

UvA-DARE (Digital Academic Repository)

Molecular simulations in electrochemistry

Electron and proton transfer reactions mediated by flavins in different molecular environments

Kılıç, M.

Publication date

2014

Document Version

Final published version

[Link to publication](#)

Citation for published version (APA):

Kılıç, M. (2014). *Molecular simulations in electrochemistry: Electron and proton transfer reactions mediated by flavins in different molecular environments*. [Thesis, fully internal, Universiteit van Amsterdam].

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Bibliography

- [1] R. A. Marcus. Electrostatic free energy and other properties of states having nonequilibrium polarization. I. *J. Chem. Phys.*, 24(5):979–989, 1956.
- [2] R. A. Marcus. On the theory of oxidation-reduction reactions involving electron transfer. *J. Chem. Phys.*, 24:966–978, 1956.
- [3] R. A. Marcus. Chemical + electrochemical electron-transfer theory. *Ann. Rev. Phys. Chem.*, 15:155–196, 1964.
- [4] R. A. Marcus. On theory of electron-transfer reactions. 6 .Unified treatment for homogeneous and electrode reactions. *J. Chem. Phys.*, 43(2):679–701, 1965.
- [5] R. A. Marcus and N. Sutin. Electron transfers in chemistry and biology. *Biochim. Biophys. Acta*, 811:265–322, 1985.
- [6] R. A. Marcus. Electron transfer reactions in chemistry. Theory and experiment. *Rev. Mod. Phys.*, 65(3):599–610, 1993.
- [7] T. Kakitani, A. Yoshimori, and N. Mataga. *Theoretical Analysis of Energy-Gap Laws of Electron-Transfer Reactions: Distribution Effect of Donor-Acceptor Distance*. Advances in Chemistry Series. American Chemical Society, 1991.
- [8] A. Warshel and W. W. Parson. Computer simulations of electron transfer reactions in solution and photosynthetic reaction centers. *Annu. Rev. Phys. Chem.*, 42:279, 1991.
- [9] P. F. Barbara, T. J. Meyer, and M. A. Ratner. Contemporary issues in electron transfer research. *J. Phys. Chem.*, 100(31):13148–13168, 1996.
- [10] A. P. Alivisatos, P. F. Barbara, A. W. Castleman, J. Chang, D. A. Dixon, M. L. Klein, G. L. McLendon, J. S. Miller, M. A. Ratner, P. J. Rossky, S. I. Stupp, and M. E. Thompson. From molecules to materials: Current trends and future directions. *Adv. Mater.*, 10(16):1297–1336, 1998.
- [11] A. Warshel. Dynamics of reactions in polar solvents. Semiclassical trajectory studies of electron-transfer and proton-transfer reactions. *J. Phys. Chem.*, 86(12):2218–2224, 1982.

- [12] G. King and A. Warshel. Investigation of the free energy functions for electron transfer reactions. *J. Chem. Phys.*, 93(12):8682–8692, 1990.
- [13] J. Blumberger, L. Bernasconi, I. Tavernelli, R. Vuilleumier, and M. Sprik. Electronic structure and solvation of copper and silver ions: a theoretical picture of a model aqueous redox reaction. *J. Am. Chem. Soc.*, 126(12):3928–3938, 2004.
- [14] J. Blumberger and M. Sprik. Free energy of oxidation of metal aqua ions by an enforced change of coordination. *J. Phys. Chem. B*, 108(21):6529–6535, 2004.
- [15] Y. Tateyama, J. Blumberger, M. Sprik, and I. Tavernelli. Density functional molecular dynamics study of the redox reactions of two anionic aqueous transition metal complexes. *J. Chem. Phys.*, 122(23):234505, 2005.
- [16] J. Blumberger, I. Tavernelli, M. L. Klein, and M. Sprik. Diabatic free energy curves and coordination fluctuations for the aqueous $\text{Ag}^+/\text{Ag}^{2+}$ redox couple: a biased Born-Oppenheimer molecular dynamics investigation. *J. Chem. Phys.*, 124(6):64507, 2006.
- [17] J. Blumberger and M. Sprik. Ab initio molecular dynamics simulation of the aqueous $\text{Ru}^{2+}/\text{Ru}^{3+}$ redox reaction: The Marcus perspective. *J. Phys. Chem. B*, 109(14):6793–6804, 2005.
- [18] J. Blumberger and M. Sprik. Quantum versus classical electron transfer energy as reaction coordinate for the aqueous $\text{Ru}^{2+}/\text{Ru}^{3+}$ redox reaction. *Theor. Chem. Acc.*, 115(2-3):113–126, 2005.
- [19] J. VandeVondele, M. Sulpizi, and M. Sprik. From solvent fluctuations to quantitative redox properties of quinones in methanol and acetonitrile. *Angew. Chem. Int. Ed.*, 45:1936–1938, 2006.
- [20] J. VandeVondele, R. Lynden-Bell, E. J. Meijer, and M. Sprik. Density functional theory study of tetrathiafulvalene and thianthrene in acetonitrile: structure, dynamics, and redox properties. *J. Phys. Chem. B*, 110(8):3614–3623, 2006.
- [21] R. Ayala and M. Sprik. A classical point charge model study of system size dependence of oxidation and reorganization free energies in aqueous solution. *J. Phys. Chem. B*, 112:257–269, 2008.
- [22] J. Cheng, M. Sulpizi, and M. Sprik. Redox potentials and $\text{p}K_a$'s for benzoquinone from Density Functional Theory based molecular dynamics. *J. Phys. Chem.*, 131:154504, 2009.
- [23] F. Costanzo, M. Sulpizi, R. G. Della Valle, and M. Sprik. The oxidation of tyrosine and tryptophan studied by a molecular dynamics normal hydrogen electrode. *J. Chem. Phys.*, 134(24):244508, 2011.

