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Co−C Bond Energies in Adenosylcobinamide and Methylcobinamide in the Gas Phase and in Silico

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Supporting Information

ABSTRACT: Essential to biological activity of adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl) is the Co−C bond cleavage step. Hence, we report an accurate determination of the homolytic gas-phase Co−C bond dissociation energies in the related adenosyl- and methylcobinamides (41.5 ± 1.2 and 44.6 ± 0.8 kcal/mol, respectively) utilizing an energy-resolved threshold collision-induced dissociation technique. This approach allows for benchmarking of electronic structure methods separate from (often ill-defined) solvent effects. Adequacy of various density functional theory methods has been tested with respect to the experimentally obtained values.

Coenzyme B_{12} (adenosylcobalamin, AdoCbl) and methylcobalamin (MeCbl) have been the subject of intense research efforts due to the involvement of these organocobalamins in essential enzymatic processes in mammals, considered relevant for red blood cell formation, neurological function, and DNA synthesis.[1] Central to much of the biological activity of AdoCbl is the homolytic Co−C bond cleavage that initiates enzymatic radical processes. In AdoCbl-dependent enzymes the rate of this cleavage has been estimated to be enhanced by up to trillion-fold relative to the background rate in aqueous solution.[2] Fundamental insights into the thermodynamics of the organometallic B_{12}-cofactors are crucial as a basis for a more detailed understanding of the enigmatic enzymatic activation. To date, advances in this field have been hampered by the discrepancies between (often indirectly determined) experimental values and computationally predicted quantitative data.[3] Indeed, the underlying factors that contribute to the Co−C bond strengths in B_{12}-cofactors remain elusive.

Experimental Co−C bond dissociation energies (BDEs) have been determined in ethylene glycol (EG) and in aqueous solution by kinetic methods (denoted k) and photoacoustic calorimetry (PAC) studies, affording 31.4 ± 1.5 (EG, k)[4] and 30 ± 2 kcal/mol (H2O, k)[5] for AdoCbl vs 37 ± 3 (EG, k)[6] and 36 ± 4 kcal/mol (H2O, PAC)[7] for MeCbl. The Co−C BDEs of adenosylcobinamide (AdoCbi$^+$) and of methylcobinamide (MeCbi$^+$) were likewise determined in aqueous solution to be 34.5 ± 1.8 (k)[8] and 37 ± 4 kcal/mol (PAC),[7] respectively. Cage effects were large in the thermolysis of AdoCbi$^+$ in aqueous solution,[9] reducing the observed effective homolysis rate and therefore increasing the apparent BDE value.

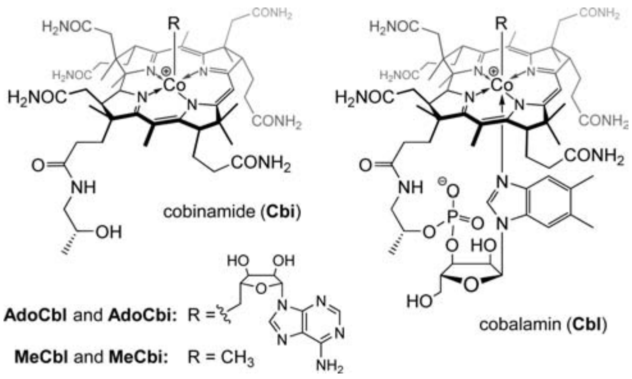

Figure 1. Structural formulas of cobinamides AdoCbi$^+$ and MeCbi$^+$ (left) and of the B_{12}-cofactors (cobalamins) AdoCbl and MeCbl (right).

Herein we report experimental gas-phase dissociation energies E_0 for AdoCbi$^+$ and MeCbi$^+$ as obtained from threshold collision-induced dissociation measurements. Our group among others[10,11] has demonstrated the general applicability of this method to various organometallic molecules.[12] The threshold energies E_0 represent Co−C bond strengths directly in B_{12}-related cobinamides, and these experimental data provide us with a benchmark for electronic structure methods. Moreover, the previously derived experimental BDEs in solution allow only a comparison with the combination of the electronic structure calculation and a solvation model; the presented gas-phase BDEs enable us to validate each part of the computations separately. We believe our experimental work on cobinamides, coupled with a validation of computational methods for such B_{12}-derivatives, also provides a model for the cobalamins; studies of the latter would include effects of the cobalt-coordinated dimethylbenzimidazole-nucleotide (DMB). Results from the literature (both, experimental[13] and computational[14]) indicate that coordination of the DMB-nucleotide decreases the Co−C bond strength by only ~1 kcal/mol or less. Absence of significant trans-ligand effect is also supported by our preliminary measurements on the full cobalamin system.

