Supporting Information for:

CPPE: An Open-Source C++ and Python Library for Polarizable Embedding

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1 Source code directory structure

Table S1: File structure of CPPE, together with the contained C++ classes.

File name	C++ classes	Description
`cppe_state.hh`	`CppeState`	top-level interface class of CPPE
`electric_fields.hh`	`NuclearFields`, `MultipoleFields`, `InducedMoments`	compute routines for nuclear fields, multipole fields, and induced moments solver
`math.hh`	-	mathematical utilities and compute routines for T-tensors
`molecule.hh`	`Atom`, `Molecule`	container for the quantum region (core) molecule
`multipole_expansion.hh`	`MultipoleExpansion`	compute routine for multipole-nuclei interaction energy
`pe_options.hh`	`PeOptions`, `BorderOptions`	Options class for the CPPE library
`pot_manipulation.hh`	`PotManipulators`	manipulate lists of Potentials (border region)
`potential.hh`	`Multipole`, `Polarizability`, `Potential`	containers for multipoles, polarizabilities, and potentials
`potfile_reader.hh`	`PotfileReader`	Reader for potential files

2 CPPE options

Table S2: `PeOptions` and `BorderOptions` with default values and explanation.

`PeOptions`

option	default value	comment
`potfile`	"potential.pot"	path to the potential file
`iso_pol`	false	make polarizabilities isotropic
`induced_thresh`	8	$10^{-\texttt{induced_thresh}}$
`do_diis`	true	enable DIIS for the ind. moments solver
`maxiter`	50	maximum number of iterations for ind. moments
`diis_start_norm`	1.0	start DIIS mixing when residual norm is below this value
`damp_induced`	false	enable Thole damping for induced moments
`damping_factor_induced`	2.1304	damping factor for induced moments
`damp_multipole`	false	enable Thole damping for electric fields created by multipole moments
`damping_factor_multipole`	2.1304	damping factor for electric fields created by multipole moments
`pe_border`	false	enable border options
`border_options`	-	container with border options

`BorderOptions`

option	default value	comment
`border_type`	`BorderType::rem`	remove (`BorderType::rem`) or redistribute (`BorderType::redist`) border sites
`rmin`	2.2	minimum radius from QM atoms to MM sites to be taken into account for removal/redistribution (in AU)
`nredist`	-1	number of neighbor sites to redistribute to. The default (-1) redistributes to all sites which are not in the border region.
`redist_order`	1	order from which moments are removed
`redist_pol`	false	redistribute polarizabilities?

3 Computational Methodology for Nile Red Case Study

3.1 Structure Preparation

Configurations of nile red in β-lactoglobulin (BLG) were obtained from extracted QM/MM MD trajectory, the starting point of which was a classical MD trajectory. The crystal structure of BLG was obtained from the protein data bank[1] (PDB ID: 1B0O), which contains bovine BLG complexed with palmitate. The protein was processed by the protein preparation tool available in the Schrödinger program suite.[2] The palmitate was removed from the protein model, and N- and C-terminals were capped by acetyl or N-methyl amide groups. Disulfide bonds were created between the cysteines in close proximity (CYS106–CYS118; CYS66–CYS160). Missing atoms were added, and protonation states were assigned with PROPKA[3,4] based on a pH of 7.0. Finally, the model was minimized, with heavy atoms restrained to a distance of 0.3Å. A nile red molecule was then docked into the protein model using the Glide program[5] from the Schrödinger suite. Default settings were used for the grid generation, and the docking protocol was done according to the XP protocol.[6]

The complex was then solvated with the tleap program from the Amber program.[7,8] An initial cubic box of water with a buffering distance of 20 Å was used. Eight sodium ions were added to ensure neutrality of the system. For the water, the TIP3P model[9] was used, whereas the protein was described by the ff14SB force field.[10] The nile red molecule was described by GAFF parameters,[11] with charges derived based on RESP[12] fitting using the Antechamber[13] program from Amber. Both structures and ESPs used in this charge assignment were derived from HF/6-31G*[14–18] calculation in Gaussian09.[19] The parameters of the final assembled system was then converted to a Gromacs[20]-compatible format using the parmed[21] program.