- [24] C. Adriaanse, J. Cheng, V. Chau, M. Sulpizi, J. VandeVondele, and M. Sprik. Aqueous redox chemistry and the electronic band structure of liquid water. *J. Phys. Chem. Lett.*, 3(23):3411–3415, 2012.
- [25] J. K. Hwang and A. Warshel. Microscopic examination of free-energy relationships for electron-transfer in polar-solvents. *J. Am. Chem. Soc.*, 109(3):715–620, 1987.
- [26] M. Tachiya. Effect of the dielectric saturation on the rates of electron-transfer in polar-solvents. *Chem. Phys. Lett.*, 159:505–510, 1989.
- [27] M. Tachiya. Relation between the electron-transfer rate and the free-energy change of reaction. *J. Phys. Chem.*, 93(20):7050–7052, 1989.
- [28] C. J. T. de Grotthuss. Sur la decomposition de l’eau et des corps qu’elle tient en dissolution a l’aide de l’electricite galvanique. *Ann. Chim. (Paris)*, 58:58–73, 1806.
- [29] D. Dominik. Proton transfer 200 years after von grotthuss: Insights from ab initio simulations. *ChemPhysChem*, 7(9):1848–1870, 2006.
- [30] A.G. Morachevskii. Theodor grotthuss (to 220th anniversary of his birthday). *Russian Journal of Applied Chemistry*, 78(1):166–168, 2005.
- [31] S. Cukierman. Et tu grotthuss! *Biochimica et Biophysica Acta*, 1757(8):876–878, 2006.
- [32] V. Massey and P. Hemmerich. Active-site probes of flavoproteins. *Biochem. Soc. Trans.*, 8:246–257, 1980.
- [33] S. Ghisla and V. Massey. Mechanisms of flavoprotein-catalyzed reactions. *Eur. J. Biochem.*, 181(1):1–17, 1989.
- [34] M. W. Fraaije and A. Mattevi. Flavoenzymes: diverse catalysts with recurrent features. *Trends Biochem. Sci.*, 25:126–132, 2000.
- [35] B. W. Lennon, Williams Jr. C. H., and M. L. Ludwig. Crystal structure of reduced thioredoxin reductase from Escherichia coli: Structural flexibility in the isoalloxazine ring of the flavin adenine dinucleotide cofactor. *Protein Sci.*, 8:2366–2379, 1999.
- [36] The CP2K Developers Group. <http://www.cp2k.org>.
- [37] J. Hutter, M. Iannuzzi, F. Schiffmann, and J. VandeVondele. cp2k: atomistic simulations of condensed matter systems. *WIREs Comput Mol Sci.*, 4:15–25, 2014.

