J. Am. Chem. Soc. **2001,** *123,* 2679−2680

Theoretical Determination of the Co−C Bond Energy Dissociation in Cobalamins

Tadeusz Andruniow,[†] Marek Z. Zgierski,[‡] and
Pawel M. Kozlowski*[,†]

Department of Chemistry, University of Louisville
Louisville, Kentucky 40292
Steacie Institute for Molecular Science, National Research
Council of Canada, Ottawa, Ontario, Canada K1A OR6

Received December 5, 2000
Revised Manuscript Received January 30, 2001

We report calculations of the Co−C_R bond dissociation energy (BDE) in six-coordinate cobalamins (models of coenzyme B_{12}) using gradient-corrected density functional theory (DFT) with the Becke−Lee−Yang−Parr composite exchange correlation functional (B3LYP).[1] The B3LYP level for computations of dissociation energies is appropriate for organometallic compounds containing a 3d-metal atom, but this level is not adequate for compounds containing metal−metal bonds as has been recently shown by Bauschlicher and co-workers.[2]

For purposes of present work, the homolytic cleavage of the Co−C_R bond in B-[Co^{III}(corrin)]-R was defined as the energy of the process shown in Figure 1, and the BDE of Co−C_R was evaluated as

$$\mathrm{BDE} = \text{B-[Co}^{\mathrm{III}}\text{(corrin)]-R}_{\mathrm{opt}} - \text{B-[Co}^{\mathrm{II}}\text{(corrin)]}_{\mathrm{opt}} - {}^{\bullet}\mathrm{R}_{\mathrm{opt}} + \Delta_{\mathrm{ZPE}} \quad (1)$$

In the above equation subscript opt indicates the energy of the DFT optimized structure, while Δ_{ZPE} stands for vibrational zero-point energy correction. The six-coordinate cobalamin models, B-[Co^{III}(corrin)]-R, used to calculate the Co−C_R BDEs (eq 1) include the actual corrin macrocycle ring as the equatorial ligand system and imidazole (Im), dimethylbenzimidazole (DBI), or water (H_2O) base as the α-*trans* ligand. The sidearm and peripheral substituents of the corrin ring were left out to simplify the calculations while still retaining the important structural features. The *β* axial ligand was modeled by a series of groups with different complexity ranging from methyl (Me), ethyl (Et), through 5′-deoxy-5′-adenosyl (Ado) and isopropyl (iProp) to *tert*-butyl (tBut). Our recent studies[3,4] on the Co−C_R bond activation in models of coenzyme B_{12} and the development[5] of a quantitative vibrational force field capable of modeling vibrational spectra of B_{12} lends strong confidence that this approach is suitable for the theoretical evaluation of homolytic Co−C_R bond cleavage.

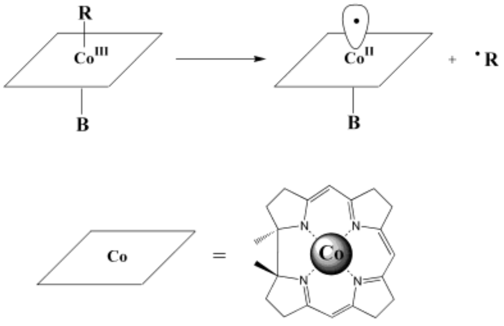

Figure 1. Homolytic bond cleavage in B-[Co^{III}(corrin)]-R cobalamins. The cobalamin corrin ring is abbreviated by a square.

Although studies directed at determining relevant Co−C_R BDEs have been carried out for almost two decades[6] and determination of the Co−C_R BDEs has been subject of intense experimental research, mainly in the Halpern[7a−h] and Finke[7i−l] laboratories, no attempt has been made to determine these BDEs quantum mechanically. The present work represents the first theoretical effort to estimate these energies theoretically (Table 1). The experimentally determined values of the Co−C_R BDEs range from 17 to 34 kcal/mol for model compounds, while these values are higher (26−37 kcal/mol) for cobalamins. Comparison with available experimental data shows that the calculated BDE energies underestimate the experimental values, although the experimentally observed pattern for MeCbl, AdoCbl, and iPropCbl is well-captured by the current DFT computations (Tables 1 and 2). Taking into account the complexity of these calculations and the fact that they were carried out for a single molecule in gas phase without interactions from the environment, the agreement between experiment and theory is surprisingly good.

