approximately from theoretical calculations of the vibrational frequencies for the species involved in the reaction. We have performed such an analysis at the B3LYP level with basis set number 4 (DZpdf/6-31G*). The results are presented in Table 4.

The zero-point energies are large and lead to a decrease in the BDE of 21 kJ/mol. This is an appreciably larger correction than what has been suggested before and also of the opposite sign (+8 kJ/mol).[12] The reason for this discrepancy is not clear, but it seems quite obvious that the zero-point energies should decrease the BDE because the Co^{III}CorImMe complex has six more vibrations than the two dissociation products together.

In Table 4, we also present enthalpies, entropies, and Gibbs

TABLE 4: Zero-Point (ZPE) and Thermodynamic Corrections (at 1 atm and 403.15 K) to the Various Energies (kJ/mol or J/mol/K) Calculated from Frequency Calculations at the B3LYP Level and Basis Set 4 (DZpdf/6-31G*)

	ZPE	ΔH	ΔH + ZPE	ΔS	ΔG	ΔG + ZPE
Co^{III}	1235.2	129.1	1364.2	892.2	-230.6	1004.5
Co^{II}	1138.9	120.2	1259.1	857.4	-225.4	913.5
Me	75.4	15.0	90.4	217.2	-72.5	2.9
BDE	-20.9	6.2	-14.7	182.3	-67.3	-88.2

TABLE 5: Uncorrected Co−C BDEs Calculated with Various Methods Using Basis Set 4 and Optimized Geometries[a]

method	BDE (kJ/mol)
HF	-177.6
B1LYP	85.1
B3LYP	102.2 (103.2)
B3PW91	108.7
B3P86	123.3
B-LYP	140.8
BPW91	147.7
BP86	155.7 (160.0)
MP2	155.9
S-VWN	261.6

[a] Values in brackets were obtained with the Gaussian-98[49] software, rather than by Turbomole.[27,30]

free energies obtained from vibrational analysis by applying the ideal gas approximation at 403 K (in the middle of the temperature range studied experimentally) and 1 atm. The enthalpy correction is small and positive, 6 kJ/mol. This could be expected because a dissociation process increases the total molecular volume ($H = U + pV$). The correction is almost the same at other reasonable temperatures (e.g., only 0.3 kJ/mol lower at 298 K).

We can now sum up all corrections to the BDE to obtain our best estimate, which can be compared to the experimental value at 403 K. If we take the result for basis set 1 (+91 kJ/mol) and add the relativistic (+6 kJ/mol), counterpoise (−3 kJ/mol), solvation (+7 kJ/mol in water), zero-point (−21 kJ/mol), and thermal corrections (+6 kJ/mol), we end up with our best estimate of 86 kJ/mol. Thus, all corrections together actually decrease the BDE by 5 kJ/mol (with basis set 1; by 16 kJ/mol with basis set 4) and gives an estimate that is 69 kJ/mol lower than the experimental value. Apparently, neither of these corrections solve our initial problem.

3.6 The Method. Up to now, all calculations have been performed with the density functional B3LYP method, which has been the method of choice for most recent theoretical investigations of metalloproteins.[15,16] This method typically gives an energy error of less than 25 kJ/mol.[15,16] However, larger errors are occasionally observed and the Co−C BDE can very well be such a pathological case. Unfortunately, there does not exist any method that is clearly superior and can be employed for systems of this size (more than 500 basis functions). We have chosen to calculate the BDE with several other methods, most of which normally give comparable or slightly worse results than B3LYP: HF, MP2, and several other density functional methods. If the best of these give similar results as B3LYP, then the latter results can probably be trusted, but if the various methods give a different result, there is a good reason to call the B3LYP results in question. All geometries were reoptimized with the relevant method and the DZpdf/6-31G* basis set (4), and the Co−C BDE was calculated from eq 1, without any corrections.

The results of the eleven methods are collected in Table 5. The HF method gives spurious results (−178 kJ/mol). This reflects that HF does not describe transition-metal systems well. On the other hand, the local density functional method S−WVN strongly overestimates the BDE (261 kJ/mol), a well-known shortcoming of this method.[52] Interestingly, the gradient-corrected, pure density functional methods (BLYP, BPW91, and BP86), together with MP2, give an appreciably larger BDE than B3LYP, 141−160 kJ/mol (different implementations of the density functional methods[27] differ by 1−4 kJ/mol). Thus, these methods give a result that is close to the experimental value, even if the correction obtained in the previous sections (−16 kJ/mol for basis set 4) deteriorates the agreement somewhat. Hence, these results suggest that the low BDE obtained with the B3LYP method actually is a shortcoming of this method and that better results can be obtained with other methods.