- [38] G. Hummer, L. R. Pratt, and A. E. Garcia. Free energy of ionic hydration. *J. Chem. Phys.*, 100(4):1206–1215, 1996.
- [39] R.A. Kuharski, J.S. Bader, D. Chandler, M. Sprik, M.L. Klein, and R.W. Impey. Molecular-model for aqueous ferrous-ferric electron transfer. *J. Chem. Phys.*, 89:3248–3257, 1988.
- [40] W. K. den Otter and W. J. Briels. The calculation of free-energy differences by constrained molecular-dynamics simulations. *J. Chem. Phys.*, 109(11):4139–4146, 1998.
- [41] D. Frenkel and B. Smith. *Understanding Molecular Simulations*. Academic Press, second edition, 2002.
- [42] R. M. Martin. *Electronic structure: Basic theory and practical methods*. Cambridge University Press, Cambridge, 2004.
- [43] E. J. Baerends and O. V. Gritsenko. A quantum chemical view of density functional theory. *J. Phys. Chem. A*, 101(30):5383–5403, 1997.
- [44] R. G. Parr and W. Yang. *Density-Functional Theory of Atoms and Molecules*. Oxford University: New York, 1989.
- [45] R. M. Dreizler and E. K. Gross. *Density-Functional Theory: An approach to the many-body problem*. Springer-Verlag: Berlin, 1990.
- [46] F. M. Bickelhaupt and E. J. Baerends. Kohn-Sham density functional theory: Predicting and understanding chemistry. *Rev. Comp. Chem.*, 15:1–86, 2000.
- [47] P. Hohenberg and W. Kohn. Inhomogeneous electron gas. *Phys. Rev.*, 136(3B):B864–871, 1964.
- [48] W. Kohn and L. J. Sham. Self-consistent equations including exchange and correlation effects. *Phys. Rev.*, 140:A1133–A1138, 1965.
- [49] A. D. Becke. Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A*, 38:3098–3100, 1988.
- [50] C. Lee, W. Yang, and R. G. Parr. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B*, 37:785–789, 1988.
- [51] J. Perdew, K. Burke, and M. Ernzerhof. Generalized gradient approximation made simple. *Phys. Rev. Lett.*, 77(18):3865–3868, 1996.
- [52] R. P. Feynman. Forces in molecules. *Phys. Rev.*, 56:340–343, 1939.

- [53] A. Warshel and M. Levitt. Theoretical studies of enzymic reactions: Dielectric, electrostatic and steric stabilization of the carbonium ion in the reaction of lysozyme. *J. Mol. Biol.*, 103:227–249, 1976.
- [54] M. J. Field, P. A. Bash, and M. Karplus. A combined quantum–mechanical and molecular mechanical potential for molecular–dynamics simulations. *J. Comput. Chem.*, 11:700–733, 1990.
- [55] U. C. Singh and P. A. Kollman. A combined ab initio quantum mechanical and molecular mechanical method for carrying out simulations on complex molecular systems: Applications to the CHSCl + Cl[−] exchange reaction and gas phase protonation of polyethers. *J. Comput. Chem.*, 7:718–730, 1986.
- [56] F. Maseras and K. Morokuma. Imomm: A new integrated ab initio + molecular mechanics geometry optimization scheme of equilibrium structures and transition states. *J. Comput. Chem.*, 16:1170–1179, 1995.
- [57] M. A. Thompson. Hybrid quantum mechanical/molecular mechanical force field development for large flexible molecules: A molecular dynamics study of 18-crown-6. *J. Phys. Chem.*, 99:4794–4804, 1995.
- [58] D. A. Yarne, M. E. Tuckerman, and G. J. Martyna. A dual length scale method for plane-wave-based, simulation studies of chemical systems modeled using mixed ab initio/empirical force field descriptions. *J. Chem. Phys.*, 115:3531–3539, 2001.
- [59] A. Crespo, D. A. Scherlis, M. A. Marti, P. Ordejon, A. E. Roitberg, and D. A. Estrin. A DFT-based QM-MM approach designed for the treatment of large molecular systems: Application to chorismate mutase. *J. Phys. Chem. B*, 107:13728–13736, 2003.
- [60] A. Laio, J. VandeVondele, and U. Rothlisberger. A hamiltonian electrostatic coupling scheme for hybrid car-parrinello molecular dynamics simulations. *J. Chem. Phys.*, 116:6941–6947, 2002.
- [61] K. Nam, J. Gao, and D. M. York. An efficient linear-scaling Ewald method for long-range electrostatic interactions in combined QM/MM calculations. *J. Chem. Theory Comput.*, 1:2–13, 2005.
- [62] H. M. Senn and W. Thiel. QM/MM methods for biomolecular systems. *Angew. Chem. Int. Edit.*, 48:1198–1229, 2009.
- [63] T. Laino and A. Curioni. A new piece in the puzzle of lithium/air batteries: Computational study on the chemical stability of propylene carbonate in the presence of lithium peroxide. *Chem. Eur. J.*, 18:3510–3520, 2012.