The initial assembled system was then simulated in Gromacs with a three-stage protocol. First, an energy minimization was carried out in order to remove any bad contacts. For this, a steepest descent minimizer was applied for 2000 steps. Next, the system was heated

at constant volume to 303 K across 50 ps using the Berendsen thermostat.[22] A time-step of 2 fs was used, and all bonds were constrained using the LINCS method.[23] Finally, a 800 ns NPT run was performed using a 2 fs time-step, with the temperature targeted at 303 K using a Nosé-Hoover thermostat[24,25] and the pressure towards 1 atm using a Parrinello-Rahman barostat.[26] Long-range electrostatics were treated with the particle-mesh ewald (PME) method,[27] with a cut-off distance of 12 Å.

The final configuration after 800 ns was extracted for use in the QM/MM MD trajectory. For this, the NAMD[28,29]/Orca[30,31] interface[32] was used. The nile red molecule was treated at a M06-L[33]/def2-SVP[34] level of theory. The RI method was applied to accelerate the calculations, using the def2/J[35] as an auxillary fitting set. CHELPG charges[36] were calculated at every step to represent the charge distribution of the nile red molecule for use in the QM/MM interaction. The system was minimized for 100 steps, followed by 3000 steps of dynamics using a 0.5 fs time step (total of 1.5 ps).

The final configuration from the QM/MM MD was extracted, and embedding parameters was calculated for this snapshot. Here, the entire protein along with water and ions within a shell of 12 Å of the nile red molecule. The embedding parameters consists of atom-centered multipoles (up to quadrupoles) and anisotropic dipole–dipole polarizabilties. The parameters were derived with the LoProp method,[37,38] based on linear response calculations using CAM-B3LYP[39] with an ANO-recontracted loprop-6-31+G* basis set. The fragmentation of the system and setup of these calculations was done using the PyFraME program.[40]

Configurations of nile red in water was obtained using an equivalent protocol, i.e., running classical MD (300 ns only) followed by a QM/MM MD using the NAMD/Orca interface. Water within a sphere of 12 Å was included in the embedding potential, which was again derived using the LoProp method.

3.2 Quantum-Chemical Calculations

The geometry of nile red in vacuum was optimized with Orca[30,31] at the ωB97X-D3BJ[41,42]/def2-SVP level of theory. For all three environments of nile red (vacuum, water, BLG), the three lowest singlet excitation energies were computed using *a)* TDA[43,44] with the CAM-B3LYP functional[39] in PySCF (version 1.6.2),[45] *b)* EOM-CC2[46,47] in Psi4 (developer version 1.4),[48] and *c)* ADC(2)[49] in Q-Chem (version 5.2).[50] All calculations were carried out with the 6-31G(d) basis set. For EOM-CC2 and ADC(2), the core orbitals were kept frozen. The inclusion of PE was performed as explained in the main text: For *a)*, PE linear response was included self-consistently, whereas for *b)* and *c)*, perturbative corrections to the excitation energies were employed. In the EOM-CC case, only perturbative state-specific (ptSS) corrections were added. For PE-ADC,[51] both ptSS and linear-response (ptLR) corrections were employed. The resulting stick spectra were convoluted with Lorentzian functions employing full width at half maximum of 0.44 eV.

4 Results for S_2 and S_3 States of Nile Red

Table S3: Summary of the second singlet excited state of nile red ($S_0 \rightarrow S_2$) with all employed methods and environments.

Environment	Method	E_{exc}[eV][a]	f[b]	ptLR [eV]	ptSS [eV]	E_{shift} [eV]
vac.	ADC(2)	3.189	0.000	–	–	–
	EOM-CC2	3.384	0.000	–	–	–
	TDA	3.574	0.000	–	–	–
water	ADC(2)	2.949	0.037	−0.003	−0.069	−0.24
	EOM-CC2	3.110	0.024	–	−0.093	−0.274
	TDA	3.456	0.047	–	–	−0.118
BLG	ADC(2)	2.969	0.003	−0.002	−0.121	−0.22
	EOM-CC2	3.097	0.000	–	−0.151	−0.287
	TDA	3.471	0.003	–	–	−0.103

[a] For ADC(2) and EOM-CC2, the perturbative corrections are added to the excitation energy.
[b] Oscillator strength.