The results of the density functionals in Table 5 give some clues of the cause of the B3LYP errors. It can be seen that all four hybrid functionals, which include HF exchange, give low values for the BDE, 85−123 kJ/mol. In fact, the B3 functionals give a 37−39 kJ/mol lower BDE than the corresponding pure functional. Furthermore, the B1LYP functional gives the lowest BDE of all density functionals tested and it also contains the highest amount of HF exchange, 28%, compared to 20% for the B3 methods.[29] Thus, the main reason for the failure of the B3LYP method seems to be the inclusion of exact HF exchange.

Moreover, the various correlation functionals also give slightly different results: P86 gives the highest BDE, whereas the PW91 and LYP functionals give 8 and 15 kJ/mol lower results. This also contributes to the poor result of B3LYP.

3.7 Geometry of Models. One possible reason for the shortcoming of the B3LYP method could be that the geometries obtained with the B3LYP are poor. Therefore, we have looked at geometries optimized with the various methods and basis set 4. The resulting Co−ligand distances are collected in Table 6.

We start with discussing the structures of Co^{III}CorDMBRib and Co^{II}CorDMB for which comparable experimental data are available (AdoCbl and Co(II)B$_{12}$).[55−59] These complexes have been optimized with the HF, B3LYP, B-LYP, and BP86 methods. We see that Co−C and Co−N$_{eq}$ distances obtained with all methods are in accordance with the experiments, even if BP86 gives Co−N$_{eq}$ distances closest to the EXAFS results (1.90 and 1.89 Å, respectively). However, the calculated Co−N$_{eq}$ distance is clearly too long with all methods, but once again BP86 gives the best results, with an error of ∼0.04 Å for both complexes. The reason for this discrepancy is the very soft potential of this bond, as has been discussed before.[14]

Turning to the corresponding complexes with Me and Im, we see that Co−C bond is shortened by 0.02−0.03 Å, in accordance with the trend observed in crystal structures of AdoCbl and MeCbl.[60−62] Likewise, the Co−N$_{ax}$ bond length is decreased by 0.02−0.19 Å (more for Co(III) than for Co(II)). Experimentally, the Co−N$_{ax}$ bond length decreases by 0.04 Å when DMB is replaced by Im in cyanocobalamin.[63]

For the Co−C bond, MP2 (1.89 Å) and S−VWN (1.90 Å) give the shortest bonds, much shorter than experimental Co−C bonds (∼1.98 Å). The pure gradient-corrected functionals (B-LYP, BPW91, and BP86, in this order) give the longest bonds (1.98−2.00 Å), whereas HF and the hybrid functionals give intermediate values (∼1.96 Å), with the same order for the correlation functionals. Thus, the Co−C bond lengths do not correlate with the calculated Co−C bond strengths.

For the Co−N bonds, S−VWN gives the shortest bonds (both axial and equatorial), followed by MP2. HF gives the longest bonds, but those obtained with methods involving the LYP correlation functional are also long, with no large difference

TABLE 6: Bond Distances of Corrin Models, Optimized with Various Methods[a]

method	R	L	Co−C	Co-N$_{ax}$	Co-N$_{eq}$(av)
HF	Me	Im	1.959	2.277	1.941
B1LYP			1.963	2.249	1.922
B3LYP			1.966	2.245 (2.235)	1.919
B3PW91			1.951	2.188	1.906
B3P86			1.946	2.160	1.902
B-LYP			2.005	2.292	1.925
BPW91			1.984	2.211	1.909
BP86			1.980 (1.981)	2.190 (2.191)	1.911 (1.909)
MP2			1.889	2.147	1.883
S-VWN			1.934	2.032	1.871
HF	−	Im		2.287	1.995
B1LYP				2.269	1.925
B3LYP				2.252	1.916
B3PW91				2.214	1.908
B3P86				2.185	1.904
B-LYP				2.217	1.926
BPW91				2.172	1.908
BP86				2.154	1.901
MP2				2.194	1.870
BPW91				2.019	1.866
HF	Rib	DMB	1.975	2.463	1.937
B3LYP			1.990	2.388	1.915
B-LYP			2.035	2.473	1.921
BP86			2.009	2.284	1.906
exp.			1.98−2.05	2.19−2.24	1.82−1.98
HF		DMB		2.302	2.002
B3LYP				2.318	1.921
B-LYP				2.277	1.925
BP86				2.201	1.907
exp.				2.13−2.16	1.86−1.90

[a] Values in brackets were obtained with the Gaussian-98[49] software, rather than by Turbomole.[27,30] Experimental data (X-ray crystallography and EXAFS) for AdoCbl and Co(II)Cbl are also included.[55−59]

between the pure and hybrid functionals. The other correlation functionals give intermediate values with unclear trends.