- [64] T. Laino, D. Donadio, and I. F. W. Kuo. Migration of positively charged defects in alpha-quartz. *Phys. Rev. B*, 76(195210), 2007.
- [65] P. Sherwood, A. H. de Vries, M. F. Guest, G. Schreckenbach, C. R. Catlow, S. French, A. Sokol, S. T. Bromley, W. Thiel, A. J. Turner, S. Billeter, F. Terstegen, S. Thiel, J. Kendrick, S. C. Rogers, J. Casci, M. Watson, F. King, E. Karlsen, M. Sjøvoll, A. Fahmi, A. Schafer, and C. Lennartz. QUASI: A general purpose implementation of the QM/MM approach and its application to problems in catalysis. *J. Mol. Struct. (THEOCHEM)*, 632:1–28, 2003.
- [66] R. E. Bulo, B. Ensing, J. Sikkema, and L. Visscher. Toward a practical method for adaptive QM/MM simulations. *J. Chem. Theory Comput.*, 5:2212–2221, 2009.
- [67] P. Sherwood. *Hybrid Quantum Mechanics/Molecular Mechanics Approaches*. Modern Methods and Algorithms of Quantum Chemistry, Proceedings, NIC Series, John von Neumann Institute for Computing, J. Grotendorst, Second edition, 2000.
- [68] Protein Data Bank. <http://www.rcsb.org>.
- [69] A. Laio and M. Parrinello. Escaping free-energy minima. *Proc. Natl. Acad. Sci. USA*, 99:12562–12566, 2002.
- [70] A. Laio, A. Rodriguez-Forteza, F. L. Gervasio, M. Ceccarelli, and M. Parrinello. Assessing the accuracy of metadynamics. *J. Phys. Chem. B*, 109:6714–6721, 2005.
- [71] E.A. Carter, G. Ciccotti, J.T. Hynes, and R. Kapral. Constrained reaction coordinate dynamics for the simulation of rare events. *Chem. Phys. Lett.*, 156:472–477, 1989.
- [72] G. Ciccotti and M. Ferrario. Blue moon approach to rare events. *Mol. Simul.*, 30:787–793, 2004.
- [73] J. D. Walsh and A. F. Miller. Flavin reduction potential tuning by substitution and bending. *J. Mol. Struct. (THEOCHEM.)*, 623:185–195, 2003.
- [74] J. C. Arents, M. A. Perez, J. Hendriks, and K. J. Hellingwerf. On the midpoint potential of the FAD chromophore in a BLUF-domain containing photoreceptor protein. *FEBS Letters*, 585(1):167–172, 2011.
- [75] T. Mathes, I. H. M. van Stokkum, M. Stierl, and J. T. M. Kennis. Redox modulation of flavin and tyrosine determines photoinduced proton-coupled electron transfer and photoactivation of BLUF photoreceptors. *J. Biol. Chem.*, 287(38):31725–31738, 2012.