Table S4: Summary of the third singlet excited state of nile red ($S_0 \rightarrow S_3$) with all employed methods and environments.

Environment	Method	E_{exc}[eV][a]	f[b]	ptLR [eV]	ptSS [eV]	E_{shift} [eV]
vac.	ADC(2)	3.724	0.009	–	–	–
	EOM-CC2	3.767	0.009	–	–	–
	TDA	4.058	0.018	–	–	–
water	ADC(2)	3.656	0.003	−0.004	−0.015	−0.068
	EOM-CC2	3.697	0.002	–	−0.013	−0.07
	TDA	3.854	0.025	–	–	−0.204
BLG	ADC(2)	3.246	0.092	−0.01	−0.066	−0.478
	EOM-CC2	3.296	0.170	–	−0.062	−0.471
	TDA	3.530	0.223	–	–	−0.528

[a] For ADC(2) and EOM-CC2, the perturbative corrections are added to the excitation energy.
[b] Oscillator strength.

References

(1) Berman, H. M. The Protein Data Bank. *Nucleic Acids Res.* **2000**, *28*, 235–242.

(2) Schrödinger Release 2018-2. 2018; Schrödinger, LLC, New York, NY.

(3) Søndergaard, C. R.; Olsson, M. H.; Rostkowski, M.; Jensen, J. H. Improved Treatment of Ligands and Coupling Effects in Empirical Calculation and Rationalization of P K a Values. *J. Chem. Theory Comput.* **2011**, *7*, 2284–2295.

(4) Olsson, M. H.; Søndergaard, C. R.; Rostkowski, M.; Jensen, J. H. PROPKA3: Consistent Treatment of Internal and Surface Residues in Empirical P K a Predictions. *J. Chem. Theory Comput.* **2011**, *7*, 525–537.

(5) Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. *J. Med. Chem.* **2004**, *47*, 1739–1749.

(6) Friesner, R. A.; Murphy, R. B.; Repasky, M. P.; Frye, L. L.; Greenwood, J. R.; Halgren, T. A.; Sanschagrin, P. C.; Mainz, D. T. Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein- Ligand Complexes. *J. Med. Chem.* **2006**, *49*, 6177–6196.

(7) Case, D. A.; Cheatham III, T. E.; Darden, T.; Gohlke, H.; Luo, R.; Merz Jr, K. M.; Onufriev, A.; Simmerling, C.; Wang, B.; Woods, R. J. The Amber Biomolecular Simulation Programs. *J. Comput. Chem.* **2005**, *26*, 1668–1688.

(8) Salomon-Ferrer, R.; Case, D. A.; Walker, R. C. An Overview of the Amber Biomolecular Simulation Package. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2013**, *3*, 198–210.

(9) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. Comparison of Simple Potential Functions for Simulating Liquid Water. *J. Chem. Phys.* **1983**, *79*, 926–935.

(10) Maier, J. A.; Martinez, C.; Kasavajhala, K.; Wickstrom, L.; Hauser, K. E.; Simmerling, C. Ff14SB: Improving the Accuracy of Protein Side Chain and Backbone Parameters From Ff99SB. *J. Chem. Theory Comput.* **2015**, *11*, 3696–3713.

(11) Wang, J.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. Development and Testing of a General Amber Force Field. *J. Comput. Chem.* **2004**, *25*, 1157–1174.

(12) Bayly, C. I.; Cieplak, P.; Cornell, W.; Kollman, P. A. A Well-Behaved Electrostatic Potential Based Method Using Charge Restraints for Deriving Atomic Charges: The RESP Model. *J. Phys. Chem.* **1993**, *97*, 10269–10280.

(13) Wang, J.; Wang, W.; Kollman, P. A.; Case, D. A. Automatic Atom Type and Bond Type Perception in Molecular Mechanical Calculations. *Journal of Molecular Graphics and Modelling* **2006**, *25*, 247–260.

(14) Ditchfield, R.; Hehre, W. J.; Pople, J. A. Self-Consistent Molecular-Orbital Methods. IX. An Extended Gaussian-Type Basis for Molecular-Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1971**, *54*.