Thus, the conclusion is that BP86 gives a good overall structure, appreciably better than B3LYP, since it models both Co−C and Co−N bonds reasonably. However, this is unlikely to be the cause of the poor BDEs obtained with the B3LYP method, because the Co−N$_{ax}$ bond has only a minor trans effect on the Co−C bond,[8,14] so the differences in Co−N bond length cannot account for the large differences in Co−C BDE. This is confirmed by a direct calculation of the BDE with the B3LYP method on geometries obtained with the BP86 method. The resulting BDE, 104 kJ/mol (uncorrected), is close to that obtained with B3LYP geometries, showing that the geometry has a small influence for the calculated BDE (however, for the HF method, the BDEs are improved by 19 kJ/mol if the B3LYP geometries are used). Instead, we can conclude that there are inherent problems with the LYP functional and the HF exchange, which are not related to structure.

3.8 Other Reactions. We have seen that B3LYP gives a result of the homolytic Co−C BDE for methylcobalamin that is widely different from those obtained with MP2 and the BP86 density functional, and also from the experimental results, even when corrected for the various effects. The question then naturally arises: How general is this problem, that is, for what systems can it be expected? This question will be addressed in this section.

First, we look at the BDE of cobalamins with various axial ligands: Im or DMB and Me or Rib. The results are collected in Table 7 (uncorrected energies obtained with basis set 4) and show that the problem is not restricted to methylcobalamin. For all four combinations of axial ligands, B3LYP gives a ∼55 kJ/mol lower BDE than BP86. There is only a minimal difference between Im and DMB, whereas the difference between Me and Rib is somewhat larger (4−5 kJ/mol).[12−14] These differences are the same with the two functionals. The largest system, CoCorDMBRib, is a reasonable model of coenzyme B$_{12}$ (AdoCbl). Interestingly, the experimental BDE of AdoCbl is appreciably lower than that of methylcobalamin, 130 kJ/mol.[64] We currently investigate why the theoretical calculations do not reproduce this trend.

TABLE 7: The Difference in B3LYP and BP86 Results (kJ/mol) for Co−C BDEs and Other Related Reactions[a]

system	BP86	B3LYP	BP86−B3LYP	exp
CoCorImMe	155.9	102.2	53.8	155 ± 13[19,20]
CoCorDMBMe	156.9	101.4	55.5	
CoCorImRib	151.6	97.5	54.0	
CoCorDMBRib	152.5	96.3	56.2	130[64]
CoDmg$_2$Im	103.7	52.7	51.0	87.8[65]
CoDmg$_2$PyrCH$_2$CH$_3$Ph	100.2	48.9	51.3	83.6[65]
CoPor(P(CH$_3$)$_2$Ph)(CH$_2$Ph)	82.9	32.1	50.8	113.3[66]
CoPorImMe	156.4	98.1	58.3	
FeCorImMe	148.0	94.5	55.4	
FePorImMe	146.7	93.4	53.3	
NiCorImMe	117.9	51.5	66.4	
Ni^{II}CorMe	59.3	65.8	-6.6	
CH$_4$	478.1	471.5	6.6	438[69]
heterolytic BDE (eq 3)	709.4	699.7	9.7	
hydrolysis (eq 4)	-58.9	-75.2	16.3	
BDE of Im (eq 5)	62.8	59.5	3.4	

[a] Dmg = dimethylglyoximate, Pyr = pyridine, Por = porphine.

Next, we examine three additional Co−C BDEs with other ring systems than corrin, viz., two cobaloximes (with a tetradentate equatorial bis-dimethylglyoximate ligand) and a cobalt porphyrin. Once again, we see from Table 7 that B3LYP gives a 51 kJ/mol lower BDE than BP86 for all these three systems. On the other hand, the experimental results vary: For the two cobaloximes, the experimental result is ∼16 kJ/mol lower than the BP86 result.[65] However, for the porphyrin, it is instead 30 kJ/mol larger than the BP86 result.[66] Thus, the B3LYP problem is a general feature of cobalt tetrapyrroles and similar systems.