- [76] J. J. Hasford and C. J. Rizzo. Linear free energy substituent effect on flavin redox chemistry. *J. Am. Chem. Soc.*, 120(10):2251–2255, 1998.
- [77] R. D. Draper and L. L. Ingraham. A potentiometric study of flavin semiquinone equilibrium. *Arch. Biochem. Biophys.*, 125:802, 1968.
- [78] R. F. Anderson. Energetics of the one-electron reduction steps of Riboflavin, FMN and FAD to their fully reduced forms. *Biochim. Biophys. Acta*, 722(1):158–162, 1983.
- [79] S. G. Mayhew. The effects of pH and semiquinone formation on the oxidation-reduction potentials of flavin mononucleotide - a reappraisal. *Eur. J. Biochem.*, 265(2):698–702, 1999.
- [80] S. Bhattacharyya, M. T. Stankovich, D. G. Truhlar, and J. Gao. Combined Quantum Mechanical and Molecular Mechanical simulations of one- and two-electron reduction potentials of flavin cofactor in water, medium-chain acyl-CoA dehydrogenase, and cholesterol oxidase. *J. Phys. Chem. A*, 111(26):5729–5742, 2007.
- [81] M. North, S. Bhattacharyya, and D. G. Truhlar. Improved density functional description of the electrochemistry and structure-property descriptors of substituted flavins. *J. Phys. Chem. B*, 114(46):14907–14915, 2010.
- [82] X. Zeng, H. Hu, X. Hu, and W. Yang. Calculating solution redox free energies with ab initio quantum mechanical/molecular mechanical minimum free energy path method. *J. Chem. Phys.*, 130(16):164111, 2009.
- [83] J. Blumberger. $\text{Cu}^+(\text{aq})/\text{Cu}^{2+}(\text{aq})$ redox reaction exhibits strong non-linear solvent response due to change in coordination number. *J. Am. Chem. Soc.*, 130(47):16065–16068, 2008.
- [84] R. Vuilleumier, K. A. Tay, G. Jeanmairet, D. Borgis, and A. Boutin. Extension of marcus picture for electron transfer reactions with large solvation changes. *J. Am. Chem. Soc.*, 134(4):2067–2074, 2012.
- [85] J. Vandevonede, M. Krack, F. Mohamed, M. Parrinello, T. Chassaing, and J. Hutter. QUICKSTEP: Fast and accurate density functional calculations using a mixed Gaussian and plane waves approach. *Comput. Phys. Comm.*, 167(2):103–128, 2005.
- [86] G. Lippert, J. Hutter, and M. Parrinello. A hybrid Gaussian and plane wave density functional scheme. *Mol. Phys.*, 92(3):477–487, 1997.
- [87] S. Goedecker, M. Teter, and J. Hutter. Separable dual-space gaussian pseudopotentials. *Phys. Rev. B*, 54(3):1703–1710, 1996.

- [88] C. Hartwigsen, S. Goedecker, and J. Hutter. Relativistic separable dual-space Gaussian pseudopotentials from H to Rn. *Phys. Rev. B*, 58(7):3641–3662, 1998.
- [89] J. VandeVondele and J. Hutter. Gaussian basis sets for accurate calculations on molecular systems in gas and condensed phases. *J. Chem. Phys.*, 127(11):114105, 2007.
- [90] G. J. Martyna and M. E. Tuckerman. A reciprocal space based method for treating long range interactions in ab initio and force field-based calculations in clusters. *J. Chem. Phys.*, 110(6):2810–2821, 1999.
- [91] G. Bussi, D. Donadio, and M. Parrinello. Canonical sampling through velocity rescaling. *J. Phys. Chem. A*, 126(1):014101, 2007.
- [92] I. F. W. Kuo, C. J. Mundy, M. J. McGrath, and J. I. Siepmann. Time-dependent properties of liquid water: A comparison of Car–Parrinello and Born–Oppenheimer molecular dynamics simulations. *J. Chem. Theory Comput.*, 2(5):1274–1281, 2006.
- [93] S. Kumar, D. Bouzida, R. H. Swendsen, P. A. Kollman, and J. M. Rosenberg. The Weighted Histogram Analysis Method for Free-Energy Calculations on Biomolecules: 1.The Method. *J. Comp. Chem.*, 13(8):1011–1021, 1992.
- [94] R. Seidel, M. Faubel, B. Winter, and J. Blumberger. Single-ion reorganization free energy of aqueous $\text{Ru}(\text{bpy})_3^{2+/3+}$ and $\text{Ru}(\text{H}_2\text{O})_6^{2+/3+}$ from photoemission spectroscopy and density functional molecular dynamics simulation. *J. Am. Chem. Soc.*, 131(44):16127–16137, 2009.
- [95] M. Kılıç and B. Ensing. First and second one-electron reduction of lumiflavin in water—a first principles molecular dynamics study. *J. Chem. Theory Comput.*, 9(9):3889–3899, 2013.
- [96] Y. W. Hsiao, J. P. Gotze, and W. Thiel. The central role of GLN63 for the hydrogen bonding network and UV-Visible spectrum of the AppA BLUF Domain. *J. Phys. Chem. B*, 116:8064–8073, 2012.
- [97] B. Rieff, S. Bauer, G. Mathias, and P. Tavan. Density Functional Theory Combined with Molecular Mechanics: The Infrared Spectra of Flavin in Solution. *Photochem. Photobiol.*, 87:511–523, 2011.
- [98] B. Rieff, S. Bauer, G. Mathias, and P. Tavan. IR spectra of flavins in solution: DFT/MM description of redox effects. *J. Phys. Chem. B*, 115:2117–2123, 2011.
- [99] B. Rieff, S. Bauer, G. Mathias, and P. Tavan. DFT/MM description of flavin IR spectra in BLUF domains. *J. Phys. Chem. B*, 115:11239–11253, 2011.