(15) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XXIII. A Polarization-Type Basis Set for Second-Row Elements. *J. Chem. Phys.* **1982**, *77*.

(16) Gordon, M. S.; Binkley, J. S.; Pople, J. A.; Pietro, W. J.; Hehre, W. J. Self-Consistent Molecular-Orbital Methods. 22. Small Split-Valence Basis Sets for Second-Row Elements. *J. Am. Chem. Soc.* **1982**, *104*.

(17) Hariharan, P. C.; Pople, J. A. The Influence of Polarization Functions on Molecular Orbital Hydrogenation Energies. *Theor. Chim. Acta* **1973**, *28*.

(18) Hehre, W. J.; Ditchfield, R.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian-Type Basis Sets for Use in Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1972**, *56*.

(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09 Revision E.01. Gaussian Inc. Wallingford CT 2009.

(20) Abraham, M. J.; Murtola, T.; Schulz, R.; Páll, S.; Smith, J. C.; Hess, B.; Lindahl, E. GROMACS: High Performance Molecular Simulations Through Multi-Level Parallelism From Laptops to Supercomputers. *SoftwareX* **2015**, *1*, 19–25.

(21) Swails, J.; Hernandez, C.; Mobley, D.; Nguyen, H.; Wang, L.; Janowski, P. ParmEd. 2010.

(22) Berendsen, H. J.; Postma, J. v.; van Gunsteren, W. F.; DiNola, A.; Haak, J. Molecular Dynamics With Coupling to an External Bath. *J. Chem. Phys.* **1984**, *81*, 3684–3690.

(23) Hess, B.; Bekker, H.; Berendsen, H. J.; Fraaije, J. G. LINCS: A Linear Constraint Solver for Molecular Simulations. *J. Comput. Chem.* **1997**, *18*, 1463–1472.

(24) Nosé, S. A Unified Formulation of the Constant Temperature Molecular Dynamics Methods. *J. Chem. Phys.* **1984**, *81*, 511–519.

(25) Hoover, W. G. Canonical Dynamics: Equilibrium Phase-Space Distributions. *Physical review A* **1985**, *31*, 1695.

(26) Parrinello, M. M. Parrinello and A. Rahman, Phys. Rev. Lett. 45, 1196 (1980). *Phys. Rev. Lett.* **1980**, *45*, 1196.

(27) Darden, T.; York, D.; Pedersen, L. Particle Mesh Ewald: An N Log (N) Method for Ewald Sums in Large Systems. *J. Chem. Phys.* **1993**, *98*, 10089–10092.

(28) Nelson, M. T.; Humphrey, W.; Gursoy, A.; Dalke, A.; Kalé, L. V.; Skeel, R. D.; Schulten, K. NAMD: A Parallel, Object-Oriented Molecular Dynamics Program. *The International Journal of Supercomputer Applications and High Performance Computing* **1996**, *10*, 251–268.

(29) Phillips, J. C.; Braun, R.; Wang, W.; Gumbart, J.; Tajkhorshid, E.; Villa, E.; Chipot, C.; Skeel, R. D.; Kale, L.; Schulten, K. Scalable Molecular Dynamics With NAMD. *J. Comput. Chem.* **2005**, *26*, 1781–1802.

(30) Neese, F. The ORCA Program System. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2012**, *2*, 73–78.

(31) Neese, F. Software Update: The ORCA Program System, Version 4.0. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2018**, *8*, e1327.

(32) Melo, M. C.; Bernardi, R. C.; Rudack, T.; Scheurer, M.; Riplinger, C.; Phillips, J. C.; Maia, J. D.; Rocha, G. B.; Ribeiro, J. V.; Stone, J. E.; Neese, F.; Schulten, K.; Luthey-Schulten, Z. NAMD Goes Quantum: An Integrative Suite for Hybrid Simulations. *Nat. Methods* **2018**, *15*, 351.

(33) Zhao, Y.; Truhlar, D. G. A New Local Density Functional for Main-Group Thermochemistry, Transition Metal Bonding, Thermochemical Kinetics, and Noncovalent Interactions. *J. Chem. Phys.* **2006**, *125*, 194101.