Next, we investigate whether other transition metals give similar problems. In Table 7, we also include the homolytic metal−carbon BDE for several porphine and corrin models with cobalt, iron, or nickel ions (and Im and Me axial ligands). The results show that the difference between B3LYP and BP86 is approximately the same for iron and cobalt, ∼55 kJ/mol. For nickel, the difference is slightly larger, 66 kJ/mol. It is calculated for the high-spin states; for the less stable low-spin states (where the imidazole ligand dissociates in the Ni^{II} state), the difference is 73 kJ/mol. Thus, the problem seems to be quite general for transition metals, even if the difference varies somewhat with the metal.

However, if the reaction involves several spin surfaces, the relation does not hold any longer, because B3LYP and BP86 give widely different spin-splitting energies. For example, for the BDE of Ni^{II}CorMe, where the reactant is most stable in the high-spin state, whereas the four-coordinate Ni^{I}Cor product is most stable in the low-spin state, the difference between the BP86 and B3LYP BDEs is −7 kJ/mol for the ground states (but 69 kJ/mol on the high-spin surface).

Finally, we also investigated several related reactions to get some clues of the origin of the difference between B3LYP and BP86. First, we calculated the homolytic C−H BDE of methane. As can be seen in Table 7, the difference between B3LYP and BP86 for this reaction is only 7 kJ/mol. Thus, the methyl radical is not the main cause of the difference. Second, we studied the *heterolytic* BDE of CoCorImMe, that is, the energy of the reaction:

$$\mathrm{Co^{III}CorImMe^+ \rightarrow Co^{I}Cor + Im + Me^+} \qquad (3)$$

Thus, it contains only closed-shell species (at the B3LYP level, the open-shell singlet of $\mathrm{Co^I}$Cor is slightly lower in energy, ~4 kJ/mol,[67] but it gave similar BDEs at the BP86 level, the closed-shell state is 0.1 kJ/mol more stable). Once again, the difference between B3LYP and BP86 is only 10 kJ/mol. Likewise, the energy of the hydrolysis reaction:

$$\mathrm{Co^{III}CorImCH_3 + H_2O \rightarrow Co^{III}CorImOH + CH_4} \qquad (4)$$

and the bond energy of the Im ligand to CoCorImMe:

$$\mathrm{Co^{III}CorImMe \rightarrow Co^{III}CorMe + Im} \qquad (5)$$

which contain $\mathrm{Co^{III}}$ on both sides of the reactions, give a small difference between B3LYP and BP86, 3 and 16 kJ/mol, respectively. Consequently, all these results indicate that the problem lies in the differing correlation energy of the $\mathrm{Co^{III}}$ and $\mathrm{Co^{II}}$ systems.

4. Conclusions

We have investigated why earlier theoretical calculations[9,12,14] have given so poor values of the homolytic Co−C BDE of MeCbl. The results indicate that the B3LYP method fails strongly for this energy. Therefore, other methods, for example, single-point MP2 calculations, have to be used to estimate this central property of cobalamin chemistry.

However, the density functional BP86 method seems to be a better alternative to both MP2 and B3LYP for several reasons. First, BP86 is more economical than MP2 both with respect to computer time and the disk space and memory resources needed. Moreover, in contrast to B3LYP, BP86 calculations can employ various density-fitting (e.g., the resolution of identity) approximations, which typically speeds up the calculations by a factor of 5.[68] Second, density functional methods are known to have a smaller basis set dependence than correlated ab initio methods.[52] Third, we have seen that the BP86 method gives geometries that are closer to experiments than B3LYP and MP2.

The corrections to the BDE for relativistic, counterpoise, solvation, thermal, and zero-point effects calculated in this paper at the B3LYP level seem to be reasonably general. We have recalculated these corrections also for the structures optimized with the BP86 method. It turned out that all the correction terms were within 3 kJ/mol of those obtained with the B3LYP method, giving a total correction of −21 kJ/mol, if the BDE is calculated with basis set 4, and −11 kJ/mol if it is calculated with a large basis set (number 1). Thus, our best result for the BDE of methylcobalamin is 135−139 kJ/mol, which is 16−20 kJ/mol lower than the experimental estimate, that is, just outside the experimental error bar but within the error expected for theoretical methods, 25 kJ/mol.

Finally, we have shown that this is a general problem of the B3LYP functional for homolytic metal−carbon BDEs in tetrapyrroles and similar systems. It is probably caused by the differing correlation energies of open- and closed-shell transition-metal complexes with a different number of unpaired electrons.

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