- [100] V. Hornak, R. Abel, A. Okur, B. Strockbine, A. Roitberg, and C. Simmerling. Comparison of multiple amber force fields and development of improved protein backbone parameters. *Proteins*, 65(3):712–725, 2006.
- [101] D. Van Der Spoel, E. Lindahl, B. Hess, G. Groenhof, A.E. Mark, and H.J. Berendsen. GROMACS: fast, flexible, and free. *J. Comput. Chem.*, 26(16):1701–1718, 2005.
- [102] W. Humphrey, A. Dalke, and K. Schulten. VMD: Visual Molecular Dynamics. *J. Mol. Graphics*, 14:33–38, 1996.
- [103] L. Michaelis, M. P. Schubert, and C. V. Smythe. Potentiometric study of the flavins. *J. Biol. Chem.*, 116:587–607, 1936.
- [104] E. J. Land and A. J. Swallow. One-electron reactions in biochemical systems as studied by pulse radiolysis. 2. Riboflavine. *Biochemistry*, 8(5):2117–2125, 1969.
- [105] S. Ghisla, P. Macheroux, and F. Müller. Ionisation properties of reduced, 1,5-dihydroflavin, rates of N(5) exchange with solvent. In *Flavins and flavoproteins, proceedings of the 10th internat. symposium*, pages 27–32, 1991.
- [106] R. W. Zwanzig. High-temperature equation of state by a perturbation method. 1. Nonpolar gases. *J. Chem. Phys.*, 22(8):1420, 1954.
- [107] M. Sulpizi and M. Sprik. Acidity constants from vertical energy gaps: Density functional theory based molecular dynamics implementation. *Phys. Chem. Chem. Phys.*, 10:5238–5249, 2008.
- [108] E. A. Carter, G. Ciccotti, J. T. Hynes, and R. Kapral. Constrained reaction coordinate dynamics for the simulation of rare events. *Chem. Phys. Lett.*, 156(5):472–477, 1989.
- [109] B. Trout and M. Parrinello. The dissociation mechanism of H₂O in water studied by first-principles molecular dynamics. *Chem. Phys. Lett.*, 288(2-4):343–347, 1998.
- [110] M. Sprik. Computation of p*K* of liquid water using coordination constraints. *Chem. Phys.*, 258(2-3):139–150, 2000.
- [111] J. Cheng and M. Sprik. Acidity of the Aqueous Rutile TiO₂(110) Surface from Density Functional Theory Based Molecular Dynamics. *J. Chem. Theory Comput.*, 6:880–889, 2010.
- [112] M Sprik. Coordination numbers as reaction coordinates in constrained molecular dynamics. *Faraday Discuss.*, 110:437–445, 1998.

- [113] B. Ensing, E. J. Meijer, P. E. Blochl, and E. J. Baerends. Solvation effects on the S_N2 reaction between $CH_3Cl + Cl^-$ in water. *J. Phys. Chem. A*, 105:3300, 2001.
- [114] S. Grimme, J. Antony, S. Ehrlich, and H. Krieg. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.*, 132:154104, 2010.
- [115] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, A. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox. Gaussian 09 Revision D.01. Gaussian Inc. Wallingford CT 2009.
- [116] P. J. Stephens, F. J. Devlin, C. F. Chabalowski, and M. J. Frisch. Ab initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *J. Phys. Chem.*, 98:11623, 1994.
- [117] Y. Zhao and D. G. Truhlar. A new local density functional for main-group thermochemistry, transition metal bonding, thermochemical kinetics, and non-covalent interactions. *J. Chem. Phys.*, 125:194101, 2006.
- [118] S. Ghisla and V. Massey. New flavins for old: artificial flavins as active site probes of flavoproteins. *Biochem. J.*, 239:1–12, 1986.
- [119] J. E. Davies, N. L. Doltsinis, A. J. Kirby, C. D. Roussev, and M. Sprik. Estimating pK_a 's for pentaoxyphosphoranes. *J. Am. Chem. Soc.*, 124:6594–6599, 2002.
- [120] N. L. Doltsinis and M. Sprik. Theoretical pK_a estimates for solvated $P(OH)_5$ from coordination constrained Car-Parrinello dynamics. *Phys. Chem. Chem. Phys.*, 5:2612–2618, 2003.
- [121] L. Bernasconi, E. J. Baerends, and M. Sprik. Long-range solvent effects on the orbital interaction mechanism of water acidity enhancement in metal ion solutions: A comparative study of the electronic structure of aqueous Mg and Zn dications. *J. Phys. Chem. B*, 110(23):11444–11453, 2006.