(34) Weigend, F.; Ahlrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*.

(35) Weigend, F. Accurate Coulomb-Fitting Basis Sets for H to Rn. *Physical chemistry chemical physics* **2006**, *8*, 1057–1065.

(36) Breneman, C. M.; Wiberg, K. B. Determining Atom-Centered Monopoles From Molecular Electrostatic Potentials. The Need for High Sampling Density in Formamide Conformational Analysis. *J. Comput. Chem.* **1990**, *11*, 361–373.

(37) Gagliardi, L.; Lindh, R.; Karlström, G. Local Properties of Quantum Chemical Systems: The LoProp Approach. *J. Chem. Phys.* **2004**, *121*, 4494–4500.

(38) Vahtras, O. LoProp for Dalton, 2014. *URL http://dx. doi. org/10.5281/zenodo 13276*.

(39) Yanai, T.; Tew, D. P.; Handy, N. C. A New Hybrid Exchange–Correlation Functional Using the Coulomb-Attenuating Method (CAM-B3LYP). *Chem. Phys. Lett.* **2004**, *393*, 51–57.

(40) Olsen, J. M. H. PyFraME: Python framework for Fragment-based Multiscale Embedding (version 0.2.0). 2018; https://doi.org/10.5281/zenodo.1443314.

(41) Chai, J.-D.; Head-Gordon, M. Systematic Optimization of Long-Range Corrected Hybrid Density Functionals. *J. Chem. Phys.* **2008**, *128*, 084106.

(42) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the Damping Function in Dispersion Corrected Density Functional Theory. *J. Comput. Chem.* **2011**, *32*, 1456–1465.

(43) Tamm, I. Relativistic Interaction of Elementary Particles. *J. Phys.(USSR)* **1945**, *9*, 449.

(44) Dancoff, S. M. Non-Adiabatic Meson Theory of Nuclear Forces. *Physical Review* **1950**, *78*, 382–385.

(45) Sun, Q.; Berkelbach, T. C.; Blunt, N. S.; Booth, G. H.; Guo, S.; Li, Z.; Liu, J.; McClain, J. D.; Sayfutyarova, E. R.; Sharma, S.; Wouters, S.; Chan, G. K. L. PySCF: The Python-Based Simulations of Chemistry Framework. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2018**, *8*.

(46) Christiansen, O.; Koch, H.; Jørgensen, P. The Second-Order Approximate Coupled Cluster Singles and Doubles Model CC2. *Chem. Phys. Lett.* **1995**, *243*, 409–418.

(47) Geertsen, J.; Rittby, M.; Bartlett, R. J. The Equation-Of-Motion Coupled-Cluster Method: Excitation Energies of Be and CO. *Chem. Phys. Lett.* **1989**, *164*, 57–62.

(48) M. Parrish, R.; A. Burns, L.; G. A. Smith, D.; C. Simmonett, A.; Eugene DePrince, A.; G. Hohenstein, E.; Bozkaya, U.; Yu. Sokolov, A.; Di Remigio, R.; M. Richard, R.; F. Gonthier, J.; M. James, A.; R. McAlexander, H.; Kumar, A.; Saitow, M.; Wang, X.; P. Pritchard, B.; Verma, P.; F. Schaefer, H.; Patkowski, K.; A. King, R.; F. Valeev, E.; A. Evangelista, F.; M. Turney, J.; Daniel Crawford, T.; David Sherrill, C. Psi4 1.1: An Open-Source Electronic Structure Program Emphasizing Automation, Advanced Libraries, and Interoperability. *J. Chem. Theory Comput.* **2017**, *13*, 3185–3197.

(49) Wormit, M.; Rehn, D. R.; Harbach, P. H.; Wenzel, J.; Krauter, C. M.; Epifanovsky, E.; Dreuw, A. Investigating Excited Electronic States Using the Algebraic Diagrammatic Construction (ADC) Approach of the Polarisation Propagator. *Mol. Phys.* **2014**, *112*, 774–784.