The gas-phase reactivity of the system was confirmed by means of tandem mass spectrometry on a Thermo Scientific TSQ Quantum Ultra EMR instrument. Upon electrospray

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ionization (ESI) from 5 μM methanol solutions, cationic AdoCbi$^+$ and MeCbi$^+$ complexes were observed at *m/z* 1239 and 1005, respectively, and were further identified by their isotope patterns. Qualitative collision-induced dissociation (CID) experiments with argon gas (0.2 mTorr) at different collision offsets (20−70 V) showed that the system undergoes clean Co−C bond cleavage. Even under harsh collision conditions (0.5 mTorr CID gas pressure and 75 V collision offset) only one reaction channel was observed.

Quantitative experimental data were obtained on a modified Finnigan MAT TSQ-700 tandem mass spectrometer.[10] The parent complexes were thermalized with 10 mTorr argon in a 24-pole ion guide prior to mass selection. Upon collisional activation with xenon gas, both parent complexes underwent homolytic cleavage of the Co−C bond to yield the cationic corrin fragment as the sole detectable product at *m/z* 990. In order to determine quantitatively the Co−C bond strengths in the gas phase, we performed energy-resolved reactive cross-section measurements under near-single-collision conditions. The intensities of parent and product ions were monitored at different pressures and collision energies, affording a series of reactive cross sections which were extrapolated to zero collision gas pressure. Subsequently, our L-CID[15] program was employed to extract the activation energies (see Supporting Information (SI) for details). Data fitting with L-CID necessitates the choice of either a "tight" or a "loose" transition-state model. The former is used when intramolecular rearrangement is rate limiting, whereas the latter is appropriate when a dissociation process determines the rate. A loose transition-state model was utilized for the Co−C bond dissociation studies, affording threshold energies E_0 for AdoCbi$^+$ and MeCbi$^+$ of 41.5 ± 1.2 and 44.6 ± 0.8 kcal/mol, respectively.

Assessment of the adequacy of the widely used density functional theory (DFT) methods remains difficult because the experimental data for corrinoid systems have been limited to the solution-phase experiments, which include additional factors which themselves need benchmarking. Especially with regard to the recently emphasized dispersion treatments applicable to large systems, either Grimme's DFT-D3 (and its antecedent versions) or Truhlar's M06 methods, the absence of gas-phase data on large systems, where the contribution of dispersion to BDEs can be expected to sum up to large values, makes the present measurements highly relevant. The MeCbi$^+$ and AdoCbi$^+$ are among the very largest molecular ions for which a bond energy has been measured cleanly in the gas phase. Given the inconsistent treatment of dispersion by DFT, which is of high relevance to any large system, one may seek a comparison of the measured bond energies in MeCbi$^+$ and AdoCbi$^+$ to highly correlated wave function methods, often CCSD(T) with a large basis set. For neither AdoCbi$^+$ nor AdoCbl is there such calculation, which is understandable, given their sizes. For the more tractable but nevertheless very challenging MeCbi$^+$ or MeCbl systems, two recent benchmarking reports[16] treat truncated model systems, which themselves are treated by methods designed to approximate a coupled-cluster result. These two reports by Ryde, Mata, and Grimme[16a] and Kozlowski, Piecuch, and co-workers[16b] lead one to expect a Co−C bond dissociation energy for MeCbi$^+$ in the range of 38−43 kcal/mol, in good agreement with our measured 44.6 ± 0.8 kcal/mol, of course with the qualification that methods were themselves designed as approximations to CCSD(T) calculations. A second, independent argument strongly supporting the reliability of the experimental gas-phase bond energies for MeCbi$^+$ and AdoCbi$^+$ comes from the subsequent agreement with solution-phase Co−C bond energies. As will be seen below, the treatment of solvation by polarizable continuum models, either PCM or SMD, shifts the BDEs for both MeCbi$^+$ and AdoCbi$^+$ to values in good agreement with solution-phase values for the same species in water. We believe that the gas-phase measurements of the Co−C bond energies for MeCbi$^+$ and AdoCbi$^+$ provide reliable data to benchmark DFT. We emphasize that having both MeCbi$^+$ and AdoCbi$^+$ makes the test of computational methods more stringent by ruling out coincidental agreements.