Two striking observations may be gleaned from the results of our calculations (Table 1 and Figure 2): (i) theoretically determined Co−C_R BDEs do not depend on the *trans* axial ligand, and (ii) these dissociation energies correlate linearly with the Co−C_R bond length. As one can expect, the dissociation energy

Table 1. DFT-Optimized Co−C_R Bond Distances (Å), Total Energies (au) and Co−C_R BDEs (kcal/mol) of B-[Co^{III}(corrin)]-R

B	R	Co−C_R bond length (Å)	total energy (au)		BDE[a] (kcal/mol)
			B-[Co^{III}(corrin)]-R	•R	
Im	Me	1.962	−2604.515610	−39.837518	28
	Et	1.989	−2643.824699	−79.156385	22
	Ado	1.994	−3452.297525	−887.633922	19
	iProp	2.033	−2683.131915	−118.475958	14
	tBut	2.103	−2722.434337	−157.795393	3
total energy of Im-[Co^{II}-corrin] = −2564.633478 au					
DBI	Me	1.962	−2836.791675	−39.837518	25
	Et	1.990	−2876.100752	−79.156385	19
	Ado	1.992	−3684.575798	−887.633922	18
	iProp	2.027	−2915.410071	−118.475958	13
	tBut	2.091	−2954.713727	−157.795393	3
total energy of DBI-[Co^{II}-corrin] = −2796.913370 au					
H_2O	Me	1.948	−2454.703789	−39.837518	29
	Et	1.975	−2494.014239	−79.156385	24
	Ado	1.975	−3302.487154	−887.633922	21
	iProp	2.015	−2533.321868	−118.475958	17
	tBut	2.083	−2572.626762	−157.795393	7
total energy of H_2O-[Co^{II}-corrin] = −2414.819493 au					

[a] Reported Co−C_R BDEs were not corrected for Δ_{ZPE} (eq 1). The Δ_{ZPE} correction evaluated for several points was systematic and equal to ∼2 kcal/mol. This value essentially cancels out with estimated correction for basis set superposition error (BSSE).

---

* Corresponding author. Telephone: (502) 852-6609. Fax: (502) 852-8149. E-mail pawel@louisville.edu.

[†] University of Louisville.

[‡] Steacie Institute for Molecular Science, National Research Council of Canada.

(1) All calculations were carried out with the GAUSSIAN suite of programs for electronic structure calculations with 6-31G(d) [for H, C, N, O] and Ahlrichs' VTZ [for Co] basis sets. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.3; Gaussian, Inc.: Pittsburgh, PA, 1998.

(2) Ricca, A.; Bauschlicher, C. W. *J. Phys. Chem.* **1997**, *101*, 8949−8955 and references therein.

(3) Andruniow, T.; Zgierski, M. Z.; Kozlowski, P. M. *Chem. Phys. Lett.* **2000**, *331*, 509−512.

(4) Andruniow, T.; Zgierski, M. Z.; Kozlowski, P. M. *J. Phys. Chem. B* **2000**, *104*, 10921−10927.

10.1021/ja0041728 CCC: $20.00

Table 2. Selected Experimental Values of the Co−C_R BDEs in Model Compounds and Cobalamins