- [122] D. Chandler. *Introduction to modern statistical mechanics*. Oxford University Press, New York, 1987.
- [123] Ivaylo Ivanov, Bin Chen, Simone Raugai, and Michael L Klein. Relative pK_a values from first-principles molecular dynamics: the case of histidine deprotonation. *J. Phys. Chem. B*, 110:16365–6371, 2006.
- [124] M. Gauden, S. Yeremenko, S. W. Laan, I. H. M. van Stokkum, J. A. Ihalainen, R. van Grondelle, K. J. Hellingwerf, and J. T. M. Kennis. Photocycle of the flavin-binding photoreceptor AppA, a bacterial transcriptional antirepressor of photosynthesis genes. *Biochemistry*, 44(10):3653–3662, 2005.
- [125] M. Gauden, I. H. M. van Stokkum, J. M. Key, D. C. Lührs, R. van Grondelle, P. Hegemann, and J. T. M. Kennis. Hydrogen-bond switching through a radical pair mechanism in a flavin-binding photoreceptor. *Proc. Natl. Acad. Sci. USA*, 103(29):10895–10900, 2006.
- [126] H. Ishikita. Influence of the protein environment on the redox potentials of flavodoxins from *Clostridium beijerinckii*. *J. Biol. Chem.*, 282(35):25240–25246, 2007.
- [127] H. Ishikita. Light-induced hydrogen bonding pattern and driving force of electron transfer in AppA BLUF domain photoreceptor. *J. Biol. Chem.*, 283(45):30618–30623, 2008.
- [128] T. R. Barends, E. Hartmann, J. J. Griese, T. Beitlich, N. V. Kirienko, D. A. Ryjenkov, J. Reinstein, R. L. Shoeman, M. Gomelsky, and I. Schlichting. Structure and mechanism of a bacterial light-regulated cyclic nucleotide phosphodiesterase. *Nature*, 459(7249):1015–1018, 2009.
- [129] H. Yuan, S. Anderson, S. Masuda, V. Dragnea, K. Moffat, and C. Bauer. Crystal structures of the synechocystis photoreceptor Slr1694 reveal distinct structural states related to signaling. *Biochemistry*, 45(42):12687–12694, 2006.
- [130] A. Kita, K. Okajima, Y. Morimoto, M. Ikeuchi, and K. Miki. Structure of a cyanobacterial BLUF protein, Tll0078, containing a novel FAD-binding blue light sensor domain. *J. Mol. Biol.*, 349(1):1–9, 2005.
- [131] A. Jung, T. Domratcheva, M. Tarutina, Q. Wu, W. H. Ko, R.L. Shoeman, M. Gomelsky, K. H. Gardner, and I. Schlichting. Structure of a bacterial BLUF photoreceptor: insights into blue light-mediated signal transduction. *Proc. Natl. Acad. Sci. USA*, 102(35):12350–12355, 2005.
- [132] S. Anderson, V. Dragnea, S. Masuda, J. Ybe, K. Moffat, and C. Bauer. Structure of a novel photoreceptor, the BLUF domain of AppA from *Rhodospira rubra*. *Biochemistry*, 44(22):7998–8005, 2005.