We compare the threshold energies E_0 to the difference in calculated electronic plus zero-point vibrational energy $E_{\mathrm{el+ZPE}}$ of the intact cobinamide (RCbi$^+$) vs the dissociated fragments ($^{\bullet}$R and $^{\bullet +}$Cbi). Geometries were optimized with Gaussian 09[18] at the BP86/6-31G(d,p),Co:6-31+G(d) level of theory, followed by frequency calculations; the BP86 functional had been recommended for geometry calculations of alkylcorrinoids.[19] As an initial screen, expectation values for the energies were computed with the ADF suite[20] of programs for 75 different functionals based on BP86/TZP electron density distributions (see SI). Based on the preliminary ADF screening, a set of 24 functionals was chosen that covers the diversity of available approaches. To ascertain accurate energies, we finally performed single-point calculations with Gaussian 09 using the cc-pVTZ basis set and the actual electron density distribution for each functional. Zero-point energy corrections (ZPEs) from the BP86 frequency calculations at the level of geometry optimization were applied to all single-point energies. Correction for BSSE was checked, and found to be small for TZP-level basis set we used (0.8 kcal/mol for MeCbi$^+$ and 2.7 kcal/mol for AdoCbi$^+$ in case of BP86). Selected results are shown in Table 1. With the various DFT calculations in hand, we benchmark the electronic structure methods against our experimental bond energies. The salient issues to be addressed are pure vs hybrid DFT methods and adequacy of the dispersion corrections.

As had been reported previously,[14,19] inclusion of exact (HF) exchange degrades the ability of density functionals to reproduce the Co−C bond strength, as may be seen in Table 1, where the agreement with experiment deteriorates dramatically with increasing HF exchange contribution. In particular, the B3LYP functional (20% HF), which had been widely used to model the solution-phase chemistry of cobalamins, underestimates the gas-phase Co−C bond strength by more than 15 kcal/mol. The poor performance of hybrid density functionals with a significant exact exchange contribution can be attributed to static (nondynamical) correlation effects, which fundamentally cannot be described adequately with single-reference wave function methods. HF itself predicts the dissociation process to be highly exothermic (ΔE_{HF}(AdoCbi$^+$) = −40.1 and ΔE_{HF}(MeCbi$^+$) = −35.5 kcal/mol), which is in obvious contradiction to the experiment. The B1 test,[21] proposed by Truhlar and co-workers to estimate the multireference character of a given system, confirms that static correlation is significant in these systems. The difference between the calculated B1LYP and BLYP bond energies for both AdoCbi$^+$ and MeCbi$^+$ (17.2 and 17.3 kcal/mol, respectively) well exceeds the suggested 10 kcal/mol limit for single-reference molecules.

In combination with a cc-pVTZ basis set, the pure functionals (PBE, BP86, pWPW91) appear at first glance to

Table 1. Gas-Phase Computational Results (kcal/mol)

		$E_{\text{el+ZPE}}$ [a]		deviation from Exp. [b]	
theoretical method	%HF	AdoCbi^+	MeCbi^+	AdoCbi^+	MeCbi^+
PBE	0	40.4	39.7	−1	−5
BP86	0	35.8	37.5	−6	−7
mPWPW91	0	35.6	37.1	−6	−8
TPSS	0	33.2	33.9	−8	−11
M06-L	0	39.5	33.8	−2	−11
BLYP	0	29.6	32.9	−12	−12
OLYP	0	18.6	27.8	−23	−17
TPSSh	10	25.8	26.8	−16	−18
B3LYP	20	18.3	20.6	−23	−24
PBE1	25	20.8	20.8	−21	−24
M06	27	35.4	30.3	−6	−14
MPW1K	43	5.2	6.7	−36	−28
M06-2X	54	15.6	11.2	−26	−33
HF	100	−50.5	−45.0	−92	−90
B97D	0	53.6	43.2	12	−1
PBE-D3	0	54.9	45.6	13	1
BP86-D3	0	58.6	47.1	17	2
BLYP-D3	0	54.3	43.9	13	−1
OLYP-D3	0	54.4	45.3	13	1
B3LYP-D3	20	39.3	29.9	−2	−15
M06-D3	27	43.0	32.6	2	−12