	compound	$\Delta H^{\ddagger}$ kcal/mol	BDE kcal/mol	ref
1	[(py)(saloph)Co−$CH_2CH_2CH_3$]	27.1 ± 1.1	25	7a
2	[(py)(saloph)Co−$CH(CH_3)_2$]	21.8 ± 1.0	20	7a
3	[(py)(saloph)Co−$CH_2C(CH_3)_3$]	20.3 ± 0.6	18	7a
4	[(py)(saloph)Co−$CH_2C_6H_5$]	23.6 ± 1.0	22	7a
5	[(4-NH_2-py)Co(DH_2)−$CH(CH_3)C_6H_5$]	23.1 ± 0.5	21.2	7b
6	[(2-NH_2-py)Co(DH_2)−$CH(CH_3)C_6H_5$]	17.7	16.6	7e
7	[(4-CH_3-py)Co(DH_2)−$CH(CH_3)C_6H_5$]	21.8 ± 0.5	20.1	7b
8	[(py)Co(DH_2)−$CH(CH_3)C_6H_5$] in acetone	21.6 ± 0.5	19.5	7b
9	[(py)Co(DH_2)−$CH(CH_3)C_6H_5$] in toluene	21.2 ± 0.5	19.9	7b
10	[(py)Co(DH_2)−CH_3]		33.1 ± 1.6	7n
11	[(py)Co(DH_2)−$CH_2C_6H_5$]		31.2 ± 2.2	7n
12	[(py)Co(DH_2)−$CH(CH_3)_2$]		21.3 ± 2.4	7n
13	[(4-CN-py)Co(DH_2)−$CH(CH_3)C_6H_5$]	20.1 ± 0.5	17.9	7b
14	[(imidazole)Co(DH_2)−$CH(CH_3)C_6H_5$]	23.0 ± 0.5	20.8	7b
15	[(acetone)Co(DH_2)−$CH(CH_3)C_6H_5$]	19.1	16.9	7e
16	[(PMe_2Ph)Co(DH_2)−$CH(CH_3)C_6H_5$]	25.9	24	7c
17	[(P($CH_2CH_2CN)_3$)Co(DH_2)−$CH(CH_3)C_6H_5$]	22.1	20	7c
18	[(P−n-Bu_3)Co(DH_2)−$CH(CH_3)C_6H_5$]	22.8	21	7c
19	[($PEtPh_2$)Co(DH_2)−$CH(CH_3)C_6H_5$]	21.3	19	7c
20	[(PPh_3)Co(DH_2)−$CH(CH_3)C_6H_5$]	19.3	17	7c
21	[(PMe_2Ph)Co$(DH)_2$−$CH_2C_6H_5$]	32.4	30.4	7d
22	[(P−n-Bu_3)Co$(DH)_2$−$CH_2C_6H_5$]	30.9	28.9	7d
23	[($PEtPh_2$)Co$(DH)_2$−$CH_2C_6H_5$] in toluene	28.8	26.8	7d
24	[($PEtPh_2$)Co$(DH)_2$−$CH_2C_6H_5$] in ethylene glycol	34.8		7f
25	[(PPh_3)Co$(DH)_2$−$CH_2C_6H_5$] in toluene	27.8	25.8	7d
26	[(PPh_3)Co$(DH)_2$−$CH_2C_6H_5$] in ethylene glycol	34.1		7f
27	[(P(c−$C_6H_{11})_3$)Co$(DH)_2$−$CH_2C_6H_5$] in toluene	24.8	22.8	7d
28	[(P(c−$C_6H_{11})_3$)Co$(DH)_2$−$CH_2C_6H_5$] in ethylene glycol	29.1		7f
29	[(PMe_2Ph)Co(OEP)−$CH_2C_6H_5$] in toluene	29.1	27.1	7d
30	[(Me_2Ph)Co(OEP)−$CH_2C_6H_5$] in ethylene glycol	33.3		7f
31	[(P−n-Bu_3)Co(OEP)−$CH_2C_6H_5$]	31.3	29.3	7d
32	[($PEtPh_2$)Co(OEP)−$CH_2C_6H_5$]	28.1	26.1	7d
33	[(PPh_3)Co(OEP)−$CH_2C_6H_5$]	25.8	23.8	7d
34	[(P(c−$C_6H_{11})_3$)Co(OEP)−$CH_2C_6H_5$]	31.6	29.6	7d
35	$(CH_3)_3CCH_2$−B_{12} (Halpern)	26.7 ± 1.2		7g
36	$(CH_3)_3CCH_2$−B_{12} (Schrauzer)	23.4 ± 0.2		7m
37	$(CH_3)_3CCH_2$−B_{12} (base-off)	32.1 ± 0.1		7m
38	c−C_5H_9−CH_2−B_{12}	26.8 ± 2		7g
39	$(CH_3)_2CH$−B_{12}	20.7 ± 0.5		7m
40	$(CH_3)_2CH$−B_{12} (base-off)	28.3 ± 0.2		7m
41	$(CH_3)_2CHCH_2$−B_{12}	26.8 ± 0.4		7m
42	$C_6H_5CH_2$−B_{12}	24.6 ± 0.6		7m
43	$C_6H_5CH_2$−B_{12} (base-off)	26.9 ± 0.5		7m
44	Ado−B_{12} (Halpern)	28.6 ± 1	26 ± 2	7h
45	Ado−B_{12} (Finke)	33 ± 2	30 ± 2	7i
46	Ado−B_{12} (base-off)	37.5 ± 1.2	34.5 ± 1.8	7j
47	Me−B_{12}	41 ± 3	37 ± 3	7k, 7l