- [133] C. Bonetti, T. Mathes, I. H. M. van Stokkum, K. M. Mullen, M. L. Groot, R. van Grondelle, P. Hegemann, and J. T. M. Kennis. Hydrogen bond switching among flavin and amino acid side chains in the bluf photoreceptor observed by ultrafast infrared spectroscopy. *Biochemistry*, 95:4790–4802, 2008.
- [134] M. A. van der Horst and K. J. Hellingwerf. Photoreceptor proteins, star actors of modern times: A review of the functional dynamics in the structure of representative members of six different photoreceptor families. *Acc. Chem. Res.*, 37:13–20, 2004.
- [135] J. M. Christie, T. E. Swartz, R. A. Bogomolni, and W. R. Briggs. Phototropin lov domains exhibit distinct roles in regulating photoreceptor function. *Plant J.*, 32:205–219, 2002.
- [136] A. Mattevi. To be or not to be an oxidase: Challenging the oxygen reactivity of flavoenzymes. *Trends Biochem. Sci.*, 31:276–283, 2006.
- [137] M. Gomelsky and G. Klug. BLUF: A novel FAD-binding domain involved in sensory transduction in microorganisms. *Trends Biochem. Sci.*, 27:497–500, 2002.
- [138] A. Udvarhelyi and T. Domratcheva. Glutamine rotamers in bluf photoreceptors: A mechanistic reappraisal. *J. Phys. Chem. B*, 117:2888–2897, 2013.
- [139] M. G. Khrenova, A. V. Nemukhin, and T. Domratcheva. Photoinduced electron transfer facilitates tautomerization of the conserved signaling glutamine side chain in bluf protein light sensors. *J. Phys. Chem. B*, 117:2369–2377, 2013.
- [140] G. Noll, G. Hauska, P. Hegemann, K. Lanzl, T. Noll, M. von Sanden-Flohe, and B. Dick. Redox properties of lov domains: chemical versus photochemical reduction, and influence on the photocycle. *ChemBioChem*, 8:2256–2264, 2007.
- [141] H. Segel. *Biochemical Calculations*. John Wiley & Sons Inc., New York, second edition, 1986.
- [142] J. M. Berg, J. L. Tymoczko, and L. Stryer. *Biochemistry*. W.H. Freeman & Company, New York., sixth edition, 2007.
- [143] V. Balland, M. Byrdin, A. P. M. Eker, M. Ahmad, and K. Brettel. What makes the difference between a cryptochrome and DNA photolyase? A spectroelectrochemical comparison of the flavin redox transitions. *J. Am. Chem. Soc.*, 131:426–427, 2009.
- [144] M. Kılıç and B. Ensing. A microscopic picture of the solvent reorganization during electron transfer to flavin in water. *in submission*, 2014.

- [145] D. W. Small, D. V. Matyushov, and G. Voth. The theory of electron transfer reactions: what may be missing? *J. Am. Chem. Soc.*, 125(24):7470–7478, 2003.
- [146] A. Jung, J. Reinstein, T. Domratcheva, R. L. Shoeman, and I. Schlichting. Crystal structures of the AppA BLUF domain photoreceptor provide insights into blue light-mediated signal transduction. *J. Mol. Biol.*, 362(4):717–732, 2006.
- [147] A. Moglich and K. Moffat. Structural basis for light-dependent signaling in the dimeric LOV domain of the photosensor YtvA. *J. Mol. Biol.*, 373(1):112–126, 2007.
- [148] D. A. Case, T. A. Darden, T. E. Cheatham, C. L. Simmerling, J. Wang, R. E. Duke, R. Luo, R. C. Walker, W. Zhang, K. M. Merz, B. Roberts, S. Hayik, A. Roitberg, G. Seabra, J. Swails, A. W. Goetz, I. Kolossvary, K. F. Wong, F. Paesani, J. Vanicek, R. M. Wolf, J. Liu, X. Wu, S.R. Brozell, T. Steinbrecher, H. Gohlke, Q. Cai, X. Ye, J. Wang, M. J. Hsieh, G. Cui, D. R. Roe, D. H. Mathews, M. G. Seetin, R. Salomon-Ferrer, C. Sagui, V. Babin, T. Luchko, S. Gusarov, A. Kovalenko, and P. A. Kollman. AMBER12, University of California, San Francisco. <http://ambermd.org/>, 2012.
- [149] D. A. Case, T. E. Cheatham, T. Darden, H. Gohlke, R. Luo, K. M. Merz, A. Onufriev, C. Simmerling, B. Wang, and R. J. Woods. The Amber Biomolecular Simulation Programs. *J. Comput. Chem.*, 26(16):1668–1688, 2005.
- [150] J. Kolafa. Numerical integration of equations of motion with a self-consistent field given by an implicit equation. *Mol. Simul.*, 18(3):193–212, 1996.
- [151] J. VandeVondele and J. Hutter. An efficient orbital transformation method for electronic structure calculations. *J. Chem. Phys.*, 118(10):4365, 2003.