[a] Single-point energies with cc-pVTZ basis set for structures optimized at BP86/6-31G(d,p),Co:6-31+G(d), including ZPE corrections; D3 corrections obtained from the DFT-D3 program.[17] [b] Experimental gas-phase E_0 for $\text{AdoCbi}^+ = 41.5 \pm 1.2$; for $\text{MeCbi}^+ = 44.6 \pm 0.8$ kcal/mol.

give good estimates for the gas-phase Co−C bond activation energies of AdoCbi^+ and MeCbi^+, although pure functionals do not include treatment of dispersion, which should be significant for these large systems. A closer examination finds that the pure functionals all underestimate the bond energies by some kcal/mol, which is consistent with the direction, if not the magnitude of dispersion corrections.

Recent work[16a,22] on a wide range of systems shows that the attractive van der Waals interactions are poorly modeled by standard DFT; they would have the net effect of raising the computed Co−C bond dissociation energy. Therefore we included Truhlar's M06-L functional in our survey. Moreover, we applied Grimme's latest DFT-D3[17] corrections, combined with a TZP-quality basis set, to test the magnitude of dispersion interactions. The results are shown in the lower part of Table 1. Whereas the calculated dispersion corrections affect both AdoCbi^+ and MeCbi^+ Co−C bond energies, those for AdoCbi^+ are systematically larger (10−18 kcal/mol) than for MeCbi^+, as would be expected. While the D3 corrections uniformly bring the DFT predictions of the Co−C bond energy in MeCbi^+ from a few kcal/mol below the experimental value to a few kcal/mol above it, the same methods uniformly predict a bond energy of 53−57 kcal/mol for AdoCbi^+, which is far above what can be explained easily. One should comment that analysis of the D3 contributions find the Co−C bond cleavage eliminates 561 attractive pairwise interactions in MeCbi^+ and over 4000 in AdoCbi^+; the largest is the Co−C interaction at 0.8 and 1.6 kcal/mol respectively, but the others fall in the range of 0−0.2 kcal/mol. The loss of the hundreds or even thousands of these interactions upon homolysis and separation of the adenosyl radical poses an immense challenge to the parametrization of the D3 method, which was done exclusively with neutral reference molecules. In a recent paper,[23] Grimme reported that the dispersion correction in cations is likely an overestimate, but we cannot judge the magnitude.

Adding to the complication is the recent report, which found that an improvement of agreement with experiment by adding a dispersion correction requires, logically, a DFT calculation which is qualitatively correct.[24] The point is especially relevant to reports of the use of DFT-D3, combined with B3LYP* (with 15% HF exchange) and a PCM solvent model applied to the solution-phase Co−C bond energy for AdoCbl.[22] Considering the results we find for hybrid DFT methods, which systematically underestimate the bond energy, combined with an overestimate of the dispersion correction, the agreement is likely coincidental. Two lines of argument support this conclusion. First, the use of B3LYP* is recommended by its author only for cases where ionization potential, electron affinity, and atomization energy (the sum of bond energies) are insensitive to the amount of HF exchange.[25] With the strong dependence of the computed Co−C bond energy on the amount of HF exchange, the preconditions for B3LYP* are not given. Second, application of the same B3LYP*-D3 with solvent correction that matches the Co−C bond energy to an adenosyl radical would grossly underestimate the bond to a methyl radical. It should be emphasized that even after extensive screening of numerous DFT methods, none of the presently tested dispersion corrected functionals could provide satisfactory agreement for both MeCbi^+ and AdoCbi^+.

To account for the solvent effects SMD[26] and PCM[27] solvation models were tested, using for the purpose of an assessment, the PBE result for the gas phase. For aqueous media both SMD and PCM models cause a significant decrease in Co−C bond strength for AdoCbi^+, which helps validate our gas-phase BDEs as compared to the experimental solution-phase values. Notably, solvation energy was found to be almost the same for different DFT functionals and can be compared separately to the experimentally observed solvation effects. In case of the SMD model, with included enthalpy correction, the Co−C BDE for AdoCbi^+ decreased to 33.0 and for MeCbi^+ to 37.8 kcal/mol. This is in acceptable agreement with experimentally derived solution-phase data for AdoCbi^+ and MeCbi^+, although one cannot exclude explicit solvent interactions which may further weaken the Co−C bond. In an attempt to account for specific solvation effects we performed calculations with the SMD solvation model and one explicit water molecule at the vacant coordination site of cobalt, which decreased Co−C bond energies even further to 29.6 kcal/mol for AdoCbi+ and to 35.6 kcal/mol for MeCbi^+.