lowering is mainly due to Co−C_R bond weakening, and the energies diminish in the order Me > Et > Ado > iProp > tBut, consistent with changes in the Co−C_R bond length. Interestingly, these calculated Co−C_R BDEs fall essentially along a straight line with slope and intercept equal to −168.25 $Å^{-1}$ kcal/mol and 355.88 kcal/mol, respectively. We also tested the possibility that three separate lines (each associated with different *trans* ligand) were required to reproduce these theoretical data (Table 1). We found that two among them (B = Im and H_2O) were almost identical, while a third (B = DBI) had an identical slope with a slightly lower intercept. We attributed these small differences to numerical inaccuracy and concluded that variation of the α-*trans* axial base does not influence the *β* axial ligand. This phenomenon may be readily understood in terms of a molecular orbital picture which shows that essentially four molecular orbitals allow the succinct description of the N_B−Co−C_R bonding.[8] The resulting potential energy surface (PES) possesses two noninteractive Co−N_B and Co−C_R energy curves which are inherently coupled to the cobalt atom of the corrin macrocycle through the cobalt d_{z^2} orbital.[8] This topology of the PES is consistent with spectroscopic[9] and our recent theoretical studies[3,4] which show that elengation of the Co−N_B bond does not influence the Co−C_R bond and vice versa. Consequently, present DFT calculations support the experimental observation that the axial base is not the key controlling the Co−C_R cleavage event. When the *trans* axial DBI base is replaced by water, upon protonation in acid solution ["base-off" cobalamin] the Co−C_R BDE increases by 4.5 kcal/mol.[7j] This energy increase is comparable to experimental error (Table 2).

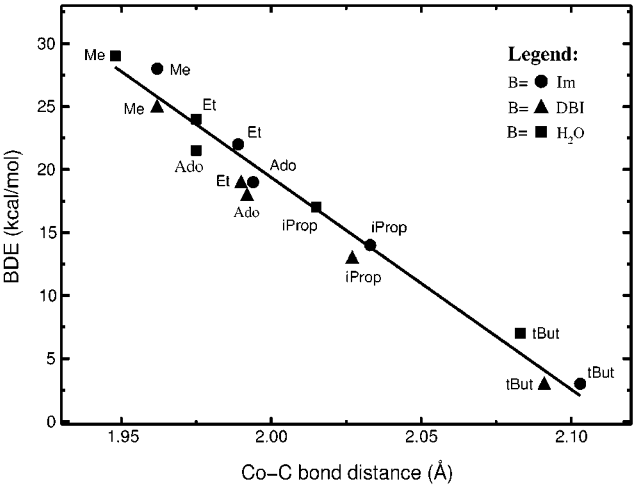

Figure 2. Theoretically determined BDEs plotted as a function of the Co−C_R bond length. Line parameters: slope = −168.25 $Å^{-1}$ kcal/mol, intercept = 355.88 kcal/mol.