(50) Shao, Y.; Gan, Z.; Epifanovsky, E.; Gilbert, A. T.; Wormit, M.; Kussmann, J.; Lange, A. W.; Behn, A.; Deng, J.; Feng, X.; Ghosh, D.; Goldey, M.; Horn, P. R.; Jacobson, L. D.; Kaliman, I.; Khaliullin, R. Z.; Kuś, T.; Landau, A.; Liu, J.; Proynov, E. I.; Rhee, Y. M.; Richard, R. M.; Rohrdanz, M. A.; Steele, R. P.; Sundstrom, E. J.; Woodcock, H. L.; Zimmerman, P. M.; Zuev, D.; Albrecht, B.; Alguire, E.; Austin, B.; Beran, G. J. O.; Bernard, Y. A.; Berquist, E.; Brandhorst, K.; Bravaya, K. B.; Brown, S. T.; Casanova, D.; Chang, C.-M.; Chen, Y.; Chien, S. H.; Closser, K. D.; Crittenden, D. L.; Diedenhofen, M.; DiStasio, R. A.; Do, H.; Dutoi, A. D.; Edgar, R. G.; Fatehi, S.; Fusti-Molnar, L.; Ghysels, A.; Golubeva-Zadorozhnaya, A.; Gomes, J.; Hanson-Heine, M. W.; Harbach, P. H.; Hauser, A. W.; Hohenstein, E. G.; Holden, Z. C.; Jagau, T.-C.; Ji, H.; Kaduk, B.; Khistyaev, K.; Kim, J.; Kim, J.; King, R. A.; Klunzinger, P.; Kosenkov, D.; Kowalczyk, T.; Krauter, C. M.; Lao, K. U.; Laurent, A. D.; Lawler, K. V.; Levchenko, S. V.; Lin, C. Y.; Liu, F.; Livshits, E.; Lochan, R. C.; Luenser, A.; Manohar, P.; Manzer, S. F.; Mao, S.-P.; Mardirossian, N.; Marenich, A. V.; Maurer, S. A.; Mayhall, N. J.; Neuscamman, E.; Oana, C. M.; Olivares-Amaya, R.; O'Neill, D. P.; Parkhill, J. A.; Perrine, T. M.; Peverati, R.; Prociuk, A.; Rehn, D. R.; Rosta, E.; Russ, N. J.; Sharada, S. M.; Sharma, S.; Small, D. W.; Sodt, A.; Stein, T.; Stück, D.; Su, Y.-C.; Thom, A. J.; Tsuchimochi, T.; Vanovschi, V.; Vogt, L.; Vydrov, O.; Wang, T.; Watson, M. A.; Wenzel, J.; White, A.; Williams, C. F.; Yang, J.; Yeganeh, S.; Yost, S. R.; You, Z.-Q.; Zhang, I. Y.; Zhang, X.; Zhao, Y.; Brooks, B. R.; Chan, G. K.; Chipman, D. M.; Cramer, C. J.; Goddard, W. A.; Gordon, M. S.; Hehre, W. J.; Klamt, A.; Schaefer, H. F.; Schmidt, M. W.; Sherrill, C. D.; Truhlar, D. G.; Warshel, A.; Xu, X.; Aspuru-Guzik, A.; Baer, R.; Bell, A. T.; Besley, N. A.;

Chai, J.-D.; Dreuw, A.; Dunietz, B. D.; Furlani, T. R.; Gwaltney, S. R.; Hsu, C.-P.; Jung, Y.; Kong, J.; Lambrecht, D. S.; Liang, W.; Ochsenfeld, C.; Rassolov, V. A.; Slipchenko, L. V.; Subotnik, J. E.; Van Voorhis, T.; Herbert, J. M.; Krylov, A. I.; Gill, P. M.; Head-Gordon, M. Advances in Molecular Quantum Chemistry Contained in the Q-Chem 4 Program Package. *Mol. Phys.* **2015**, *113*, 184–215.

(51) Scheurer, M.; Herbst, M. F.; Reinholdt, P.; Olsen, J. M. H.; Dreuw, A.; Kongsted, J. Polarizable Embedding Combined With the Algebraic Diagrammatic Construction: Tackling Excited States in Biomolecular Systems. *J. Chem. Theory Comput.* **2018**, *14*, 4870–4883.