In conclusion, the (homolytic) Co−C BDEs for AdoCbi^+ and MeCbi^+ in the gas phase were determined from CID experiments. The obtained accurate experimental values indicate the Co−C BDEs of AdoCbi^+ and of MeCbi^+ were roughly 7 kcal/mol larger than corresponding values in aqueous solution. Axial cobalt coordination of a water molecule could come up with part of the solvation effect. According to the experimental gas-phase Co−C BDEs, the strength of the Co−C bond of MeCbi^+ exceeds that of AdoCbi^+ by ~3 kcal/mol, in qualitative agreement with the aqueous solution data.

An extensive evaluation of DFT methods finds that there are numerous issues at technically accessible levels of theory that remain to be resolved. In the course of the analysis, the relative paucity of experimental bond energies, or bond energies computed at a coupled-cluster level, for large molecular species significantly impedes the validation of more approximate computational methods. The present measurements for

AdoCbi$^+$ and MeCbi$^+$ thus represent a stringent test for theory. The difference between gas- and solution-phase bond energies indicates that even a homolysis may be affected by the medium. Clearly, not only solvation effects lower the Co−C BDE in AdoCbl, but in AdoCbl-dependent enzymes specific interactions (H-bonding and nonpolar) are responsible for tight binding of the Ado radical,[3,28] which further promotes Co−C homolysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Computational details, energies and geometries, experimental details, including energy-resolved collision-induced dissociation experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Vitamin B12 and B12-Proteins*; Kräutler, B., Arigoni, D., Golding, B. T., Eds.; Wiley-VCH: Weinheim, 1998. (b) *Chemistry and Biochemistry of B12*; Banerjee, R., Ed.; Wiley: New York, 1999. (c) Herbert, V. *Vitamin B12 in Present Knowledge in Nutrition*, International Life Sciences Institute Press: Washington, DC, 1996. (d) Solomon, L. R. *Blood Rev.* **2007**, *21*, 113−130.

(2) Halpern, J. *Science* **1985**, *227*, 869.

(3) Bucher, D.; Sandala, G. M.; Durbeej, B.; Radom, L.; Smith, D. M. *J. Am. Chem. Soc.* **2012**, *134*, 1591.

(4) (a) Finke, R. G.; Hay, B. P. *Inorg. Chem.* **1984**, *23*, 3041−3043. (b) Garr, C. D.; Finke, R. G. *Inorg. Chem.* **1993**, *32*, 4414.

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

(6) Martin, B. D.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 585.

(7) Hung, R. R.; Grabowski, J. J. *J. Am. Chem. Soc.* **1999**, *121*, 1359.

(8) Hay, B. P.; Finke, R. G. *J. Am. Chem. Soc.* **1987**, *109*, 8012.

(9) Garr, C. D.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 10440.

(10) Couzijn, E. P. A.; Zocher, E.; Bach, A.; Chen, P. *Chem.−Eur. J.* **2010**, *16*, 5415.

(11) (a) Armentrout, P. B.; Ervin, K. M.; Rodgers, M. T. *J. Phys. Chem. A* **2008**, *112*, 10071. (b) Armentrout, P. B. *J. Am. Soc. Mass Spectrom.* **2013**, *24*, 173.

(12) See ref 10 and (a) Serra, D.; Moret, M. E.; Chen, P. *J. Am. Chem. Soc.* **2011**, *133*, 8914. (b) Fedorov, A.; Batiste, L.; Couzijn, E. P. A.; Chen, P. *Chem. Phys. Chem.* **2010**, *11*, 1002. (c) Fedorov, A.; Moret, M. E.; Chen, P. *J. Am. Chem. Soc.* **2008**, *130*, 8880. (d) Torker, S.; Merki, D.; Chen, P. *J. Am. Chem. Soc.* **2008**, *130*, 4808. (e) Zocher, E.; Dietiker, R.; Chen, P. *J. Am. Chem. Soc.* **2007**, *129*, 2476.