How can these findings be associated with the possible implications for catalytic Co−C_R activation in coenzyme B_{12}-dependent enzymes? The Co−C_R dissociation enthalpy is 33 ± 2 kcal/mol for AdoCbl and the thermal homolysis rate at 25 °C is only 4×10^{-10} s^{-1}.[7i] In AdoCbl-dependent enzymes this rate is increased by a factor of $10^{12\pm1}$, implying a ∼15 kcal/mol destabilization of the Co−C_R bond.[7j,10] According to the present work, ∼15 kcal/mol BDE lowering for B-[Co^{III}(corrin)]-Ado requires ∼0.1 Å elongation of the Co−C_R bond. This estimate is exactly the same as one obtained on the basis of crystallographic considerations[11] and consistent with calculations in the presence of an external electric field required for Co−C_R bond labilization.[3,4]

JA0041728

---

(5) Andruniow, T.; Zgierski, M. Z.; Kozlowski, P. M. *Chem. Phys. Lett.* **2000**, *331*, 502−508.

(6) Marzilli, L. G. In *Bioinorganic Catalysis*; Reedijk, J., Ed.; Marcel Dekker: New York, 1993; pp 227−259.

(7) Experiment BDEs (a) Tsou, T.-T.; Loots, M.; Halpern, J. *J. Am. Chem. Soc.* **1982**, *104*, 623−624. (b) Ng, F. T. T.; Rempel, G. L..; Halpern, J. *J. Am. Chem. Soc.* **1982**, *104*, 621−623. (c) Ng, F. T. T.; Rempel, G. L.; Halpern, J. *Inorg. Chim. Acta* **1983**, *77*, L165-L166. (d) Geno, M. K.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1238−1240. (e) Ng, F. T. T.; Rempel, G. L.; Halpern, J. *Organometallics* **1990**, *9*, 2762−2772. (f) Geno, M. K.; Halpern, J. *J. Chem. Soc. Chem. Commun.* **1987**, 1052−1253. (g) Kim, S.-H.; Chen, H. L.; Feilchenfeld, N.; Halpern, J. *J. Am. Chem. Soc.* **1988**, *110*, 3120−3126. (h) Halpern, J.; Kim, S.-H.; Leung, T. W. *J. Am. Chem. Soc.* **1984**, *106*, 8317−8319. (i) Hay, B. P.; Finke, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 4820−4829. (j) Hay, B. P.; Finke, R. G. *J. Am. Chem. Soc.* **1987**, *109*, 8012−8016. (k) Martin, B. M.; Finke, *J. Am. Chem. Soc.* **1990**, *112*, 2419−2420. (l) Martin, B. M.; Finke, *J. Am. Chem. Soc.* **1992**, *114*, 585−592. (m) Schrauzer, G. N.; Grate, J. H. *J. Am. Chem. Soc.* **1981**, *103*, 5541−546. (n) Toscano, P. J.; Seligson, A. L.; Curran, M. T.; Skrobutt, A. T.; Sonnenberger, D. C. *Inorg. Chem.* **1989**, *28*, 166−168.

(8) Kozlowski, P. M.; Andruniow, T.; Zgierski, M. Z., submitted for publication.

(9) (a) Puckett, J. M.; Mitchell, M. B.; Hirota, S.; Marzilli, L. *Inorg. Chem.* **1996**, *35*, 4656−4662. (b) Dong, S.; Padmakumar, R.; Banerjee, R.; Spiro, T. G. *J. Am. Chem. Soc.* **1996**, *118*, 9182−9189. (c) Dong, S.; Padmakumar, R.; Banerjee, R.; Spiro, T. G. *Inorg. Chim. Acta* **1998**, *270*, 392−398.

(10) (a) Finke, R. G.; Martin, B. D. *J. Inorg. Biochem.* **1990**, *40*, 19−22. (b) Garr, C. D.; Sirovatka, J. M.; Finke, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 11142−11154. (c) Sirovatka, J. M.; Finke, R. G. *J. Am. Chem. Soc.* **1997**, *119*, 3057−3067.

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