(13) (a) Dong, S.; Padmakumar, R.; Banerjee, R.; Spiro, T. *J. Am. Chem. Soc.* **1996**, *118*, 9182. (b) Kräutler, B. *Helv. Chim. Acta* **1987**, *70*, 1268.

(14) Jensen, K. P.; Ryde, U. *J. Phys. Chem. A* **2003**, *107*, 7539.

(15) Narancic, S.; Bach, A.; Chen, P. *J. Phys. Chem. A* **2007**, *111*, 7006.

(16) (a) Ryde, U.; Mata, R. A.; Grimme, S. *Dalton Trans.* **2011**, *40*, 11176. (b) Kozlowski, P. M.; Kumar, M.; Piecuch, P.; Li, W.; Bauman, N. P.; Hansen, J. A.; Lodowski, P.; Jaworska, M. *J. Chem. Theory Comput.* **2012**, *8*, 1870.

(17) (a) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104. (b) Grimme, S.; Ehrlich, S.; Goerigk, L. *J. Comput. Chem.* **2011**, *32*, 1456.

(18) Frisch, M. J. et al. *Gaussian 09*, revision A.1; Gaussian, Inc.: Wallingford, CT, 2009. Full reference in the SI.

(19) (a) Kuta, J.; Patchkovskii, S.; Zgierski, M. Z.; Kozlowski, P. M. *J. Comput. Chem.* **2006**, *27*, 1429. (b) Kozlowski, P. M.; Kuta, J.; Galezowski, W. *J. Phys. Chem. B* **2007**, *111*, 7638. (c) Galezowski, W.; Kuta, J.; Kozlowski, P. M. *J. Phys. Chem. B* **2008**, *112*, 3177. (d) Hirao, H. *J. Phys. Chem. A* **2011**, *115*, 9308.

(20) (a) *ADF2012*; SCM, Vrije Universiteit: Amsterdam, The Netherlands, 2012; http://www.scm.com. (b) Velde, G.; Bickelhaupt, F. M.; Gisbergen, S. J. A.; Fonseca Guerra, C.; Baerends, E. J.; Snijders, J. G.; Ziegler, T. *J. Comput. Chem.* **2001**, *22*, 931. (c) Fonseca Guerra, C.; Snijders, J. G.; Velde, G.; Baerends, E. J. *Theor. Chem. Acc.* **1998**, *99*, 391.

(21) Schultz, N. E.; Zhao, Y.; Truhlar, D. *J. Phys. Chem. A* **2005**, *109*, 11127.

(22) (a) Siegbahn, P. E. M.; Blomberg, M. R. A.; Chen, S.-L. *J. Chem. Theory Comput.* **2010**, *6*, 2040. (b) Chen, S.-L.; Blomberg, M. R. A.; Siegbahn, P. E. M. *J. Phys. Chem. B* **2011**, *115*, 4066.

(23) Grimme, S.; Hujo, W.; Kirchner, B. *Phys. Chem. Chem. Phys.* **2012**, *14*, 4875.

(24) Liao, M.-S.; Huang, M.−J.; Watts, J. D. *Mol. Phys.* **2012**, *110*, 3061.

(25) (a) Reiher, M.; Salomon, O.; Hess, B. A. *Theor. Chem. Acc.* **2001**, *107*, 48. (b) Salomon, O.; Reiher, M.; Hess, B. A. *J. Chem. Phys.* **2002**, *117*, 4729.

(26) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.

(27) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.

(28) (a) Gruber, K.; Reitzer, R.; Kratky, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 3322. (b) Banerjee, R. *Chem. Rev.* **2003**, *103*, 2083. (c) Marsh, E. N. G.; Patterson, D. P.; Li, L. *ChemBioChem* **2010**, *11*, 604. (d) Kräutler, B.; Puffer, B. *Handbook of Porphyrin Science*, Kadish, K. M., Smith, K. M., Guilard, R., Eds.; World Scientific: Singapore, 2012; Vol. 25, pp 131−263. (e) Friedrich, P.; Baisch, F.; Harrington, R.; Lyatuu, F. E.; Zhou, K.; Zelder, F.; McFarlane, W.; Buckel, W.; Golding, B. T. *Chem.−Eur. J.* **2012**, *18*, 16114.